Open Access Maced J Med Sci **electronic publication ahead of print, published on April 23, 2019 as https://doi.org/10.3889/oamjms.2019.218**

ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences.
https://doi.org/10.3889/oamjms.2019.218
eISSN: 1857-9655
Basic Science

Correlations between Insulin Receptor Substrate-1 with Phosphoinositide 3-Kinase and P38 Mitogen-Activated Protein Kinase Levels after Treatment of Diabetic Rats with Puguntano (*Curanga Fel-Terrae* [Merr.]) Leaf Extract

Santi Syafril[1*], Dharma Lindarto[1], Aznan Lelo[2], Rosita Juwita Sembiring[3], Awaluddin Saragih[4]

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, H. Adam Malik General Hospital, Medan, Indonesia; [2]Department of Pharmacology and Therapeutics, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [3]Department of Clinical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [4]Department of Biological Pharmacy, Faculty of Pharmacy, Universitas Sumatera Utara, Medan, Indonesia

Citation: Syafril S, Lindarto D, Lelo A, Sembiring RJ, Saragih A. Correlations between Insulin Receptor Substrate-1 with Phosphoinositide 3-Kinase and P38 Mitogen-Activated Protein Kinase Levels after Treatment of Diabetic Rats with Puguntano (*Curanga Fel-Terrae* [Merr.]) Leaf Extract. Open Access Maced J Med Sci. https://doi.org/10.3889/oamjms.2019.218

Keywords: Puguntano; IRS-1; PI3K; p38 MAPK; T2DM

***Correspondence:** Santi Syafril. Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara-H. Adam Malik General Hospital, Medan, Indonesia. E-mail: syafril.santi@yahoo.com

Received: 14-Mar-2019; **Revised:** 21-Apr-2019; **Accepted:** 22-Apr-2019; **Online first:** 23-Apr-2019

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Defects in post-receptor insulin signalling are the major cause of insulin resistance in type 2 diabetes mellitus (T2DM).

AIM: This study aimed to investigate the correlations between insulin receptor substrate (IRS)-1 with phosphoinositide 3-kinase (PI3K) and p38 mitogen-activated protein kinase (MAPK) levels after puguntano (*Curanga fel-terrae* [Merr.]) leaf extract treatment in a rat model of T2DM.

METHODS: A combination of high-fat diet-feeding (HFD) and multiple low dose intraperitoneal injections of streptozotocin was used to induced T2DM in 48 Wistar rats, which were then randomly divided into control and treatment groups (n = 24 per group). Puguntano leaf extract was administered to the treatment group once daily (200 mg/kg.bw) for 10 days. IRS-1, PI3K and p38 MAPK levels were measured in skeletal muscle using sandwich ELISAs in control group after becoming T2DM and in the treatment group after 10 days of puguntano treatment. Data were analysed using the Wilcoxon test and Spearman's correlation.

RESULTS: IRS-1, PI3K and p38 MAPK levels were significantly higher in the treatment group than in the control group. There were also significant positive correlations between IRS-1 with PI3K and p38 MAPK levels ($r = 0.375$, $p = 0.035$; $r = 0.552$, $p = 0.003$; respectively) after the treatment.

CONCLUSION: This study demonstrated significant positive correlations between IRS-1 with PI3K and p38 MAPK levels after puguntano leaf extract treatment of T2DM rats.

Introduction

Insulin resistance is a fundamental pathophysiologic defect in type 2 diabetes (T2DM), and this leads to reductions in glucose uptake and utilisation in skeletal muscle, the tissue that is responsible for the majority of the postprandial glucose disposal [1]. Defects in insulin signal transduction are generally regarded as the underlying cause of this insulin resistance [2].

Insulin exerts its intracellular effects via signal transduction pathways that are activated following binding to insulin receptors on the plasma membrane [2], [3]. The insulin receptor consists of two extracellular α subunits and two β subunits that possess tyrosine kinase activity, which is activated upon insulin binding. Post-receptor signalling involves the phosphorylation of insulin receptor substrate (IRS)-1 and IRS-2, and of the β subunit itself (autophosphorylation) by the receptor tyrosine kinase [4]. Phosphorylation of IRS-1 leads to the activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and/or the Ras/Raf/mitogen-activated protein kinase (MAPK) signalling pathway. The PI3K/Akt

signalling pathway is the primary pathway stimulating glucose uptake, which occurs via glucose transporter-4 (GLUT-4) [1], [2], [3]. Activation of Akt initiates the translocation of GLUT-4 from its intracellular storage site to the plasma membrane, where it acts as a facilitative glucose transporter [5].

