Journal of Advances in Medical and Biomedical Research | ISSN:2676-6264

Soy Isoflavone Genistein Is a Potential Agent for Metabolic Syndrome Treatment: A Narrative Review

Darya Ghadimi[1*], Mina Hemmati[1], Negar Karimi[1], Tooka Khadive[1]

1. *Dept. of Biochemistry, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran*

Article Info

10.30699/jambs.28.127.64

Received: 2019/12/25;
Accepted: 2020/02/08;
Published Online: 01 Mar 2020;

Use your device to scan and read the article online

Corresponding Information:
Darya Ghadimi,
Dept. of Biochemistry, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
E-Mail: d.ghadimi@zums.ac.ir

ABSTRACT

Metabolic syndrome has a high prevalence (about 22.4% in adult individuals) in developed countries. Inflammation due to obesity and fat accumulation is the most important factor in the progression of metabolic syndrome. In cells which have a receptor for insulin hormone, inflammatory mediators target the insulin signaling pathway and cause insulin resistance. Peroxisome proliferator-activated receptors are a group of ligand inducible transcription factors, whose activation can improve insulin resistance and their agonists such as Genistein, which seems to be useful in prevention of insulin resistance development. Genistein is one of the soy derived isoflavonoids that affects carbohydrate and lipid metabolism resulting in prevention of insulin resistance. The current narrative review has concentrated mainly on highlighting the usefulness of Genistein in the improvement of insulin resistance and therapeutic potential of it in both in-vitro and in-vivo models. Genistein can increase fatty acid β-oxidation, decrease lipogenesis and improve insulin resistance in hepatocytes. In adipocytes, Genistein prevents downregulation of adiponectin expression and facilitates the upregulation of adiponectin expression. In β-islet cells, Genistein initiates the special cascade which leads to proliferation of β cells, resulting in increased secretion of insulin. Based on findings of the studies, it can be concluded that Genistein can be a useful agent in prevention of de novo lipid synthesis as well as proliferation of β cells. In this way the development of metabolic syndrome can be prevented.

Keywords: Genistein, Inflammation, Hyperglycemia, Insulin resistance, Metabolic syndrome, Soy isoflavone

Introduction

Metabolic syndrome is a group of states that take place together**,** increasing the risk of type 2 diabetes mellitus and steatohepatitis. These states consist of high blood glucose and pressure, extra fat around the waist, and dyslipidemia **(1)**. It has a high prevalence in developed countries (about 22.4 % in adult individuals) **(2)**. There is a body of growing evidence suggesting that obesity is the most important factor in the development of metabolic syndrome **(3-5)**.

The pathogenesis of metabolic syndrome is still controversial; 3 pathways are under the spot light including insulin signaling, hepatic lipogenesis and fatty acid β-oxidation **(6-8)**. Because of high calorie diet and a sedentary life style, especially in developed countries, researchers believe that by adding supplements containing agents whose can affect the 3 mentioned pathways, lipid metabolism can be improved. Recent studies demonstrate that fat accumulation leads to inflammation. Inflammatory mediators, in cells which have receptors for insulin hormone, will cause insulin resistance. In this state; muscles, adipose tissue, and liver fail to respond well to insulin and cannot easily take up glucose from blood circulation **(9-11)**. Hepatocytes and adipocytes are two important groups of cells which can develop insulin resistance; which is regarded as the most effective factor in the pathogenesis of hyperglycemia and hepatic steatosis **(12)**. It seems that adipocytes, hepatocytes and pancreatic β-islet cells are vertices of a triangle in the progression of the metabolic disorders which lead to insulin resistance and its consequences **(13-15)**.

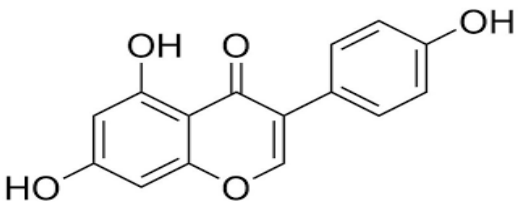
Peroxisome proliferator-activated receptors (PPARs) are a group of ligand inducible transcription factors that play an important role in expression of proteins which are involved in lipid metabolism. Studies indicate that PPARs activation can improve insulin resistance. Based on previous studies, PPARs agonists seem to be useful and effective in prevention of development of insulin resistance **(16-19)**.

Isoflavonoids are a cluster of flavonoid phenolic compounds. They are well known as phytoestrogens because of biological effects through estrogen

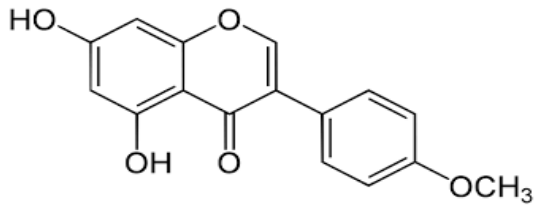
receptors. In addition to estrogenic effects, some other biological effects of isoflavonoids have been identified recently such as activation of PPARs **(16)**.

Genistein is one of the better-known soy derived isoflavonoids that has attracted the attention of scientists because of its beneficial effects on insulin resistance **(20)**. The effects of Genistein in balancing carbohydrate and lipid metabolisms have been proved. Biochanin A and Formononetin are methylated forms of Genistein and demethylation of these compounds usually takes place in the intestine by acetogenic bacteria (Figure 1) **(17,21-23)**.

Although diverse metabolic effects of Genistein have been clearly indicated, this narrative review will mostly focus and highlight the effect of Genistein in insulin resistance development in both in vitro and in vivo models from different studies.



Genistein



Biochanin A

Figure 1. Chemical formula of Genistein and Biochanin A (17).

