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Original Article

The Effect of Resistance Training and Cannabis Extract Supplementation on the Expression of PI3K/Akt/mTOR Signaling Pathway Genes in the Pancreas of Obese Male Rats

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Abstract

Background and aims: Obesity has become a worldwide epidemic and is a major public health concern. This study aimed to evaluate the effect of resistance training and cannabis extract supplementation on the expression of PI3K/Akt/mTOR signaling pathway genes in the pancreas of obese male rats.

Methods: Thirty male Wistar rats (twelve weeks old and weighing 180–200 g) were chosen for examination. The animals were randomly assigned to healthy control, obese control, supplement, exercise, and exercise + supplement groups (n = 6 per group). The exercise protocol involved ladder climbing on a custom-built rodent apparatus set at an 80° incline, measuring 110 cm in height with 2 cm-spaced rungs. The supplement, initially in solid form, was dissolved in distilled water and orally administered via gavage at a dose of 4 mg/kg body weight, five times a week for eight weeks. The data were statistically analyzed using one-way ANOVA followed by Tukey's post hoc test to assess group differences ($P<0.05$).

Results: Obesity significantly decreased *mTOR* ($P=0.001$), *PI3K* ($P=0.001$), and *AKT* ($P=0.001$) expression. Resistance training significantly increased all three ($P=0.001$), while cannabis alone elevated *PI3K* ($P=0.006$) and *AKT* ($P=0.001$) but not *mTOR*. Combined treatment significantly restored *mTOR*, *PI3K*, and *AKT* levels close to those of healthy controls ($P=0.001$).

Conclusion: The results revealed that obesity reduced the expression of *AKT*, *PI3K*, and *mTOR* in the pancreas of obese rats. However, resistance training and cannabis administration increased their expression levels.

Keywords: Resistance training, Cannabis, Obesity, mTOR

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Introduction

Obesity has become a global epidemic and represents a major public health concern (1). Individuals with obesity frequently demonstrate insulin resistance in the metabolism of glucose and lipids (1). Intracellular communication depends on the interaction of various molecules (2, 3). These interactions initiate the activation of intracellular signaling cascades, including the class I phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway (4). It is noteworthy that interference with insulin-mediated signaling pathways, particularly the PI3K/AKT/mTOR axis, is associated with insulin resistance (5). This disruption can lead to the formation and accumulation of advanced glycation end products, along with the production of reactive oxygen and nitrogen species (5). Insulin resistance or reduced insulin secretion from pancreatic β-cells is commonly observed in individuals with obesity or metabolic syndrome. The maintenance of pancreatic β-cell mass and the stimulation of insulin release in response to glucose are primarily regulated by insulin signaling pathways (5). Dysfunctional insulin signaling within pancreatic β-cells may lead to reduced cell mass and impaired insulin secretion (6). The molecule mTOR plays a pivotal role in the insulin signaling pathway and is essential for preserving the mass and function of pancreatic β-cells, which are critical for regulating blood glucose levels. MTOR supports the maintenance of β-cell populations and their functional capacity (7). According to most studies, exercise has a positive effect on β-cell function (8). A study revealed that endurance exercise training can improve glucose metabolism. Additionally, Li et al demonstrated that diabetic rats subjected to swimming exercise exhibited significantly reduced blood glucose and insulin levels compared to the diabetic control group. Furthermore, pancreatic expression levels of PI3K, AKT, and mTOR proteins were significantly increased in the exercised diabetic group compared to the control group (9).

Likewise, non-psychoactive compounds from the cannabis plant have been proven to improve obesity and insulin resistance, which are complications of diabetes

and its related consequences. The mentioned compounds exhibit anti-inflammatory and antioxidant properties (10). In addition, cannabis is widely recognized for its medicinal and recreational applications, and numerous studies have highlighted its anti-diabetic and anti-obesity characteristics (11). Nevertheless, the precise mechanisms by which cannabis influences adipose tissue, insulin sensitivity, and inflammatory processes remain incompletely understood. Furthermore, it is still unclear whether cannabis extract, alone or combined with physical activity, can enhance metabolic function. Due to inconsistent findings, there is ongoing debate about the independent effects of obesity and insulin resistance on beta-cell function. These discrepancies may result from methodological differences, particularly regarding the indices used to investigate beta-cell performance. Accordingly, gaining a deeper understanding of the interplay among obesity, insulin resistance, and beta-cell function, especially in the context of exercise and novel interventions (e.g., cannabis extract), can be valuable for developing innovative therapeutic strategies. Therefore, this study seeks to evaluate the effect of resistance training and cannabis extract supplementation on the expression of *PI3K*/*Akt*/*mTOR* signaling pathway genes in the pancreas of obese male rats.