Multiple post-receptor intracellular defects have been identified in insulin-resistant skeletal muscle, including in the IRS/PI3K pathway, which therefore represents a promising therapeutic target for T2DM [6], [7]. Some data also show that p38 MAPK is necessary for insulin-stimulated glucose uptake through GLUT-4, but the role of p38 MAPK in the regulation of glucose transport in skeletal muscle is controversial [8]. However, another previous report has suggested that therapeutic targeting of p38 MAPK activity remain potential approaches for the treatment of T2DM [9].

The currently available therapeutic options for T2DM have some limitations, and many natural products and herbal medicines have been recommended for the treatment of this disease [10]. Puguntano (*Curanga fel-terrae* [Merr.]) The leaf has long been used as traditional medicine by the inhabitants of Tiga Lingga Village, Dairi, North Sumatera Province of Indonesia, for the treatment of diabetes [11]. Its secondary metabolites are thought to mediate its beneficial effects because tannins increase muscle glucose uptake by enhancing PI3K, activating p38 MAPK, and increasing GLUT-4 translocation [12]; flavonoids increase GLUT-4 translocation by activating the PI3K/Akt pathways [13]; triterpenoids increase the activation of IRS-1 [14]; and saponins increase GLUT-4 expression via the PI3K/Akt pathway [15]. A previous study has shown that puguntano improves glucose metabolism and ameliorates insulin resistance, alongside an increase in expression of adiponectin receptor (AdiporR) in diabetic rats [16]. Furthermore, another previous study has demonstrated that quercetin which contains a flavonoid compound, activates both the PI3K/Akt and MAPK pathways in skeletal muscle [17].

This study aimed to determine the correlations between insulin receptor substrate (IRS)-1 with phosphoinositide 3-kinase (PI3K) and p38 mitogen-activated protein kinase (MAPK) levels after puguntano *(Curanga fel-terrae* [Merr.]*)* leaf extract treatment in a rat model of T2DM.

Material and Methods

Forty-eight specific-pathogen-free 8-week-old male Wistar rats weighing 180-200 g were used in the present study. The rats were housed under a natural light cycle at 22-25°C. Diabetes was induced by feeding a high-fat diet (HFD) for 5 weeks, followed by two intraperitoneal injections of streptozotocin (30 mg/kg; Sigma-Aldrich, Munich, Germany). After this, fasting plasma glucose was measured in blood obtained from a lateral tail vein using a glucometer, and rats with a fasting plasma glucose (FPG) of 200 md/dL were deemed to have diabetes [18]. The study was approved by the Ethics Committee of Universitas Sumatera Utara, Medan, Indonesia (Reference 42/TGL/KPEK FK USU-RSUP HAM/2018).

After verifying the presence of diabetes in the rats, they were randomly divided into a control group and a treatment group (n = 24 per group), which was treated with 200 mg/kg/day ethanolic extract of puguntano leaves using an orogastric cannula for 10 days. Control rats were sacrificed on the day their diabetes was confirmed, while the puguntano-treated rats were sacrificed after 10 days treatment period was complete.

After anaesthesia with ketamine, the rats were decapitated, and blood was obtained from the left ventricle for the measurement of FPG by spectrophotometry and fasting insulin using a sandwich ELISA. Gastrocnemius muscles were dissected for the subsequent measurement of IRS-1, PI3K, and p38 MAPK levels. Insulin resistance was assessed using the homeostasis model assessment–insulin resistance (HOMA-IR) equation, which is calculated using fasting insulin and glucose concentrations [19]. The study was conducted in the Molecular Genetics Laboratory, Medical Faculty of Universitas Padjajaran. The ethanolic extract of puguntano leaves was obtained by maceration methods in the Department of Biological Pharmacy, Faculty of Pharmacy, Universitas Sumatera Utara, Medan, Indonesia [20].