Abbreviations' list

ACC: Acetyl CoA Carboxylase

AMPK: Adenosine Monophosphate-activated Protein Kinase

ACOX: Acyl-coenzyme A Oxidase

AP-1: Activating Protein 1

AS160: Akt Substrate of 160 kDa

CPT1: Carnitine Palmitoyltransferase I

CRE: CREB Response Element

CREB: cAMP Response Element-binding Protein

Epac1: Exchange factor directly activated by cAMP 1

ERK: Extracellular Signal-regulated kinase

FAS: Fatty Acid Synthase

FOXO1: Forkhead Box O1

G6pase: Glucose 6-phosphatase

Grb2: Growth Factor Receptor-bound protein 2

GSK3: Glycogen Synthase Kinase 3

IRS: Insulin Receptor Substrate

JAK2: Janus Kinase 2

JNK: c-Jun N-terminal Kinase

LXR: Liver X Receptor

MAPK: Mitogen Activated Protein Kinase

MEK: MAPK/ERK Kinase

p-CREB: Phosphorylated cAMP Response Element-binding Protein

PDPK1: Phosphoinositide-dependent Protein Kinase 1

PEPCK: Phosphoenolpyruvate Carboxykinase

PGC1α: PPARγ Coactivator 1 alpha

PI3K: Phosphatidylinositol 3 Kinase

p-IRS: Phosphorylated Insulin Receptor Substrate

PKB: Protein Kinase B

PLC: Phospholipase C

p-LXR: Phosphorylated Liver X Receptor

PPARα: Peroxisome Proliferator-activated Receptor α

PPRE: PPAR Response Element

p70S6k1: p70 S6 Kinase 1

Raf-1: Rapidly Accelerated Fibrosarcoma

Ras: Rat Sarcoma

SCD1: Stearoyl-coA Desaturase

SOS: Son of Sevenless

SREBP-1c: Sterol Regulatory Element-binding Protein 1-c

TNF(α): Tumor Necrosis Factor (α)

UCP2: Uncoupling Protein 2

Metabolic Effects of Genistein on Liver

Liver is the main center of carbohydrate and lipid metabolism in human organism; in other words, the liver regulates the homeostasis of glucose and lipids in blood circulation. After meal and glucose absorption, insulin, is secreted from β-islet cells of the pancreas into blood circulation **(13)**. Insulin binds to its receptor in hepatocytes and autophosphorylation of insulin receptor will occur in tyrosine residues. Insulin receptor is a tyrosine kinase protein, which phosphorylates insulin

receptor substrate1,2 (IRS 1, 2) in tyrosine residues and initiates the insulin signaling cascade. P-IRS binds to PI3k and helps the PI3k to phosphorylate the PIP_2 to PIP_3. Akt (PKB) activates when it binds to PIP_3 and will have been phosphorylated by PDPK1. Activated Akt phosphorylates the serine and threonine residues in GSK3; in this way, inactivates the GSK3. Due to inactivation of GSK3, GS continues the synthesis of glycogen; resulting in glucose gradient from blood to liver **(24-26)**. Additionally, activated Akt phosphorylates the FOXO1 transcription factor. FOXO1 inactivates during phosphorylation and in this way, mRNA expression of enzymes which have important roles in gluconeogenesis such as PEPCK and G6pase, will decrease. Actually, hepatocytes uptake the blood glucose and downregulate the gluconeogenesis pathway for homeostasis of blood glucose **(27)**.

Obesity is the most important risk factor of hyperglycemia. Since the liver is the main center of lipogenesis, in obese persons, lipid accumulation in hepatocytes usually occurs. Peroxidation of fatty acids produces free radicals which lead to oxidative stress. Inflammation initiates in response to oxidative stress and inflammatory mediators accumulate in the liver. Inflammatory mediators activate different kinases; p70S6k1 is one of the important enzymes. p70s6k phosphorylates the IRS in serine residues. If IRS phosphorylates in the serine residues, it will degrade in proteasomes; so, insulin signaling cascade will not initiate and insulin resistance will occur **(24,25)**. Genistein is an AMPK activator and PPARα agonist **(28)**. AMPK is a kinase which activates in response to AMP and phosphorylates the CREB transcription factor. P-CREB binds to CRE in the promoter of *PPARα* gene and increases the mRNA expression of PPARα transcription factor **(29)**. Proteins, which are involved in fatty acid β-oxidation such as CPT1, ACOX and UCP2, have PPRE in promoter region of own genes, therefore the expression of these proteins will increase in response to increased PPARα protein expression (Table 1) **(30-32)**. Furthermore, AMPK phosphorylates and inactivates the LXR nuclear receptor in threonine residues; in this way, AMPK decreases the mRNA expression of SREBP-1c transcription factor. SREBP-1c is a transcription factor which upregulates the mRNA expression of enzymes involved in lipogenesis such as FAS, ACC and SCD1. That is to say, decreased protein expression of SREBP-1c leads to decreased expression of proteins involved in lipogenesis resulting in decreased lipogenesis (Table 1) **(33,34)**. Also, it should be noted that AMPK phosphorylates and inactivates the p70S6K1, the enzyme which secretes from inflammatory mediators and inhibits the initiation of insulin signaling cascade. P70S6K1 is an effective factor in mRNA expression of SREBP-1c. It has been otherwise stated that p70S6K1 phosphorylates the LXR in serine residues and then p-LXR upregulates the SREBP-1c mRNA expression **(34,35)**.

As a result, Genistein can increase fatty acid β-oxidation, reduce lipogenesis and improve insulin resistance in hepatocytes.

Metabolic Effects of Genistein on Adipose Tissue

Another group of cells which have receptors for insulin are adipocytes. Insulin binds to its receptor on adipocytes and PI3K/Akt signaling cascade will initiate. In adipocytes, activated p-Akt inactivates the AS160 protein during phosphorylation in tyrosine residues. Activated AS160, changes the Rab-GTP to Rab-GDP. On the other hand, GLUT4 translocation to the cell membrane is dependent on Rab-GTP. Therefore, by increased number of Rab-GTP due to inactivated AS160, the number of GLUT4 on the cell membrane of adipocytes will increase. Also, it can be said that by increasing the number of GLUT4 on cell membranes, glucose uptake by adipocytes will increase and as a result, the glucose concentration in the blood circulation will decrease **(36,37)**.

As previously mentioned, obesity is the most important risk factor for insulin resistance. Lipid accumulation in adipocytes will cause inflammation and secretion of inflammatory mediators. TNFα is one of the inflammatory mediators which activates the p70S6K1. This enzyme, like in hepatocytes, phosphorylates the IRS in serine residues and in this way inhibits the insulin signaling cascade. The result of insulin signaling inhibition in adipocytes is the decreased number of GLUT4 on cell membrane. By decreasing the number of GLUT4 on adipocytes' membrane, the rate of glucose uptake will decrease and because of this, the glucose concentration in the blood circulation will increase, which means insulin resistance **(34,35)**.

In addition to PI3K/Akt cascade, insulin initiates the other signaling cascade which is called MAPK/Ras signaling cascade. Similar to PI3k/Akt pathway, tyrosine phosphorylation of IRS is the first step of the MAPK/Ras pathway. In the next step, p-IRS interacts with Grb2; the protein which recruits SoS to change the Ras-GDP to Ras-GTP. A complex is made by binding the Ras-GTP to Raf-1 and phosphorylates the MEK protein family. Likewise, p-MEK phosphorylates the MAPK protein family such as ERK1/2/5, p38MAPK and JNK. Finally, p-MAPKs, through phosphorylation of various transcription factors in serine and tyrosine

residues at the nucleus, regulate the expression of various genes. It should be noted that, in addition to insulin, Ras/MAPK pathway activates in response to growth factors, environmental stress and pro-inflammatory mediators **(38,39)**.