Materials and Methods

This study considered an experimental design using laboratory rats maintained under strictly controlled environmental conditions. Thirty male Wistar rats, aged 12 weeks and weighing between 180 g and 200 g, were selected for investigation. The animals were obtained from the Pasteur Institute in Tehran and housed at the Histogenotech Laboratory on Bagarkhan Street, Shahrat, Tehran. Environmental conditions were consistently maintained, including a temperature of 22 ± 3°C and a 12-hour light/dark cycle. The rats were housed in standard cages during the dark phase, with three rats per cage. Throughout the study, all animals had ad libitum access to water and a specially formulated rat diet. They were randomly divided into healthy control, obese control, supplement only, exercise only, and combined exercise and supplement groups (six animals per group).

Obesity Protocol

To induce obesity, all rats in the obese groups were orally administered a high-fat emulsion for 4 weeks, at a dose of 0.5 mL per 100 g of body weight, five days per week. The emulsion was prepared using 70% powdered standard chow, 10% sucrose, 10% corn oil (as a fat source), 5% powdered milk, and 5% Tween 80 for homogenization. To induce obesity, this high-energy emulsion is commonly used in rodent models in studies performed in Iran. Body weight was weekly recorded, and rats with a ≥ 20% increase in body weight compared to healthy controls were considered obese (12).

To validate obesity induction beyond weight gain, previous studies reported that the use of high-fat emulsions similar to the current protocol leads to significant metabolic changes, including elevated serum triglycerides, total cholesterol, low-density lipoprotein, and reduced high-density lipoprotein levels. Although the serum lipid profile was not measured in this study, the applied protocol is consistent with previous validated models of diet-induced obesity in rodents (12).

Exercise Protocol

The exercise protocol involved rats climbing a ladder specifically designed for rodents, set at an 80% incline and measuring 110 cm in height, with rungs spaced 2 cm apart. The load carried during climbing was gradually increased to determine each rat's one-repetition maximum (1RM). The animals' body weights were measured after a one-week acclimatization period. In addition, a load equivalent to 50% of each rat's body weight was attached to the base of its tail. An additional 30 g was added to the load following each successful climb. The highest weight a rat could lift in a single climb was recorded as its 1RM. In the initial training session, rats started by lifting 50% of their established 1RM, with 140 seconds of rest between sets. Then, the intensity was progressively increased to 75%, 90%, and finally 100% of the rat's 1RM. If a rat could successfully lift 100% of its 1RM, 30 g was added to the load. This progression continued until the rat failed to complete the climb with the given weight, setting the highest successfully lifted load as its new 1RM. In subsequent sessions, each rat began training with the maximum weight lifted during the previous session, which was applied as its calculated 1RM for that day (13).

Supplementary Protocol

The supplement used in this study was an extract of the cannabis plant, specially formulated at the Karaj Medicinal Plants Research Institute. The solid-form supplement was dissolved in distilled water and administered to rats by gavage at a dose of 4 mg per kg of body weight, five times a week for eight weeks.

Tissue Collection and Storage

Forty-eight hours after the final intervention, all rats underwent an 8–10-hour fasting period and were weighed prior to tissue collection. Further, anesthesia was induced via the inhalation of chloroform. The animals were euthanized once full anesthesia was confirmed by the absence of pain response to ensure unconsciousness. Furthermore, pancreatic tissue was promptly excised, and any mucus, blood, or extraneous material was removed by rinsing with phosphate-buffered saline. The cleaned tissue was then placed into coded 1.5 mL microtubes, which were immediately transferred to a liquid nitrogen tank and subsequently stored at -80°C until further cellular analysis.