Skeletal muscle samples were homogenized in ice-cold homogenization buffer (100 mM Tris, pH 7.4; 150 mM NaCl; 1 mM EGTA; 1 mM EDTA; 1% Triton X-100; 0.5% Sodium deoxycholate) supplemented with phosphatase and protease inhibitor cocktails, and 1 mM polymethyl sulfonyl fluoride, immediately before use. The homogenates were then frozen at -80°C and subsequently used to determine IRS-1, PI3K, and p38 MAPK levels using kits supplied by Qayeebio (China).

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 software. All data are expressed as the mean ± standard deviation, and the Wilcoxon test was used to compare the groups. The relationships between IRS-1 with PI3K and p38 MAPK levels were analysed using Spearman's correlation. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Body weight and FPG levels in the treatment group was significantly lower than in the control group as shown in Table 1.

Table 1: Body weight and FPG levels in the control and treatment groups

	Groups		
Variable	Control (n = 24)	Treatment (n = 24)	p
Body weight (g)	386 ± 20	245 ± 35	0.001
FPG (mg/dl)	355 ± 105	136 ± 33	0.001

Data are expressed as mean ± standard deviation. FPG: fasting plasma glucose. Wilcoxon test. P < 0.05 is statistically significant.

IRS-1, PI3K and p38 MAPK levels were significantly higher in the treatment group than in the control group as shown in Table 2.

Table 2: IRS-1, PI3K and p38 MAPK levels in control and treatment groups

	Groups		
Variable	Control (n = 24)	Treatment (n = 24)	p
IRS-1 (ng/mL)	0.28 ± 0.11	0.52 ± 0.21	0.001
PI3 Kinase (ng/mL)	14.22 ± 2.03	18.23 ± 5.20	0.0015
p38 MAPK (ng/mL)	20.81 ± 3.02	23.70 ± 4.04	0.0025

Data are expressed as mean ± standard deviation; IRS-1: insulin receptor substrate-1; PI3K: phosphoinositide 3-kinase; p38 MAPK: p38 mitogen-activated protein kinase; Wilcoxon test; P < 0.05 is statistically significant.

There was a significant positive correlation between IRS-1 with PI3K and p38 MAPK levels in skeletal muscle of rats after treatment with puguntano leaf extract as shown in Table 3.

Table 3. Correlations between IRS-1 with PI3K and p38 MAPK levels in skeletal muscle after treatment with puguntano leaf extract

Variable	r	p
PI3 Kinase (ng/mL)	0.375	0.035
p38 MAPK (ng/mL)	0.552	0.003

Data were analysed using Spearman's correlation; PI3K: phosphoinositide 3-kinase; p38 MAPK: p38 mitogen-activated protein kinase; P < 0.05 is statistically significant.

Discussion

The incidence of T2DM is increasing worldwide, with more rapid increases occurring in developing countries. Therefore, it is of great importance to study the pathogenesis of T2DM and search for effective and economical treatments [2]. Skeletal muscle is a key site of peripheral insulin resistance in T2DM [6], [21], and this tissue, therefore, represents an important target for potential anti-diabetic substances [22].

This present study has demonstrated significantly lower body weight and FPG levels in the skeletal muscle of T2DM rats that were administered with puguntano leaf extract. These findings are consistent with lower levels of obesity and hyperglycemia and with the results of a previous study demonstrating that treatment with puguntano extract tends to reduce body weight and significantly reduces FPG in patients with newly diagnosed T2DM [23].

Two signal transduction pathways mediate insulin-stimulated glucose transport in skeletal muscle. The binding of insulin to its receptor causes tyrosine phosphorylation of IRS-1 and IRS-2 [22], [24], which activates the PI3K/Akt signaling pathway that include IRS, PI3K, Akt, AS160 and GLUT-4, and MAPK signaling pathway which is necessary for insulin-stimulated glucose uptake through GLUT-4 [8], [22].

