

Roles of Ferulic acid on muscle atrophy and grip strength in diabetic mice

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Abstract: Diabetes is an inducement of muscle atrophy to cause motor disturbance. Ferulic Acid (FA) possessed various pharmacological effects in diabetes and muscle function. This research aimed to appraise potential role of FA on muscle atrophy in high glucose environment. Our result displayed FA promoted myofiber size and grip strength to reduce high glucose-mediated muscle function discords. In serum, FA exhibited its anti-oxidative and anti-inflammatory capabilities via enhancing T-AOC, SOD and CAT levels and reducing MDA, TNF- α and IL-6 levels. In skeletal muscle, FA suppressed FBXO-32 and MURF-1 expressions to improve ubiquitin-proteasome system. Moreover, GA restrained DDIT-3 and GRP-78 expressions to relieve high glucose-mediated endoplasmic reticulum stress. Lastly, GA increased BAX expressions and decreased BCL-2 expressions to attenuate high glucose-mediated apoptosis. In conclusion, FA preserve against muscle atrophy by meliorating ubiquitin-proteasome system, endoplasmic reticulum stress and apoptosis in high glucose environment.

Keywords: Diabetes, ferulic acid, muscle atrophy, grip strength.

INTRODUCTION

Diabetes mellitus has become a fastest growing health problem and its prevalence in adult population was over 10.5% in 2021. Diabetes is harm for life expectancy in human (Heald *et al.* 2020). The expenditure on diabetes-associated health is about 783 million in 2045 (Sun *et al.* 2022). Diabetes is closely related to many complications, such as cardiomyopathy, nephropathy and myopathy (Bassi-Dibai *et al.* 2022, Murtaza *et al.* 2019, Refardt *et al.* 2020). Skeletal muscle is a locomotive organ and metabolic organ, which can utilize and uptake glucose in our body. The main characteristic of diabetes is hyperglycemia. Hyperglycemia is a cause of skeletal muscle injury and has vital influence on skeletal muscle atrophy (Richter-Stretton *et al.* 2022). Skeletal muscle atrophy easily results in dyskinesia and metabolic disorders, which is strongly linked with disabling and life threatening diseases. Hence, treatment of diabetic muscle atrophy has become a research focus.

The pathogenesis of muscle atrophy is multifarious. Hyperglycemia causes injury to multiple organs, especially muscle. Clinically, hyperglycemia results in weakness and wasting in skeletal muscle (Perry *et al.* 2016). Hyperglycemia can also induce fibrosis and affect cells differentiation in skeletal muscle (Khromova *et al.* 2021). In diabetes, skeletal muscle is a common target organ attacked by hyperglycemia, which cause different types of cell damage. The mechanism of muscle loss associated with diabetes is complex. Endoplasmic reticulum stress is triggered by hyperglycemia to aggravate muscle atrophy (Afroze and Kumar 2019, Mustapha *et al.*, 2021). Ubiquitin-

proteasome system is abnormal to induce protein degradation and proteolysis during the development of skeletal muscle atrophy (Singh *et al.* 2021). In addition, hyperglycemia-induced endoplasmic reticulum stress is linked to cell death.

Ferulic Acid (FA) is a phenolic compound and has protective effects on management of diabetic complication (Li *et al.* 2022). In pancreatic tissues, FA prevented STZ-mediated β -cells damage to exert a hypoglycemic effect (Roy *et al.* 2013). In liver, FA was proved to regulate glycogenesis to ameliorate glucose homeostasis (Son *et al.* 2011). Moreover, FA could improve lipid metabolism characterized by reducing free fatty acid in STZ-mediated diabetic animal (Ohnishi *et al.* 2004, Sri *et al.* 2003). In skeletal muscle, FA also possesses several pharmacological effects. In weaned piglets, FA was proved to convert muscle fiber type to enhance the quality of pork (Wang *et al.* 2021). In zebrafish, FA accelerated muscle growth by promoting protein synthesis capacity (Wen and Ushio 2017). In C2C12, FA was involved in fiber type formation (Chen *et al.* 2019). However, the defensive function of FA on hyperglycemia-related skeletal muscle atrophy was not clarified.

MATERIALS AND METHODS

Experimental design

C57BL/6 mice were obtained from Hunan SJA Laboratory animal (Changsha, China). The age of mice were about 8 weeks. Mice were kept at SPF conditions. Ferulic Acid was obtained from Sangon Biotech. Diabetic mice were established by streptozotocin (STZ). Then, blood was gained from tail to evaluate hyperglycemia. Diabetic mice were administration of FA (50 mg/kg/day)

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for 8 weeks. Experimental animal included three different groups: control (CON), mice intervened by streptozotocin (STZ) and diabetes treated by Ferulic Acid (STZ + FA).

Grip strength

The grip strength meter was purchased from Anhui Zhenghua Bioinstrumentation (Huaibei, China). Mice were allowed to grasped and pull backward plate. Grip strength was obtained by 3 repeated detections.