Gene Expression Measurement

Total RNA was extracted from pancreatic tissue using the

TRIzol™ Reagent (Invitrogen, Thermo Fisher Scientific, USA) following the manufacturer's instructions. The samples were incubated at 65°C for 5 minutes to denature secondary structures. In addition, RNA quantity and purity were assessed using the NanoDrop™ One spectrophotometer (Thermo Fisher Scientific, USA), and integrity was confirmed by observing 18S and 28S bands on 2% agarose gel electrophoresis (Bio-Rad, USA).

Moreover, complementary DNA (cDNA) was synthesized using the RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific) with oligo(dT) primers (Table 1).

Additionally, real-time polymerase chain reaction was performed on the StepOnePlus™ system (Applied Biosystems, USA) using SYBR Green Master Mix (Ampliqon, Denmark). Reactions (20 µL) contained 10 µL Master Mix, 1 µL of each primer (10 µM), 2 µL of cDNA, and 6 µL of water. The thermal cycling program included 95°C for 10 minutes and 40 cycles of 95°C for 15 seconds and 60°C for 60 seconds. Melting curve analysis confirmed amplification specificity.

Finally, relative gene expression was calculated using the 2^−ΔΔCt method, normalized to glyceraldehyde 3-phosphate dehydrogenase. All samples were analyzed in triplicate, and the expression levels were determined relative to the healthy control group.

RNA integrity was confirmed by electrophoresis on a 2% agarose gel, illustrating distinct 28S and 18S rRNA bands (Figure 1).

The Shapiro-Wilk test was separately applied for each dependent variable (mTOR, PI3K, and AKT) within each experimental group to confirm the assumption of normality before applying the analysis of variance (ANOVA). After confirming normality, a one-way ANOVA was performed to compare differences across the groups. Tukey's post hoc test was subsequently conducted to identify which groups differed significantly. All statistical analyses were conducted using SPSS (version 28), with the significance level set at $P<0.05$. Graphs and statistical comparisons were performed using GraphPad Prism, version 9.5.1 (GraphPad Software Inc., San Diego, CA, USA).

Table 1. Primer Sequence

Primer Sequence	Genes
GAPDH_F	AACCCATCACCATCTTCCAG
GAPDH_R	CCAGTAGACTCCACGACATAC
r-Akt-f	TGTGGGAAGATGTGTATGAGAA
r-Akt-r	TTGATGAGGCGGTGTGATGGTGA
rPik3r1 F	TTAAACGCGAAGGCAACGA
rPik3r 1R	CAGTCTCCTCCTGCTGTCGAT
mTOR-F	ACTATAGAACCACATGCCACAC
mTOR-R	TGTCCATCAGCCTCCAATTC

Results

The results of the ANOVA test demonstrated a significant difference in *mTOR* expression among the groups ($P=0.001$). Moreover, post hoc analysis revealed that *mTOR* expression in the obese control group was considerably decreased compared to the healthy control group ($P=0.001$), with an average expression level of 0.465 ± 0.13 and a fold change of 0.49, representing approximately a 51% reduction. Similarly, the cannabis group showed a decrease in *mTOR* expression in comparison to healthy controls (fold change = 0.59), with an average of 0.559 ± 0.06, although this reduction was not statistically significant compared to the obese control group ($P=0.29$). Both the training group (fold change = 0.92, mean ± standard deviation [SD] = 0.872 ± 0.07) and the training + cannabis group (fold change = 0.99, mean ± SD = 0.939 ± 0.09) exhibited increased *mTOR* expression compared to the obese control group, with increases being statistically meaningful ($P=0.001$). No significant difference was observed between the training and training + cannabis groups ($P=0.29$). These findings suggest that training, alone or in combination with cannabis, has a beneficial effect on maintaining *mTOR* expression levels in the context of obesity (Table 2, Figure 2).