TNFα is one of the pro-inflammatory mediators which can phosphorylate and activate JNK through MAPK/Ras pathway. P-JNK, phosphorylates c-jun in cytoplasm and then, c-jun binds to c-fos to make Ap-1 complex. Ap-1 is a transcription factor which translocates to the nucleus and downregulates the expression of adiponectin mRNA in adipocytes so synthesis and secretion of adiponectin will decrease subsequently **(40)**. Adiponectin is a peptide hormone which is secreted from adipocytes into the blood circulation **(41-43)**. Adiponectin binds to its receptors on skeletal muscle cells and hepatocytes; facilitates the insulin signaling cascade through the phosphorylation of PkB in an alternative pathway. As a result, by decreased expression of adiponectin mRNA and decreased concentration of adiponectin in the bloodstream subsequently, insulin sensitivity in skeletal muscle cells and hepatocytes will decrease **(44,45)**. On the other hand, p-JNK phosphorylates the IRS in serine and threonine residues. As stated above, p-IRS in serine and threonine residues cannot initiate the insulin signaling cascade; it consequently will cause insulin resistance **(34)**.

Genistein, in adipocytes, prevents phosphorylation of JNK, in other words the mRNA expression of adiponectin will not inhibite. That is to say, Genistein is an agonist of PPARγ transcription factor which is one the most important transcription factors in upregulating the expression of adiponectin mRNA. As a result, Genistein prevents from downregulation of adiponectin mRNA expression and facilitates the upregulation of adiponectin mRNA expression simultaneously (Table 1) **(46)**.

Metabolic Effects of Genistein on Skeletal Muscle

The other group of cells which have a receptor for insulin are skeletal muscle cells. That is to say, the insulin-receptor complex stimulates the cellular uptake of glucose. Obesity and hyperlipidemia lead to lipid deposition in skeletal muscle cells **(47,48)**. Insulin resistance, as previously mentioned, is the consequence of lipid accumulation. In other words, in insulin resistant state, insulin-dependent glucose uptake is markedly decreased in skeletal muscle cells **(49)**.

Leptin is a peptide hormone dominantly secreted by adipocytes and has receptors on skeletal muscle cells. When leptin binds to its specific receptor, it phosphorylates the JAK. In the next step, p-JAK phosphorylates and activates AMPK. It should be added that AMPK is the key protein in fatty acid β-oxidation signaling pathway **(50-53)**. Activated AMPK (p-AMPK), phosphorylates and inactivates ACC. During the inactivation of ACC, the concentration of Malonyl-CoA will decrease. Malonyl-CoA is regarded as a fatty acid β-oxidation inhibitor agent. As a result, by decreased concentration of Malonyl-CoA, fatty acid β-oxidation will increase. On the other hands; p-AMPK translocates to the nucleus and activates the PPAR-α and PGC1α transcription factors. By the PPARα and PGC1α activation, the mRNA expression of genes involved in fatty acid β-oxidation like CPT-1 and UCP2 will increase **(54-61)**. In conclusion, leptin signaling pathway prevents lipid accumulation in skeletal muscle cells.

The development of obesity and lipid accumulation in skeletal muscle cells result in leptin resistance and lipid deposition in skeletal muscle cells will severely intensify **(62-64)**. In other words, leptin resistance is associated with insulin resistance.

Genistein stimulates fatty acid β-oxidation in skeletal muscle cells in a way independent of leptin receptor. Based on recent studies, Genistein activates the AC in skeletal muscle cells and the concentration of cAMP increase. In the next step, increased cAMP activates Epac1, which in turn activates the PLC **(65-68)**. Activated PLC phosphorylates the JAK2 and as a consequence, the phosphorylation of AMPK occurs. As mentioned previously, activated AMPK stimulates the fatty acid β-oxidation and in this way, prevents lipid accumulation. In conclusion, the cAMP-JAK-AMPK pathway plays an important role in regulating the fatty acid β-oxidation. Through stimulating the mentioned pathway, Genistein can be a beneficial agent in prevention of lipid accumulation in skeletal muscle cells.

Effects of Genistein on Pancreas

After meal and glucose absorption, the increased concentration of blood glucose leads to glucose uptake by pancreatic β cells, which is the main stimulator of insulin secretion. Insulin facilitates the glucose uptake by adipocytes and skeletal myocytes and in this way prevents hyperglycemia. It should be noted that insulin is the most important agent in the pathophysiology of hyperglycemia. In other words, in hyperglycemic patients, there is an insufficient secretion of insulin due to complete or partial destruction of pancreatic β-islet cells. It seems feasible that preventing from destruction

of the pancreatic β-islet cells can be a therapeutic target in hyperglycemic patients **(69)**.

Due to recent studies on β-islet cells, Genistein initiates the Ac/cAMP/pKA/p-ERK1,2 cascade which leads to proliferation of β cells. Also, β-islet cells proliferation is accompanied with increased secretion of insulin (Table 1) **(70-73)**.

Genistein is an estrogen receptor agonist but its effect on β-islet cells proliferation is independent of estrogen receptors. In other words, by blocking the estrogen receptors, the effect of Genistein on β-islet cell proliferation remains **(74)**.

Genistein stimulates the GIIS in an alternative pathway. On the basis of previous studies, Genistein stimulates GIIS through the cAMP/pKA pathway; which leads to increase intracellular ca^{2+}. This pathway is controversial; proteins which are specific in this pathway are still unknown. Blocking the intracellular protein synthesis lead to decreased secretion of insulin (Table 1) **(74,75)**.