In this study, we have shown significantly higher IRS-1, PI3K and p38 MAPK levels in puguntano extract-treated rats than in controls, which may have been caused by one or more secondary metabolites of the tannins, flavonoids, triterpenoids, and saponins that are present in the leaf extract. This finding was consistent with those of some previous studies that evaluated the efficacy of another similar plant products in muscle or muscle cell lines. Rajendran et al. demonstrated that quercetin, which contains a flavonoid compound, increases IRS-1, IRS-2, PI3K, Akt, p38 MAPK, adenosine monophosphate-activated protein kinase (AMPK) and GLUT-4 expression in L6 myotubes [17]. The administration of a mulberry *(Folium Mori)* leaf extract containing flavonoids and polyphenols to T2DM rats caused significant increases in IRS-1, PI3K p85a and GLUT-4 expression through activation of the IRS-1/PI3K signalling pathway in skeletal muscles [25]. Furthermore, administration of *Momordica charantia* extract, which contains triterpenoids, increased glucose uptake in C2C12 myotubes by increasing the activation of IRS-1 and downstream signaling pathways, resulting in GLUT-4 translocation [14]. Previous research has also shown that a ginsenosides extract from *Panax ginseng,* containing a triterpenoid saponin compound, increases the expression of the insulin receptor, IRS-1, PI3Kp85, phosphorylated Akt and GLUT-4 in the skeletal muscle of diabetic rats [26]. Cinnamon (*Cinnamomum cassia*) extract, which contains tannins, also caused increases in IRS-1, PKB, PI3K and protein kinase C (PKC) gene expression in the skeletal muscle of diabetic Wistar rats [27]. Finally, a study of the effects of guava (*Folium Psidii Guajavae Psidiumguajava L*.) leaf extract in diabetic rats demonstated increases in expression of IRS-1, Akt, and PI3K p85, which was suggested to be mediated through the tannins, flavonoids, pentacyclic triterpenoids, and/or other chemical compounds it contains [6]. Together, these findings demonstrate that secondary metabolites in a variety of plant extracts can influence the expression of key insulin signaling intermediates, potentially ameliorating defects in insulin sensitivity, and increase glucose uptake into skeletal muscle cells.

The potential role of p38 MAPK in the regulation of glucose transport in skeletal muscle has been controversial, even though a previous study has

shown that p38α and p38β MAPK activity is required for insulin-stimulated glucose uptake [8]. Jiang et al. demonstrated that inhibition of p38α and p38β MAPK reduces insulin-stimulated glucose uptake in L6 myotubes, but GLUT-4 translocation is not affected, leading them to hypothesise that a p38 MAPK-dependent signalling pathway may regulate GLUT-4 activation [26]. Consistent with this finding, other studies showed that inhibitors of p38α and p38β MAPK do not affect GLUT-4 translocation, suggesting that p38 MAPK may increase the intrinsic activity of GLUT-4 in response to insulin stimulation [28,29]. Also, a study by Lawan et al. demonstrated that inhibition of p38 MAPK/c-jun n-terminal kinase (JNK) module signalling in skeletal muscle promotes insulin resistance and metabolic dysfunction [30].

The present study is the first to demonstrate that after puguntano leaf extract treatment there are significant positive correlations between IRS-1 with PI3K and p38 MAPK levels in the skeletal muscle of T2DM rats. We have shown that puguntano leaf extract increases the muscle expression of PI3K/Akt and MAPK pathway intermediates and ameliorates hyperglycemia. These effects of puguntano are similar to those reported by Rajendran et al., who demonstrated that the effect of quercetin is not predominantly through the PI3K signalling pathway, but instead through AMPK and its downstream target p38 MAPK in L6 myotubes.

This was the first study to show an antidiabetic effect of quercetin mediated through activation of multiple therapeutic targets for T2DM (in both the PI3K/Akt and MAPK pathways) and manifesting in an increase in glucose uptake, achieved through greater GLUT-4 expression and translocation [17].

In conclusion, puguntano leaf extract treatment caused an increase in the expression of several post-receptor insulin signalling intermediates in the skeletal muscle of T2DM rats, and there was a significant positive correlation between IRS-1 with PI3K and p38 MAPK levels. These changes are likely to be accompanied by an amelioration of insulin resistance in this tissue, but further studies are required to fully elucidate the molecular mechanisms associated with the anti-diabetic effects of puguntano leaf extract.

Acknowledgement

The authors acknowledge the assistance of the Molecular Genetics Laboratory, Faculty of Medicine, Universitas Padjajaran, Bandung.