ANOVA results confirmed a considerable difference in *PI3K* expression among the groups ($P=0.001$). Based

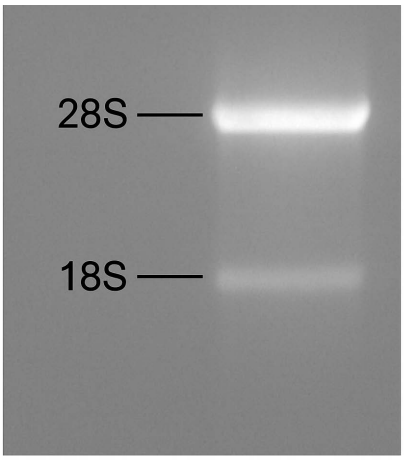

Figure 1. Electrophoresis on a 2% Agarose Gel Displaying Intact 28S and 18S Ribosomal RNA Bands Indicating Good RNA Quality

Table 2. ANOVA Results for mTOR, PI3K, and AKT

Marker	Healthy Control (Mean ± SD)	Obese Control (Mean ± SD)	Cannabis (Mean ± SD)	Training (Mean ± SD)	Training + Cannabis (Mean ± SD)	*P*-Value
mTOR	0.947 ± 0.08	0.465 ± 0.13	0.559 ± 0.06	0.872 ± 0.07	0.939 ± 0.09	0.001
PI3K	0.947 ± 0.03	0.362 ± 0.03	0.474 ± 0.03	0.795 ± 0.05	0.927 ± 0.03	0.001
AKT	0.970 ± 0.03	0.271 ± 0.04	0.414 ± 0.04	0.792 ± 0.06	0.874 ± 0.09	0.001

Note. ANOVA: Analysis of variance; mTOR: Mammalian target of rapamycin; PI3K: Class I phosphoinositide 3-kinase; AKT: Protein kinase B; SD: Standard deviation.

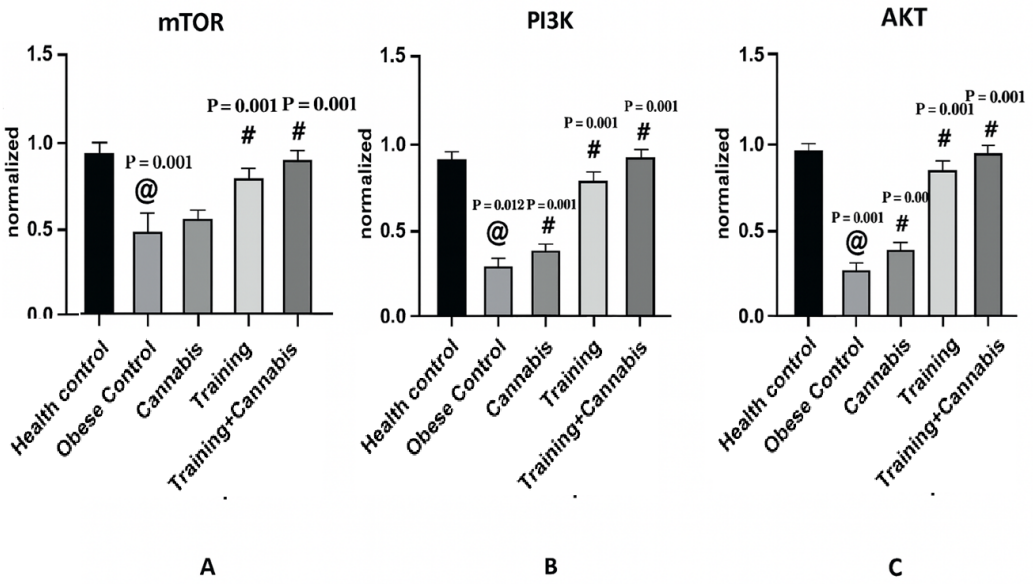

Figure 2. Expression of All Three Variables in Different Groups: **(A)** *mTOR* Expression in Five Groups, **(B)** *PI3K* Expression in Five Groups, and **(C)** *AKT* Expression in Five Groups