Table 1. Summary of researches' results about metabolic effects of Genistein

Animal Model/ Cell Line	Genistein Dose/ Duration	Mechanism Described	Effects	Ref
6 weeks old, Male, Sprage Dawly rats (150– 200g), Fructose induced insulin resistance	0.25 mg/kg/day, SC injection, for 10 weeks SC: subcutaneous	Genistein consumption in fructose induced insulin resistant rats, improved insulin resistance and lipid status markers in addition to its anti-inflammatory and anti-oxidative effects.	1-Significant decrease in plasma: Glucose, LDL-c, VLDL, TAG, ALT, HOMA-IR, insulin, 8-isoprostane, visfatin, IL-6 2-Significant decrease in hepatic: TNFα, IL-6	(74)
10 weeks old, Female, Wistar Albino rats (180–220g), Ovariectomized, HFD+ STZ induced hyperglycemia HFD: High fat Diet STZ: Streptozotocin	1 mg/kg/day, SC injection, for 8 weeks	Genistein protected islet β-cells in HFD + STZ induced hyperglycemic rats through two ways: 1-activation of Akt /ERK 1,2 pathway 2-regulation of some apoptotic agents	1-Significant decrease in plasma: Glucose, LDL-c, TAG, TC 2-Significant increase in β-cells: p-Akt, p-ERK1,2, Bcl-2 3-Significant increase in plasma HDL-c 4-Significant decrease in caspase3	(68)
8 weeks old, Male, Sprage Dawly rats (180– 220 g) , Alloxan induced pancreatic damage	9 , 18 , 30 mg/kg/day , Intragastrical, for 4 weeks	Genistein reduced islet β-cells loss in Alloxan induced hyperglycemic rats in a dosage dependent manner.	1-Significant decrease in plasma Glucose 2-Significant increase in plasma insulin and percent of total cell area per islet	(69)
Islet β-cells of 8 weeks old, Male, Sprage Dawly rats (180– 220g) , Alloxan induced pancreatic damage	6.25, 12.5, 25 µmol/L for 24, 48, 72 hours	Genistein improved the survival and proliferation of islet β-cells which were exposed to Alloxan.	1-Significant increase in insulin concentration level and survival of islet β-cells (percent of fold changes relative to vehicle control)	(69)
9 weeks old, Male, Sprage Dawly rats (180– 220g), which were treated with Genistein in neonatal period, HFD induced NASH NASH: Non-Alcoholic Steatohepatitis	4, 40, 160 mg/kg/day, SC injection, for 5 days	Increased fatty acid β-oxidation and decreased hepatic lipogenesis in rats which were treated with Genistein in neonatal period, prevented from development of NASH.	1-Significant decrease in plasma: TAG, ALT, insulin, T-Cholesterol 2-Significant increase in plasma: Glucagon, TNFα, IL-6 3-Significant decrease in hepatic TAG 4-Significant increase in mRNA and protein expression of PPARα, CPT1 5-Significant decrease in mRNA and protein expression of: FAS, SREBP-1C, TNFα	(28)

Animal Model/ Cell Line	Genistein Dose/ Duration	Mechanism Described	Effects	Ref
6 weeks old, Male, Sprage Dawly rats(180– 220g), HFSD induced steatosis HFSD: High Fat Sugar Diet	4 ,8 mg/kg/day , Intragastrical, for 12 weeks	Genistein consumption improved steatosis in rats which were under the HFSD, through stimulating fatty acid β- oxidation and inhibiting hepatic lipogenesis as well as activation of AMPK pathway.	1-Significant decrease in plasma: TAG, FFA, LDL-c 2-Significant decrease in hepatic: TAG, TC, FFA 3-Significant increase in hepatic: p-AMPK, p-ACC 4-Significant decrease in hepatic SREBP-1c 5-Significant decrease in mRNA expression of hepatic: FAS, GPAT 6-Significant increase in mRNA expression of: ACO, CPT1, PPARα	(31)
6 weeks old, Male, Sprage Dawly rats (180– 220g), HFD induced steatosis	4, 8 mg/kg/day, Intragastrical, for 12 weeks	Genistein consumption in rats which were under the HFD, via suppressing the JNK pathway, prevented from steatohepatitis development.	1-Significant decrease in serum enzymes activity: ALT, AST 2-Significant decrease in inflammation score 3-Significant decrease in serum and hepatic TBARS 4-Significant decrease in serum and hepatic: TNF-α, IL-6 5-Significant decrease in hepatic mRNA expression: IL-6, TNF-α 6-Significant decrease in hepatic p-JNK, NF-κB, p-lκB 7-Significant increase in hepatic lκB	(75)
4 weeks old, Male, Albino mice (25-26g), HFD fed	1 mg/kg/day, Intragastrical, for 45 days	Genistein consumption in HFD fed mice improved hepatic insulin signaling via inhibiting the SKq which is a negative modulator of insulin signaling.	1-Significant decrease in plasma and hepatic: TC, TAG, FFA 2-Significant increase in hepatic: p-Y-IRβ, p-AKt ser, p-Y-IRS 1, 2, p-AMPK Thr ^{172} 3-Significant decrease in p-s6k1Thr^{389}, p-s-IRS1,2 4-Significant decrease in mRNA expression of hepatic lipogenesis involved genes: SREBP-1c, FAS, ACC, SCD1, LXR-α 5-Significant increase in hepatic mRNA expression of fatty acid β-oxidation involved genes: PPARα, ACO, UCP2, CPT1	(33)
3T3-L1 Cells	10, 25, 50 µM , for one hour	Genistein pretreated 3T3-L1 cells could inhibit the TNFα downregulation of adiponectin through inactivation of JNK pathway.	1-Significant increase in adiponectin mRNA and protein expression 2-Significant decrease in p-JNK 3-Significant increase in p-SEK, Foxo1	(44)