References

1. Tian C, Chang H, La X, Li J. Wushenziye Formula Improves Skeletal Muscle Insulin Resistance in Type 2 Diabetes Mellitus via PTP1B-IRS1-Akt-GLUT4 Signaling Pathway. Evid-Based Compl Alt. 2017; 1-8. https://doi.org/10.1155/2017/4393529

2. Song C, Liu D, Yang S, Cheng L, Xing E, Chen Z. Sericin enhances the insulin-PI3K/AKT signalling pathway in the liver of a type 2 diabetes rat model. Exp Ther Med. 2018; 16:3345-52. https://doi.org/10.3892/etm.2018.6615

3. Horita S, Nakamura M, Suzuki M, Satoh N, Suzuki A, Seki G. Selective Insulin Resistance in the Kidney. Bio Med Res Intern. 2016; 1-8. https://doi.org/10.1155/2016/5825170

4. Bilous, R and Donnelly, R. Normal physiology of insulin secretion and action. In: Handbook of Diabetes: Blackwell Publishing Ltd 4th edition, 2010; 22-34. https://doi.org/10.1002/9781444391374.ch5

5. Khorami SAH, Movahedi A, Huzwah K, Sokhini AMM. PI3K/Akt pathway in modulating glucose homeostasis and its alteration in diabetes. Annals of Medical and Biomedical Sciences. 2015; 1(2):46-55.

6. Guo X, Yoshitomi H, Gao M, Qin L, Duan Y, Sun W, et al. Guava leaf extracts promote glucose metabolism in SHRSP. Z-Leprfa/Izm rats by improving insulin resistance in skeletal muscle. BMC Complement Altern Med. 2013; 13(52):1-8. https://doi.org/10.1186/1472-6882-13-52

7. Vergotine Z. Molecular investigation of genetic factors associated with insulin resistance and obesity in a South African population. [Desertation]. Stellenbosch University. 2015.

8. Ho RC, Alcazar O, Fujii N, Hirshman MF, Goodyear LJ. p38 MAPK regulation of glucose transporter expression and glucose uptake in L6 myotubes and mouse skeletal muscle. Am J Physiol Regul Integr Comp Physiol. 2003; 286(2):R342-9. https://doi.org/10.1152/ajpregu.00563.2003

9. Talbot NA, Wheeler-Jones C.P, Cleasby ME. Palmitoleic acid prevents palmitic acid-induced macrophage activation and consequent p38 MAPK-mediated skeletal muscle insulin resistance. Mol Cell Endocrinol. 2014; 393(1-2):129-42. https://doi.org/10.1016/j.mce.2014.06.010

10. Hussain SA and Marouf BH. Flavonoids as alternatives in treatment of type 2 diabetes mellitus. Acad J Med Plants. 2013; 1(2):31-6.

11. Harahap U, Patilaya P, Marianne, Yuliasmi S, Husori DI, Prasetyo BE, et al. Phytochemical Profile of Ethanol Extract of The Puguntano Leaf (CurangaFel-Terrae [Lour].) which has Potential as Anti-asthma. National Seminar on Science & Technology V, Research Institute of Lampung University, 2013.

12. Kumari M and Jain S. Tannins. An antinutrient with positive effect to manage diabetes. Res J Recent Sci. 2012; 1(12):70-3.

13. Vinagayam, R and Xu, B. Antidiabetic properties of dietary flavonoids: a celluler mechanism review. Nutrition & Metabolism. 2015; 12(60):1-20. https://doi.org/10.1186/s12986-015-0057-7

14. Han JH, Tuan NQ, Park MH, Quan KT, Oh J, Heo KS, et al. Cucurbitane Triterpenoids from the Fruits of Momordica Charantia Improve Insulin Sensitivity and Glucose Homeostasis in Streptozotocin-Induced Diabetic Mice. Mol Nutr Food Res. 2018; 62(7):1-37. https://doi.org/10.1002/mnfr.201700769 PMid:29405623

15. Bhavsar SK, Foller M, Gu S, Vir S, Shah MB, Bhutani KK, et al. Involvement of the PI3K/AKT pathway in the hypoglycemic effects of saponins from Helicteresisora. J Ethnopharmacol. 2009; 126(3):386-96. https://doi.org/10.1016/j.jep.2009.09.027 PMid:19781620

16. Lindarto D, Machrina Y, Syafril S, Saragih A. The Effect of Puguntano (CurangaFel-Terrae [Lour.]) Extract on Adiponectin Receptor (Adipor) in Rats with Type 2 Diabetes Mellitus. Asian J Pharm Clin Res. 2019; 12(3):1-3.