Note. mTOR: Mammalian target of rapamycin; PI3K: Class I phosphoinositide 3-kinase; AKT: Protein kinase B; SD: Standard deviation. @: significant to healthy control; #: significant to obese control

on the post hoc analysis results, *PI3K* expression in the obese control group was significantly decreased when compared to the healthy control group ($P = 0.001$), with an average expression level of 0.362 ± 0.03 and a fold change of 0.38, indicating an approximate reduction of 62%. A reduced level of expression with a fold change of 0.50 and an average expression of 0.474 ± 0.03 was also detected in the cannabis group. However, both exercise and cannabis alone considerably increased *PI3K* expression in comparison to the obese control group ($P = 0.001$ and $P = 0.006$, respectively), with the training group displaying an average expression of 0.795 ± 0.05 (fold change = 0.84). The training + cannabis group demonstrated expression levels closest to the healthy controls, with a fold change of 0.98 and an average expression of 0.927 ± 0.03, noticeably higher compared to both the obese control group and the cannabis or training groups alone ($P = 0.001$ for both). These findings imply that training, especially when combined with cannabis, helps maintain *PI3K* gene expression levels (Table 2, Figure 2).

The results of the ANOVA test revealed a significant difference in *AKT* expression among the groups ($P = 0.001$). According to post hoc analysis results, *AKT* expression in the obese control group was significantly decreased in comparison to the healthy control group ($P = 0.001$), with an average expression level of 0.271 ± 0.04 and a fold change of approximately 0.28, indicating substantial downregulation. The cannabis group showed a moderate increase in *AKT* expression compared to the obese controls (with an average expression of 0.414 ± 0.04 and a fold change of 0.43). Moreover, exercise alone resulted in a higher fold change of 0.82 (with an average expression of 0.792 ± 0.06 relative to healthy controls), while the combined training + cannabis group exhibited expression levels close to healthy controls (with a fold change of 0.90 and an average expression of 0.874 ± 0.09). Furthermore, the cannabis + training group demonstrated noticeably higher *AKT* expression when compared to the obese control group ($P = 0.001$), as well as the cannabis ($P = 0.001$) and training ($P = 0.006$) groups. The findings confirmed that obesity considerably reduces *AKT* expression, whereas training and cannabis treatment, especially in combination, effectively mitigate this downregulation. Additionally, exercise ($P = 0.001$) and cannabis ($P = 0.001$) alone increased *AKT* expression in comparison to the obese control group (Table 2, Figure 2).

Discussion

Obesity is associated with chronic elevations of free fatty acids, insulin resistance, systemic inflammation, and oxidative stress, all disrupting the PI3K/Akt/mTOR signaling pathway. This pathway is normally activated by the binding of insulin to its receptor, leading to the activation of PI3K, Akt, and mTOR, respectively, which play key roles in glucose uptake, cell growth, and protein synthesis.

Additionally, during obesity, elevated levels of tumor necrosis factor-alpha and interleukin-6 activate inflammatory pathways, such as JNK and IKKβ. These pathways impair PI3K activation by inducing the serine phosphorylation of insulin receptor substrate 1 (IRS-1) (14). On the other hand, IRS-1, which mediates the interaction between the insulin receptor and PI3K, loses its function, leading to a failure in transmitting the signal to Akt and subsequently to mTOR (15).

In obesity, elevated free fatty acids accumulate in the skeletal muscle and liver, activating PKCθ. This enzyme phosphorylates IRS-1 at inhibitory sites, thereby reducing PI3K activation (16). It has also been shown that excessive cytokine production disrupts Akt phosphorylation in

chronic inflammatory conditions. In particular, reduced Akt activity in skeletal muscle leads to decreased glucose transporter type 4 translocation and impaired glucose uptake by cells (17). In obesity, oxidative stress induced by reactive oxygen species can inhibit mTOR, either directly or indirectly, through the activation of adenosine monophosphate-activated protein kinase. Reduced mTOR activity negatively impacts cell growth and protein synthesis (18).