Animal Model/ Cell Line	Genistein Dose/ Duration	Mechanism Described	Effects	Ref
Male ICR mice, 6-8 weeks of age, Macrophage-derived conditioned medium induced insulin resistance (inflammatory condition)	10, 25, 50 mg/kg, once, Intragastrical	Genistein consumption, in inflammatory condition, improved insulin sensitivity through activation of IRS/ Akt and AMPK pathways in adipose tissue.	1-Significant decrease in blood Glucose and Insulin resistance 2-Significant decrease in adipocytic p-IκKβ, TNFα, IL-6 3-Significant increase in adipocytic p-IRS(Tyr), p-Akt, GLUT4, p-AMPK 4-Significant decrease in p-IRS (S307)	(76)
9 weeks old, Female, Sprage Dawly rats (180–220g) , Ovariectomized, HFD induced insulin resistance	0.1% supplementation to HFD, for 4 weeks	Genistein consumption in dietary food, decreased the insulin resistance in ovariectomized HFD fed rats. This effect caused partly by decreased rate of hepatic lipogenesis and increased rate of fatty acid β-oxidation in adipocytes.	1-Significant decrease in blood Glucose, Insulin and Insulin resistance 2-Significant decrease in hepatic FAS enzyme activity 3-Significant increase in adipocytic CPT, SDH enzyme activity	(29)
INS1 cells, Treated with 1mM Glucose for 24 hours (pancreatic damage)	0.01, 0.1, 1, 5, 10 μM for 24 hours	Genistein increased β-cells growth and proliferation via upregulating the cyclin D_1 and activating the cAMP/pKA/ERK1,2 pathway.	1-Significant increase in proliferation and growth of β-cells and cyclin D_1 2-Significant increase in p-ERK1/2, intracellular cAMP, pKA activity	(70)
4 weeks old, Male, C57BL/6 mice, STZ induced hyperglycemia	0.25 g/ kg diet for 6 weeks (2 weeks before STZ injection and 4 weeks after STZ injection)	Genistein improved hyperglycemia and insulin resistance via increasing the β-cells proliferation in hyperglycemic mice which were induced by STZ.	1-Significant decrease in blood Glucose 2-Significant increase in β-cells proliferation and plasma insulin	(70)
10-month- old, Male, C57BL/6 mice, HFD + STZ induced hyperglycemia	250 mg/kg diet for 8 weeks	Genistein dietary supplementation improved hyperglycemia through preventing from β-cell apoptosis.	1-Significant decrease in blood Glucose and apoptosis 2-Significant increase in plasma insulin and β-cell mass	(71)
Human pancreatic β-cells, High Glucose induced damage	100 nM for 24 hours	Genistein protected against high Glucose induced cell apoptosis and inhibition of cell proliferation in human pancreatic β-cells via increasing the expression of Bcl-2 through the estrogen receptor.	1-Significant increase in β-cells proliferation 2-Significant decrease in β-cells apoptosis 3-Significant increase in Bcl-2 mRNA and protein expression	(77)
Insulin secreting (INS-1E cells)	1, 5, 10 μM for 48 hours	Genistein potentiated GIIS in INS-1E cells via cAMP/ pKA mediated pathway involving elevation of intracellular Ca^{2+} concentration. GSIS: Glucose Induced Insulin Secretion	1-Significant increase in GSIS and intracellular Ca^{2+}	(73)
INS-1E Cells	0.001, 0.01, 0.1, 1, 2.5, 5, 10, 100 μM for 30 minutes	Genistein activated the AC/cAMP/pKA cascade and potentiated GIIS in pancreatic islet β-cells.	1-Significant increase in: GIIS, cAMP accumulation, AC activity, cAMP dependent pKA activity	(72)

Conclusion

In conclusion, Genistein is a natural cost-effective compound which exerts no toxic biological effects. Dozens of animal-model and cell-culture studies indicate the positive effects of Genistein on improving insulin resistance. Based on findings of recent studies, it is found that Genistein can be a useful agent in prevention from de novo hepatic lipid synthesis and development of steatosis. Lipid deposition in liver is the main cause of metabolic syndrome. On the other hand, in adipocytes, Genistein stimulates adiponectin secretion into blood circulation and in this way facilitates insulin signaling in hepatocytes, adipocytes and skeletal muscle cells. As mentioned, insulin resistance or insulin deficiency is the most effective cause of metabolic syndrome. Genistein stimulates proliferation of β-islet cells; in this way it can compensate for insulin deficiency. In skeletal muscle cells, Genistein prevents fat deposition which is the main cause of inflammation and destruction of insulin signaling cascade. Metabolic syndrome is a very complex disorder and requires therapeutic agents with numerous ways of action that can regulate etiological pathways. In recent studies, researchers have strongly recommended Genistein as a pluripotent agent in modulating insulin resistance and hyperglycemia. Genistein reduces inflammation and production of reactive oxygen species in obese individuals. However, further studies require to prove the exact therapeutic potential in order to determine the most effective dose of Genistein consumption.

Acknowledgments

The authors would like to show their gratitude to Biochemistry Department and Zanjan University of Medical Sciences for their support; and to thank the reviewers for their so-called insights.

Conflict of Interest

Authors declared no conflict of interest.

References

1. Samson SL, Garber AJ. Metabolic syndrome. Endocrinol Metab Clin North Am. 2014;43(1):1-23. [DOI:10.1016/j.ecl.2013.09.009]
2. Ansarimoghaddam A, Adineh HA, Zareban I, Iranpour S, HosseinZadeh A, Kh F. Prevalence of metabolic syndrome in Middle-East countries: Meta-analysis of cross-sectional studies. Diabetes Metab Syndr. 2018;12(2):195-201. [DOI:10.1016/j.dsx.2017.11.004]
3. Sherling DH, Perumareddi P, Hennekens CH. Metabolic Syndrome. J Cardiovasc Pharmacol Ther. 2017;22(4):365-7. [DOI:10.1177/1074248416686187]
4. Ghahremanloo A, Hajipour R, Hemmati M, Moossavi M, Mohaqiq Z. The beneficial effects of pumpkin extract on atherogenic lipid, insulin resistance and oxidative stress status in high-fat diet-induced obese rats. Journal of complementary & integrative medicine. 2017;15(2). [DOI:10.1515/jcim-2017-0051]
5. Hoshyar R, Hosseinian M, Rajabian Naghandar M, Hemmati M, Zarban A, Amini Z, et al. Anti-Dyslipidemic Properties of Saffron: Reduction in the Associated Risks of Atherosclerosis and Insulin Resistance. Iranian Red Crescent Medical Journal. 2016;18(12):22. [DOI:10.5812/ircmj.36226]
6. Kim MJ, Lim Y. Protective effect of short-term genistein supplementation on the early stage in diabetes-induced renal damage. Mediators Inflamm. 2013;2013:510212. [DOI:10.1155/2013/510212]
7. Motamedrad M, Shokouhifar A, Hemmati M, Moossavi M. The regulatory effect of saffron stigma on the gene expression of the glucose metabolism key enzymes and stress proteins in streptozotocin-induced diabetic rats. Research in pharmaceutical sciences. 2019;14(3):255-62. [DOI:10.4103/1735-5362.258494]
8. Mahboob Z, Hemmati M, Khorashadizadeh M, M G. Additive Effects of Resveratrol and Resveratrol/Quercetin in Prevention of Hyperglycemia-Mediated Cell Death through Downregulation of NADPH Oxidase and RAGE Expression. JOP J Pancreas. 2017;18(1):7.
9. Brown AE, Walker M. Genetics of Insulin Resistance and the Metabolic Syndrome. Curr Cardiol Rep. 2016;18(8):75. [DOI:10.1007/s11886-016-0755-4]
10. Sankar P, Zachariah B, Vickneshwaran V, Jacob SE, Sridhar MG. Amelioration of oxidative stress and insulin resistance by soy isoflavones (from Glycine max) in ovariectomized Wistar rats fed with high fat diet: the molecular mechanisms. Exp Gerontol. 2015;63:67-75. [DOI:10.1016/j.exger.2015.02.001]
11. Gilbert ER, Liu D. Anti-diabetic functions of soy isoflavone genistein: mechanisms underlying its effects on pancreatic beta-cell function. Food Funct. 2013;4(2):200-12. [DOI:10.1039/C2FO30199G]
12. Johar D, Maher A, Aboelmagd O, Hammad A, Morsi M, Warda HF, et al. Whole-food phytochemicals antioxidative potential in alloxan-

diabetic rats. Toxicol Rep. 2018;5:240-50. [DOI:10.1016/j.toxrep.2018.01.002]