Gastrocnemius harvest

Experimental animal was executed via pentobarbital sodium. Gastrocnemius were weighed. Parts of gastrocnemius was stored at -80°C for western blotting. Other gastrocnemius was placed in 4% paraformaldehyde for histological analysis.

Biochemical determination

The blood was centrifuged and utilized to test biological indicators. T-AOC, SOD, CAT and MDA contents were analyzed by spectrophotometer. TNF- α and IL-6 concentrations were measured by ELISA. Biochemical indices were determined with corresponding commercial kits, which were reported previously (Liu *et al.* 2021, Xia 2010).

Histological analysis

Gastrocnemius histopathology was observed by Haematoxylin and Eosin (HE) test. Gastrocnemius was treated with different concentrations of alcohol and xylems. The image was magnified up to 200 times to analyze gastrocnemius histopathology.

Western blotting

Gastrocnemius was ground with RIPA for protein extraction. The homogenate was centrifuged to collect supernatant. The protein contents were measured by BCA method. The proteins were separated by SDS-PAGE. The antibodies were reported previously (Liu *et al.* 2021). Protein signal was visualization by ECL system. The expression was analyzed after standardizing band intensity quantification.

Ethical approval

The experiments were approved by the Ethics Committee of the Hunan University of Arts and Science (No. HUAS-2021-TY-231).

STATISTICAL ANALYSIS

The results were analyzed by SPSS 16.0. Statistical difference was demonstrated by one-way ANOVA test. $p < 0.05$ was deemed statistically significant.

RESULTS

Roles of FA on skeletal muscle atrophy

In fig. 1A-B, hyperglycemia markedly decreased muscle fiber size ($p < 0.01$), while FA remarkably augmented

myocyte cross-sectional area via Haematoxylin and Eosin test ($p < 0.01$). In fig. 1C, hyperglycemia markedly reduced grip strength, while FA remarkably increased muscle function ($p < 0.01$).

Roles of FA on oxidation damage

In fig. 2, hyperglycemia markedly reduced T-AOC, SOD and CAT contents ($p < 0.01$), while MDA content was markedly enhanced in serum of STZ group ($p < 0.01$). However, FA remarkably alleviated oxidative damage by reversing these adverse changes ($p < 0.01$).

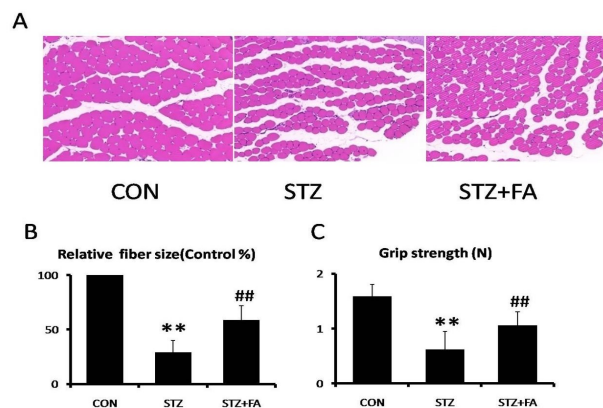


Fig. 1: Roles of FA on (A, B) muscle fiber size and (C) grip strength. ** $p < 0.01$ vs CON. ## $p < 0.01$ vs STZ.

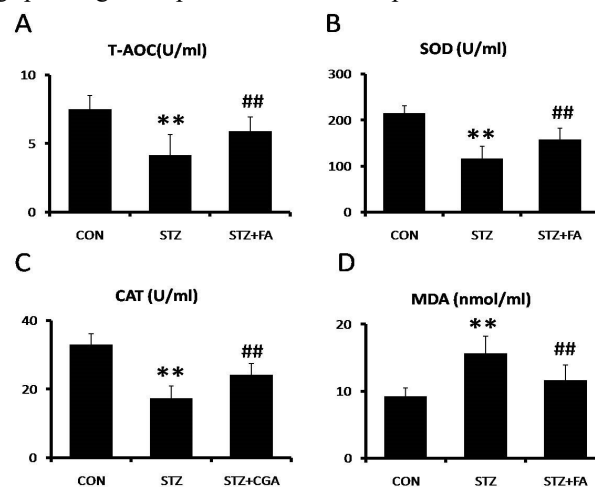


Fig 2: Roles of FA on (A) T-AOC, (B) SOD, (C) CAT and (D) MDA in serum. ** $p < 0.01$ vs CON. ## $p < 0.01$ vs STZ.

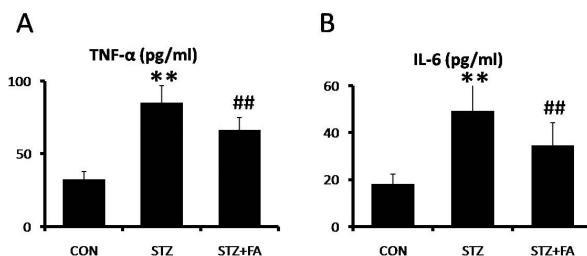


Fig. 3: Roles of FA on (A) TNF-a and (B) IL-6 in serum. ** $p < 0.01$ vs CON. ## $p < 0.01$ vs STZ.