Our results demonstrated that resistance training and cannabis consumption increased the expression of *AKT*, *PI3K*, and *mTOR* in the pancreas of obese mice. Similar findings were reported in other studies, indicating that resistance training enhances the availability of free AKT and PI3K in obese individuals (18). Soares et al also found that combined training reduced *mTOR* expression in lymphocytes (19). The mTOR pathway integrates multiple signaling processes, including protein synthesis and anabolic metabolism, and coordinates cell growth, proliferation, and fate determination (19). In addition, resistance exercise stimulates the phosphorylation of the insulin receptor and IRS-1/2, thereby restoring the PI3K signaling cascade in skeletal muscle, liver, and adipose tissue. In obese models, PI3K/Akt is typically impaired by inflammation and lipid accumulation; resistance training reverses this impairment by enhancing the gene expression and protein levels of PI3K and Akt (20). On the other hand, activated PI3K produces *phosphatidylinositol 3,4,5-trisphosphate*, which recruits and phosphorylates Akt at Ser473. This active Akt subsequently promotes glucose transporter type 4 translocation to the plasma membrane, markedly enhancing insulin-stimulated glucose uptake in obese subjects (21).

Resistance training enhances the activation of both mTORC2, which supports Akt activation, and mTORC1 pathways, evidenced by the increased phosphorylation of downstream targets S6K1 and 4E-BP1, thus promoting protein synthesis and muscle hypertrophy. Notably, excessive mTORC1 activity in obesity contributes to insulin resistance; however, exercise rebalances this activity in favor of mTORC2, improving overall insulin sensitivity (22). Furthermore, resistance training increases insulin-like growth factor-1 levels, which further activate the PI3K/Akt/mTOR pathway, inhibit FoxO-mediated muscle degradation, and promote muscle protein synthesis, thereby helping to combat sarcopenic obesity (23). The activation of the Akt/mTOR pathway improves mitochondrial function, reduces oxidative stress, and supports efficient metabolic responses, thus counteracting obesity-related mitochondrial dysfunction (24).

Cannabis (delta-9-*tetrahydrocannabinol*/cannabichromene: THC/CBD) has been shown in obese diabetic rodent models to reduce *PTEN* expression, an inhibitor of PI3K, thereby enhancing PI3K/Akt signaling and promoting cardiac cell survival (25). Low-dose THC transiently activates mTOR in neural tissue, supporting brain metabolism while simultaneously downregulating mTORC1 in adipocytes, thus favorably influencing lipid metabolism and insulin sensitivity (26). While THC directly modulates PI3K/Akt signaling, CBD (cannabidiol) has been observed to partially restore PI3K/Akt/mTOR pathway activity in inflammatory conditions (e.g., multiple sclerosis models). However, high-dose CBD can suppress this pathway in neuronal cells, confirming dose-dependent effects (27).

Regarding the combined effect of resistance training and cannabis, resistance exercise robustly activates the PI3K/Akt/mTOR cascade, thereby enhancing glucose uptake, protein synthesis, and overall metabolic health (28). Low-dose THC enhances this effect by further increasing PI3K/Akt signaling through PTEN downregulation while selectively suppressing mTORC1 in adipose tissue, thus improving insulin sensitivity (29). Overall, resistance training and cannabis synergistically enhance energy metabolism, promote lean mass gain, reduce insulin resistance, and support muscle regeneration.

Conclusion

Our results revealed that obesity decreased the expression of *AKT*, *PI3K*, and *mTOR* in the pancreas of obese rats. However, resistance training and cannabis use increased *AKT*, *PI3K*, and *mTOR* expression levels. It is suggested that future research investigate the effects of different doses of cannabis compounds (THC and CBD) on the PI3K/Akt/mTOR pathway in different tissues (e.g., muscle, liver, and adipose tissue) in chronic obesity in order to determine the effective and safe dose range. In addition, studying the precise mechanism of the combined effects of resistance training and cannabis on the balance between mTORC1 and mTORC2 can help better understand the improvement of insulin sensitivity and protein synthesis. Finally, evaluating the long-term effects of this combined intervention on pancreatic function and metabolic indices in obese humans will pave the way for the clinical use of complementary approaches in the treatment of insulin-resistant obesity.

Authors' Contribution

Conceptualization: Mahdie Abdi.
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Methodology: Mahdie Abdi, Vahid Moghadam, Forouzan Fattahi Masrour.
Supervision: Vahid Moghadam.
Writing–original draft: Mahdie Abdi, Vahid Moghadam.
Writing–review & editing: Mahdie Abdi, Vahid Moghadam, Forouzan Fattahi Masrour.