13. Abharzanjani F, Afshar M, Hemmati M, Moossavi M. Short-term High Dose of Quercetin and Resveratrol Alters Aging Markers in Human Kidney Cells. International journal of preventive medicine. 2017;8:64. [DOI:10.4103/ijpvm.IJPVM_139_17]
14. Thangavel N, Al Bratty M, Javed SA, Ahsan W, Alhazmi HA. Critical Insight into the Design of PPAR-gamma Agonists by Virtual Screening Techniques. Curr Drug Discov Technol. 2019;16(1):82-90. [DOI:10.2174/1570163815666180227164028]
15. Wang L, Waltenberger B, Pferschy-Wenzig EM, Blunder M, Liu X, Malainer C, et al. Natural product agonists of peroxisome proliferator-activated receptor gamma (PPARgamma): a review. Biochem Pharmacol. 2014;92(1):73-89. [DOI:10.1016/j.bcp.2014.07.018]
16. Guo L, Tabrizchi R. Peroxisome proliferator-activated receptor gamma as a drug target in the pathogenesis of insulin resistance. Pharmacol Ther. 2006;111(1):145-73. [DOI:10.1016/j.pharmthera.2005.10.009]
17. Shen P, Liu M, Ng T, Chan Y, Yong E. Differential effects of isoflavones, from Astragalus membranaceus and Pueraria thomsonii, on the activation of PPARα, PPARγ, and adipocyte differentiation in vitro. The Journal of nutrition. 2006;136(4):899-905. [DOI:10.1093/jn/136.4.899]
18. Choi JS, Song J. Effect of genistein on insulin resistance, renal lipid metabolism, and antioxidative activities in ovariectomized rats. Nutrition. 2009;25(6):676-85. [DOI:10.1016/j.nut.2008.11.027]
19. Behloul N, Wu G. Genistein: a promising therapeutic agent for obesity and diabetes treatment. Eur J Pharmacol. 2013;698(1-3):31-8. [DOI:10.1016/j.ejphar.2012.11.013]
20. Sureda A, Sanches Silva A, Sanchez-Machado DI, Lopez-Cervantes J, Daglia M, Nabavi SF, et al. Hypotensive effects of genistein: From chemistry to medicine. Chem Biol Interact. 2017;268:37-46. [DOI:10.1016/j.cbi.2017.02.012]
21. Huang G, Xu J, Lefever DE, Glenn TC, Nagy T, Guo TL. Genistein prevention of hyperglycemia and improvement of glucose tolerance in adult non-obese diabetic mice are associated with alterations of gut microbiome and immune homeostasis. Toxicol Appl Pharmacol. 2017;332:138-48. [DOI:10.1016/j.taap.2017.04.009]
22. Ghadimi D, Goodarzi M T , Ziamajidi N , Moradkhani S. The influence of biochanin a consumption on c-CBL-associated protein level in adipose tissue of streptozotocine-nicotinamide induced diabetic rats. International Journal of medical research and health sciences. 2016;5(7):195-201.
23. Khorami SAH, Movahedi A, Sokhini AMM. Review Article; PI3K/AKT pathway in modulating glucose homeostasis and its alteration in Diabetes. Annals of Medical and Biomedical Sciences. 2015;1(2).
24. Petersen MC, Shulman GI. Mechanisms of Insulin Action and Insulin Resistance. Physiol Rev. 2018;98(4):2133-223. [DOI:10.1152/physrev.00063.2017]
25. Leclercq IA, Da Silva Morais A, Schroyen B, Van Hul N, Geerts A. Insulin resistance in hepatocytes and sinusoidal liver cells: mechanisms and consequences. J Hepatol. 2007;47(1):142-56. [DOI:10.1016/j.jhep.2007.04.002]
26. Kim J, Yang G, Kim Y, Kim J, Ha J. AMPK activators: mechanisms of action and physiological activities. Exp Mol Med. 2016;48:e224. [DOI:10.1038/emm.2016.16]
27. Thomson DM, Herway ST, Fillmore N, Kim H, Brown JD, Barrow JR, et al. AMP-activated protein kinase phosphorylates transcription factors of the CREB family. J Appl Physiol (1985). 2008;104(2):429-38. [DOI:10.1152/japplphysiol.00900.2007]
28. Huang C, Qiao X, Dong B. Neonatal exposure to genistein ameliorates high-fat diet-induced non-alcoholic steatohepatitis in rats. Br J Nutr. 2011;106(1):105-13. [DOI:10.1017/S0007114510005799]
29. Choi JS, Koh IU, Song J. Genistein reduced insulin resistance index through modulating lipid metabolism in ovariectomized rats. Nutr Res. 2012;32(11):844-55. [DOI:10.1016/j.nutres.2012.10.002]
30. Ghadimi D, Goodarzi MT, Bahmani M, Khajehahmadi Z. The Effect of Biochanin A as PPAR γ agonist on LDL Particles Diameter and Type 2 Diabetic Dyslipidemia. International Journal of Medical Laboratory. 2019. [DOI:10.18502/ijml.v6i2.1028]
31. Liu H, Zhong H, Yin Y, Jiang Z. Genistein has beneficial effects on hepatic steatosis in high fat-high sucrose diet-treated rats. Biomed Pharmacother. 2017;91:964-9. [DOI:10.1016/j.biopha.2017.04.130]
32. Hwahng SH, Ki SH, Bae EJ, Kim HE, Kim SG. Role of adenosine monophosphate-activated protein kinase-p70 ribosomal S6 kinase-1 pathway in repression of liver X receptor-alpha-dependent lipogenic gene induction and hepatic steatosis by a novel class of dithiolethiones. Hepatology. 2009;49(6):1913-25. [DOI:10.1002/hep.22887]

33. Arunkumar E, Karthik D, Anuradha CV. Genistein sensitizes hepatic insulin signaling and modulates lipid regulatory genes through p70 ribosomal S6 kinase-1 inhibition in high-fat-high-fructose diet-fed mice. Pharm Biol. 2013;51(7):815-24. [DOI:10.3109/13880209.2013.766896]

34. Miinea CP, Sano H, Kane S, Sano E, Fukuda M, Peranen J, et al. AS160, the Akt substrate regulating GLUT4 translocation, has a functional Rab GTPase-activating protein domain. Biochem J. 2005;391(Pt 1):87-93. [DOI:10.1042/BJ20050887]

35. Peck GR, Chavez JA, Roach WG, Budnik BA, Lane WS, Karlsson HK, et al. Insulin-stimulated phosphorylation of the Rab GTPase-activating protein TBC1D1 regulates GLUT4 translocation. The Journal of biological chemistry. 2009;284(44):30016-23. [DOI:10.1074/jbc.M109.035568]

36. Gutierrez-Rodelo C, Roura-Guiberna A, Olivares-Reyes JA. [Molecular Mechanisms of Insulin Resistance: An Update]. Gac Med Mex. 2017;153(2):214-28.