17. Rajendran D, Nisha P, Arya D, Murthy J. Quercetin, a Lead Compound against Type 2 Diabetes Ameliorates Glucose Uptake via AMPK Pathway in Skeletal Muscle Cell Line. Front Pharmacol. 2017; 8(336):1-9. https://doi.org/10.3389/fphar.2017.00336

18. Zhang M, Lv XY, Li J, Xu ZG, Chen L. The Characterization of high-fat diet and multiple low-dose streptozotocin induced type 2 diabetes rat model. Exp Diabetes Res. 2008; 1-9. https://doi.org/10.1155/2008/704045

19. Bitoska I, Krstevska B, Milenkovic T, Subeska-Stratrova S, Petrovski G, Mishevska SJ, et al. Effects of Hormone Replacement Therapy on Insulin Resistance in Postmenopausal Diabetic Women. Open Access Maced J Med Sci. 2016; 4(1):83-8. https://doi.org/10.3889/oamjms.2016.024 PMid:27275336 PMCid:PMC4884259

20. Kemenkes RI. Farmakope Herbal Indonesia Ed. I Suplemen II. Kemenkes RI Jakarta, 2013:106-7.

21. Brown AE, Palsgaard J, Borup R, Avery P, Gunn DA., Meyts PD, et al. p38 MAPK activation upregulates proinflammatory pathways in skeletal muscle cells from insulin-resistant type 2 diabetic patients. Am J Physiol Endocrinol Metab. 2015; 308(1):E63-70. https://doi.org/10.1152/ajpendo.00115.2014

22. Xu P-T, Song Z, Zhang W-C, Jiao B, Yu Z-B. Impaired Translocation of GLUT4 Results in Insulin Resistance of Atrophic Soleus Muscle. Bio Med Res Int. 2015; 1-11. https://doi.org/10.1155/2015/291987

23. Lindarto D, Syafril S, Zein U, Saragih A. The Effect of Dhawalsan-1 (Curanga Fel-Terrae [Lour.]) Extract Versus Metformin on The Metabolic and Inflammatory Characteristics of Patients with Newly Diagnosed Type 2 Diabetes Mellitus. Asian J Pharm Clin Res. 2016; 9(1):225-8.

24. Henriksen EJ, Diamond-Stanic MK, Marchionne EM. Oxidative Stress and the Etiology of Insulin Resistance and Type 2 Diabetes. Free Radic Biol Med. 2011; 51(5):993-9. https://doi.org/10.1016/j.freeradbiomed.2010.12.005 PMid:21163347 PMCid:PMC3071882

25. Cai S, Sunb W, Fane Y, Guof X, Xuf G, Xug T, et al. Effect of mulberry leaf (Folium Mori) on insulin resistance via IRS-1/PI3K/Glut-4 signalling pathway in type 2 diabetes mellitus rats. Pharm Biol. 2016; 54(11): 2685-91. https://doi.org/10.1080/13880209.2016.1178779 PMid:27158744

26. Jiang S, Ren D, Li J, Yuan G, Li H, Xu G, et al. Effects of compound K on hyperglycemia and insulin resistance in rats with type 2 diabetes mellitus. Fitoterapia. 2014; 95:58-64. https://doi.org/10.1016/j.fitote.2014.02.017 PMid:24613802

27. Eijaz S, Salim A, Waqar MA. Possible Molecular Targets of Cinnamon in the Insulin Signaling Pathway. J Biochem Tech. 2014; 5(2):708-17.

28. Niu W, Huang C, Nawaz Z, Levy M, Somwar R, Li D, et al. Maturation of the Regulation of GLUT4 Activity by p38 MAPK during L6 Cell Myogenesis. J Biol Chem. 2003; 278(20):17953-62. https://doi.org/10.1074/jbc.M211136200 PMid:12637564

29. Gehart H, Kumpf S, Ittner A, Ricci R. MAPK signaling in celluler metabolism: stress or wellness? EMBO reports. 2010; 11(11):834-40. https://doi.org/10.1038/embor.2010.160 PMid:20930846 PMCid:PMC2966959

30. Lawan A, Min K, Zhang L, Canfran-Duque A, Jurczak MJ, Camporez JPG, et al. Skeletal Muscle-Specific Deletion of MKP-1 Reveals a p38 MAPK/JNK/Akt Signaling Node That Regulates Obesity-Induced Insulin Resistance. Diabetes. 2018; 67(4):624-35. https://doi.org/10.2337/db17-0826 PMid:29317435 PMCid:PMC5860856