Competing Interests

The authors declare that there is no conflict of interests.

Ethical Approval

This article received approval from the Ethics Committee of Islamic Azad University, Central Tehran Branch (IR.IAU.SARI.REC.1402.214).

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References

1. Heindel JJ, Lustig RH, Howard S, Corkey BE. Obesogens: a unifying theory for the global rise in obesity. Int J Obes (Lond). 2024;48(4):449-60. doi: 10.1038/s41366-024-01460-3.
2. Bunsick DA, Matsukubo J, Aldbai R, Baghaie L, Szewczuk MR. Functional selectivity of cannabinoid type 1 G protein-coupled receptor agonists in transactivating glycosylated receptors on cancer cells to induce epithelial-mesenchymal transition metastatic phenotype. Cells. 2024;13(6):480. doi: 10.3390/cells13060480.
3. Hilgendorf KI, Myers BR, Reiter JF. Emerging mechanistic understanding of cilia function in cellular signalling. Nat Rev Mol Cell Biol. 2024;25(7):555-73. doi: 10.1038/s41580-023-00698-5.
4. Huang L, Wang D, Zhou A, Qian M, Zhou C. Regulation of ovary function in aged mice by reactive oxygen species through the PI3K/Akt/mTOR pathway. Biol Bull. 2024;51(3):490-500. doi: 10.1134/s1062359023604640.
5. Szablewski L. Changes in cells associated with insulin resistance. Int J Mol Sci. 2024;25(4):2397. doi: 10.3390/ijms25042397.
6. Losada-Barragán M. Physiological effects of nutrients on insulin release by pancreatic beta cells. Mol Cell Biochem. 2021;476(8):3127-39. doi: 10.1007/s11010-021-04146-w.
7. Sun K, Luo J, Guo J, Yao X, Jing X, Guo F. The PI3K/AKT/mTOR signaling pathway in osteoarthritis: a narrative review. Osteoarthritis Cartilage. 2020;28(4):400-9. doi: 10.1016/j.joca.2020.02.027.
8. de Barros Pimentel Villaça C, de Paula CC, de Oliveira CC, Vilas-Boas EA, Dos Santos-Silva JC, de Oliveira SF, et al. Beneficial effects of physical exercise for β-cell maintenance in a type 1 diabetes mellitus animal model. Exp Physiol. 2021;106(7):1482-97. doi: 10.1113/ep088872.
9. Li L, He D, Jiang K, Zhao Y. Effects of forced swimming stress on expression and phosphorylation of PI3K/Akt signal pathway in pancreas of type 2 diabetic rats. Ann Transl Med. 2020;8(16):1006. doi: 10.21037/atm-20-5304.
10. Kopustinskiene DM, Masteikova R, Lazauskas R, Bernatoniene J. *Cannabis sativa* L. bioactive compounds and their protective role in oxidative stress and inflammation. Antioxidants (Basel). 2022;11(4):660. doi: 10.3390/antiox11040660.
11. Kaushal N, Kaur R, Garg A, Sharma T, Mehmood I. Antihypercholesterolemic effects of hemp (*Cannabis sativa*). In: Preedy VR, Patel VB, Martin CR, eds. Medicinal Usage of Cannabis and Cannabinoids. Academic Press; 2023. p. 427-40. doi: 10.1016/b978-0-323-90036-2.00044-2.
12. Shabbir F, Khan S, Yousaf MJ, Khan MA, Rajput TA. Comparison of effect of high fat diet induced obesity and subsequent atorvastatin administration on different anthropometric measures in Sprague-Dawley rats. Pak Armed Forces Med J. 2016;66(5):699-704.
13. Ahn N, Kim K. Effects of aerobic and resistance exercise on myokines in high fat diet-induced middle-aged obese rats. Int J Environ Res Public Health. 2020;17(8):2685. doi: 10.3390/ijerph17082685.