37. Whitmarsh AJ. Regulation of gene transcription by mitogen-activated protein kinase signaling pathways. Biochimica et biophysica acta. 2007;1773(8):1285-98. [DOI:10.1016/j.bbamcr.2006.11.011]

38. Chang E, Choi JM, Kim WJ, Rhee EJ, Oh KW, Lee WY, et al. Restoration of adiponectin expression via the ERK pathway in TNFalpha-treated 3T3-L1 adipocytes. Mol Med Rep. 2014;10(2):905-10. [DOI:10.3892/mmr.2014.2278]

39. Esmaeili S, Motamedrad M, Hemmati M, Mehrpour O, Khorashadizadeh M. Prevention of kidney cell damage in hyperglycaemia condition by adiponectin. Cell biochemistry and function. 2019;37(3):148-52. [DOI:10.1002/cbf.3380]

40. Esmaili S, Hemmati M, Karamian M. Physiological role of adiponectin in different tissues: a review. Archives of physiology and biochemistry. 2018:1-7. [DOI:10.1080/13813455.2018.1493606]

41. Hemmati M, Asghari S, E Z. Effects of Alcoholic and Aqueous Extract of Barberry, Jujube and Saffron Petals on Serum Level of Adiponectin and Lipid Profile in Diabetic Rats. Iranian Journal of Endocrinology and Metabolism. 2015;16(5):9.

42. Fang H, Judd RL. Adiponectin Regulation and Function. Compr Physiol. 2018;8(3):1031-63. [DOI:10.1002/cphy.c170046]

43. Ghadimi D, Goodarzi MT, Ziamajidi N, Moradkhani S. The effect of Biochanin A on the expression of Adiponectin in adipose tissue of Streptozotocin-Nicotinamide induced diabetic rats. International Journal of medical research and health sciences. 2016;5(7):223-30.

44. Yanagisawa M, Sugiya M, Iijima H, Nakagome I, Hirono S, Tsuda T. Genistein and daidzein, typical soy isoflavones, inhibit TNF-alpha-mediated downregulation of adiponectin expression via different mechanisms in 3T3-L1 adipocytes. Mol Nutr Food Res. 2012;56(12):1783-93. [DOI:10.1002/mnfr.201200284]

45. Muoio DM, Newgard CB. Obesity-related derangements in metabolic regulation. Annual review of biochemistry. 2006;75:367-401. [DOI:10.1146/annurev.biochem.75.103004.142512]

46. Unger RH, Orci L. Diseases of liporegulation: new perspective on obesity and related disorders. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2001;15(2):312-21. [DOI:10.1096/fj.00-0590]

47. Reaven GM. The insulin resistance syndrome: definition and dietary approaches to treatment. Annual review of nutrition. 2005;25:391-406. [DOI:10.1146/annurev.nutr.24.012003.132155]

48. Kim SJ, Tang T, Abbott M, Viscarra JA, Wang Y, Sul HS. AMPK Phosphorylates Desnutrin/ATGL and Hormone-Sensitive Lipase To Regulate Lipolysis and Fatty Acid Oxidation within Adipose Tissue. Molecular and cellular biology. 2016;36(14):1961-76. [DOI:10.1128/MCB.00244-16]

49. Carling D. AMPK signalling in health and disease. Current opinion in cell biology. 2017;45:31-7. [DOI:10.1016/j.ceb.2017.01.005]

50. Tabe Y, Yamamoto S, Saitoh K, Sekihara K, Monma N, Ikeo K, et al. Bone Marrow Adipocytes Facilitate Fatty Acid Oxidation Activating AMPK and a Transcriptional Network Supporting Survival of Acute Monocytic Leukemia Cells. Cancer research. 2017;77(6):1453-64. [DOI:10.1158/0008-5472.CAN-16-1645]

51. Boufroura FZ, Le Bachelier C, Tomkiewicz-Raulet C, Schlemmer D, Benoist JF, Grondin P, et al. A new AMPK activator, GSK773, corrects fatty acid oxidation and differentiation defect in CPT2-deficient myotubes. Human molecular genetics. 2018;27(19):3417-33. [DOI:10.1093/hmg/ddy254]

52. St-Pierre J, Tremblay ML. Modulation of leptin resistance by protein tyrosine phosphatases. Cell metabolism. 2012;15(3):292-7. [DOI:10.1016/j.cmet.2012.02.004]

53. Uotani S, Abe T, Yamaguchi Y. Leptin activates AMP-activated protein kinase in hepatic cells via a JAK2-dependent pathway. Biochemical and biophysical research communications.

2006;351(1):171-5. [DOI:10.1016/j.bbrc.2006.10.015]

54. Janovska A, Hatzinikolas G, Staikopoulos V, McInerney J, Mano M, Wittert GA. AMPK and ACC phosphorylation: effect of leptin, muscle fibre type and obesity. Molecular and cellular endocrinology. 2008;284(1-2):1-10. [DOI:10.1016/j.mce.2007.12.013]

55. Minokoshi Y, Kim YB, Peroni OD, Fryer LG, Muller C, Carling D, et al. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. Nature. 2002;415(6869):339-43. [DOI:10.1038/415339a]

56. Lee WJ, Kim M, Park HS, Kim HS, Jeon MJ, Oh KS, et al. AMPK activation increases fatty acid oxidation in skeletal muscle by activating PPARalpha and PGC-1. Biochemical and biophysical research communications. 2006;340(1):291-5. [DOI:10.1016/j.bbrc.2005.12.011]

57. Suzuki A, Okamoto S, Lee S, Saito K, Shiuchi T, Minokoshi Y. Leptin stimulates fatty acid oxidation and peroxisome proliferator-activated receptor alpha gene expression in mouse C2C12 myoblasts by changing the subcellular localization of the alpha2 form of AMP-activated protein kinase. Molecular and cellular biology. 2007;27(12):4317-27. [DOI:10.1128/MCB.02222-06]

58. Vega RB, Huss JM, Kelly DP. The coactivator PGC-1 cooperates with peroxisome proliferator-activated receptor alpha in transcriptional control of nuclear genes encoding mitochondrial fatty acid oxidation enzymes. Molecular and cellular biology. 2000;20(5):1868-76. [DOI:10.1128/MCB.20.5.1868-1876.2000]