14. Feng J, Lu S, Ou B, Liu Q, Dai J, Ji C, et al. The role of JNk signaling pathway in obesity-driven insulin resistance. Diabetes Metab Syndr Obes. 2020;13:1399-406. doi: 10.2147/dmso.S236127.
15. Zheng M, Wang P. Role of insulin receptor substance-1 modulating PI3K/Akt insulin signaling pathway in Alzheimer's disease. 3 Biotech. 2021;11(4):179. doi: 10.1007/s13205-021-02738-3.
16. Engin A. Protein kinases in obesity, and the kinase-targeted therapy. Adv Exp Med Biol. 2024;1460:199-229. doi: 10.1007/978-3-031-63657-8_7.
17. Llanos P, Palomero J. Reactive oxygen and nitrogen species (RONS) and cytokines-myokines involved in glucose uptake and insulin resistance in skeletal muscle. Cells. 2022;11(24):4008. doi: 10.3390/cells11244008.
18. Zhao Y, Hu X, Liu Y, Dong S, Wen Z, He W, et al. ROS signaling under metabolic stress: cross-talk between AMPK and AKT pathway. Mol Cancer. 2017;16(1):79. doi: 10.1186/s12943-017-0648-1.
19. Soares JP, Cardoso R, Almeida V, Pereira AF, Silva AM, Mota MP. The impact of 8 weeks of combined physical exercise training on SIRT3 and mTOR in lymphocytes, and on lipid peroxidation. Healthcare (Basel). 2024;12(3):350. doi: 10.3390/healthcare12030350.
20. Wang H, Wang J, Zhu Y, Yan H, Lu Y. Effects of different intensity exercise on glucose metabolism and hepatic IRS/PI3K/AKT pathway in SD rats exposed with TCDD. Int J Environ Res Public Health. 2021;18(24):13141. doi: 10.3390/ijerph182413141.
21. Huang X, Liu G, Guo J, Su Z. The PI3K/AKT pathway in obesity and type 2 diabetes. Int J Biol Sci. 2018;14(11):1483-96. doi: 10.7150/ijbs.27173.
22. Levitt DE, Luk HY, Vingren JL. Alcohol, resistance exercise, and mTOR pathway signaling: an evidence-based narrative review. Biomolecules. 2022;13(1):2. doi: 10.3390/biom13010002.
23. Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: molecular mechanisms and promising therapies. Nat Rev Drug Discov. 2015;14(1):58-74. doi: 10.1038/nrd4467.
24. Li J, Sun M, Tang M, Song X, Zheng K, Meng T, et al. Mechanism of PI3K/Akt-mediated mitochondrial pathway in obesity-induced apoptosis (review). Biomed Rep. 2025;22(3):40. doi: 10.3892/br.2024.1918.
25. Bukowska B. Current and potential use of biologically active compounds derived from *Cannabis sativa* L. in the treatment of selected diseases. Int J Mol Sci. 2024;25(23):12738. doi: 10.3390/ijms252312738.
26. Lin L, Jung KM, Lee HL, Le J, Colleluori G, Wood C, et al. Adolescent exposure to low-dose THC disrupts energy balance and adipose organ homeostasis in adulthood. Cell Metab. 2023;35(7):1227-41.e7. doi: 10.1016/j.cmet.2023.05.002.
27. Ni B, Liu Y, Dai M, Zhao J, Liang Y, Yang X, et al. The role of cannabidiol in aging. Biomed Pharmacother. 2023;165:115074. doi: 10.1016/j.biopha.2023.115074.
28. Ahtiainen JP, Walker S, Silvennoinen M, Kyröläinen H, Nindl BC, Häkkinen K, et al. Exercise type and volume alter signaling pathways regulating skeletal muscle glucose uptake and protein synthesis. Eur J Appl Physiol. 2015;115(9):1835-45. doi: 10.1007/s00421-015-3155-3.
29. Zhao X, Gao Z, Wen W, Zheng S. Impacts of delta 9-tetrahydrocannabinol against myocardial ischemia/reperfusion injury in diabetic rats: role of PTEN/PI3K/Akt signaling pathway. Chin J Physiol. 2023;66(6):446-55. doi: 10.4103/cjop.CJOP-D-23-00103.