59. Mezei O, Banz WJ, Steger RW, Peluso MR, Winters TA, Shay N. Soy isoflavones exert antidiabetic and hypolipidemic effects through the PPAR pathways in obese Zucker rats and murine RAW 264.7 cells. The Journal of nutrition. 2003;133(5):1238-43. [DOI:10.1093/jn/133.5.1238]

60. Martin TL, Alquier T, Asakura K, Furukawa N, Preitner F, Kahn BB. Diet-induced obesity alters AMP kinase activity in hypothalamus and skeletal muscle. The Journal of biological chemistry. 2006;281(28):18933-41. [DOI:10.1074/jbc.M512831200]

61. Steinberg GR, Parolin ML, Heigenhauser GJ, Dyck DJ. Leptin increases FA oxidation in lean but not obese human skeletal muscle: evidence of peripheral leptin resistance. American journal of physiology Endocrinology and metabolism. 2002;283(1):E187-92. [DOI:10.1152/ajpendo.00542.2001]

62. Yu X, McCorkle S, Wang M, Lee Y, Li J, Saha AK, et al. Leptinomimetic effects of the AMP kinase activator AICAR in leptin-resistant rats: prevention of diabetes and ectopic lipid deposition. Diabetologia. 2004;47(11):2012-21. [DOI:10.1007/s00125-004-1570-9]

63. Irrcher I, Ljubicic V, Kirwan AF, Hood DA. AMP-activated protein kinase-regulated activation of the PGC-1alpha promoter in skeletal muscle cells. PloS one. 2008;3(10):e3614. [DOI:10.1371/journal.pone.0003614]

64. Palacios-Gonzalez B, Zarain-Herzberg A, Flores-Galicia I, Noriega LG, Aleman-Escondrillas G, Zarinan T, et al. Genistein stimulates fatty acid oxidation in a leptin receptor-independent manner through the JAK2-mediated phosphorylation and activation of AMPK in skeletal muscle. Biochimica et biophysica acta. 2014;1841(1):132-40. [DOI:10.1016/j.bbalip.2013.08.018]

65. van Bree BW, Lenaers E, Nabben M, Briede JJ, Jorgensen JA, Schaart G, et al. A genistein-enriched diet neither improves skeletal muscle oxidative capacity nor prevents the transition towards advanced insulin resistance in ZDF rats. Scientific reports. 2016;6:22854. [DOI:10.1038/srep22854]

66. Palacios-Gonzalez B, Vargas-Castillo A, Velazquez-Villegas LA, Vasquez-Reyes S, Lopez P, Noriega LG, et al. Genistein increases the thermogenic program of subcutaneous WAT and increases energy expenditure in mice. The Journal of nutritional biochemistry. 2019;68:59-68. [DOI:10.1016/j.jnutbio.2019.03.012]

67. Moore WT, Bowser SM, Fausnacht DW, Staley LL, Suh KS, Liu D. Beta Cell Function and the Nutritional State: Dietary Factors that Influence Insulin Secretion. Curr Diab Rep. 2015;15(10):76. [DOI:10.1007/s11892-015-0650-1]

68. Yousefi H, Karimi P, Alihemmati A, Alipour MR, Habibi P, Ahmadiasl N. Therapeutic potential of genistein in ovariectomy-induced pancreatic injury in diabetic rats: The regulation of MAPK pathway and apoptosis. Iran J Basic Med Sci. 2017;20(9):1009-15.

69. Yang W, Wang S, Li L, Liang Z, Wang L. Genistein reduces hyperglycemia and islet cell loss in a high-dosage manner in rats with alloxan-induced pancreatic damage. Pancreas. 2011;40(3):396-402. [DOI:10.1097/MPA.0b013e318204e74d]

70. Fu Z, Zhang W, Zhen W, Lum H, Nadler J, Bassaganya-Riera J, et al. Genistein induces pancreatic beta-cell proliferation through activation of multiple signaling pathways and prevents insulin-deficient diabetes in mice. Endocrinology. 2010;151(7):3026-37. [DOI:10.1210/en.2009-1294]

71. Fu Z, Gilbert ER, Pfeiffer L, Zhang Y, Fu Y, Liu D. Genistein ameliorates hyperglycemia in a mouse model of nongenetic type 2 diabetes. Appl Physiol Nutr Metab. 2012;37(3):480-8. [DOI:10.1139/h2012-005]

72. Liu D, Zhen W, Yang Z, Carter JD, Si H, Reynolds KA. Genistein acutely stimulates insulin secretion in pancreatic beta-cells through a cAMP-dependent protein kinase pathway. Diabetes. 2006;55(4):1043-50. [DOI:10.2337/diabetes.55.04.06.db05-1089]

73. Fu Z, Liu D. Long-term exposure to genistein improves insulin secretory function of pancreatic beta-cells. Eur J Pharmacol. 2009;616(1-3):321-7. [DOI:10.1016/j.ejphar.2009.06.005]

74. Incir S, Bolayirli IM, Inan O, Aydin MS, Bilgin IA, Sayan I, et al. The effects of genistein supplementation on fructose induced insulin resistance, oxidative stress and inflammation. Life Sci. 2016;158:57-62. [DOI:10.1016/j.lfs.2016.06.014]

75. Ji G, Yang Q, Hao J, Guo L, Chen X, Hu J, et al. Anti-inflammatory effect of genistein on non-alcoholic steatohepatitis rats induced by high fat diet and its potential mechanisms. Int Immunopharmacol. 2011;11(6):762-8. [DOI:10.1016/j.intimp.2011.01.036]

76. Wang M, Gao XJ, Zhao WW, Zhao WJ, Jiang CH, Huang F, et al. Opposite effects of genistein on the regulation of insulin-mediated glucose homeostasis in adipose tissue. Br J Pharmacol. 2013;170(2):328-40. [DOI:10.1111/bph.12276]

77. Zhong WW, Liu Y, Li CL. Mechanisms of genistein protection on pancreas cell damage in high glucose condition. Intern Med. 2011;50(19):2129-34. [DOI:10.2169/internalmedicine.50.5320]

How to Cite This Article:

Ghadimi D, Hemmati M, Karimi N, Khadive T. Soy Isoflavone Genistein Is a Potential Agent for Metabolic Syndrome Treatment: A Narrative Review. J Adv Med Biomed Res. 2020; 28 (127:64-75

Download citation:
BibTeX | RIS | EndNote | Medlars | ProCite | Reference Manager | RefWorks

Send citation to:
Mendeley Zotero RefWorks