Roles of FA on inflammatory response

In fig. 3, hyperglycemia markedly elevated TNF- α and IL-6 concentrations in serum ($p < 0.01$). However, FA remarkably showed its anti-inflammatory function by alleviating diabetic-evoked increase of inflammatory cytokine ($p < 0.01$).

Roles of FA on ubiquitin-proteasome system

In fig. 4, hyperglycemia markedly strengthened FBXO-32 and MURF-1 expressions in skeletal muscle ($p < 0.01$). However, FA remarkably suppressed FBXO-32 and MURF-1 expressions to improve ubiquitin-proteasome system ($p < 0.01$).

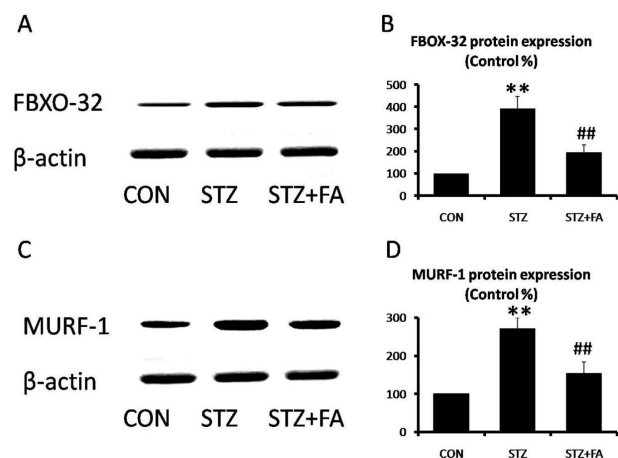


Fig. 4: Roles of FA on (A, B) FBXO-32 and (C, D) MURF-1 in skeletal muscle. ** $p < 0.01$ vs CON. ## $p < 0.01$ vs STZ.

Roles of FA on endoplasmic reticulum stress

In fig. 5, hyperglycemia markedly heightened DDIT-3 and GRP-78 expressions in skeletal muscle ($p < 0.01$). However, GA remarkably restrained DDIT-3 and GRP-78 expressions to relieve high glucose-mediated endoplasmic reticulum stress ($p < 0.01$).

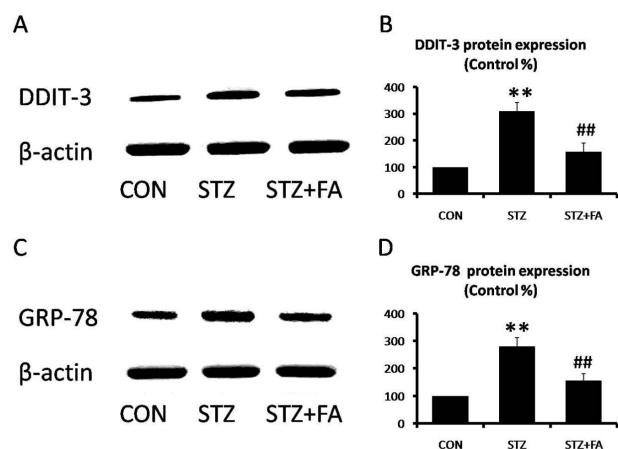


Fig. 5: Roles of FA on (A, B) DDIT-3 and (C, D) GRP-78 in skeletal muscle. ** $p < 0.01$ vs CON. ## $p < 0.01$ vs STZ.

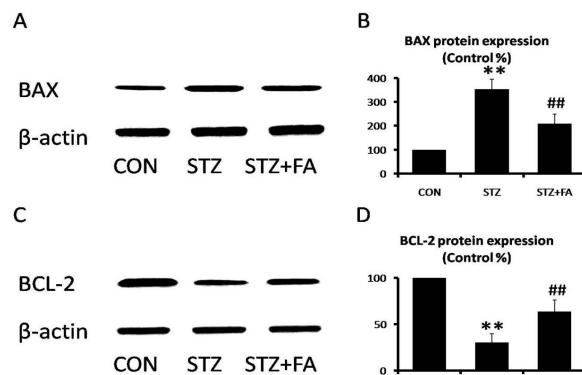


Fig. 6: Roles of FA on (A, B) Bax and (C, D) BCL-2 expressions in skeletal muscle. ** $p < 0.01$ vs CON. ## $p < 0.01$ vs STZ.

Roles of FA on apoptosis pathway

In fig. 6, hyperglycemia markedly increased Bax expression ($p < 0.01$), while BCL-2 expression was markedly reduced in skeletal muscle of STZ group ($p < 0.01$). However, FA remarkably increased BAX expressions and decreased BCL-2 expressions to attenuate high glucose-mediated apoptosis ($p < 0.01$).

DISCUSSION

FA possesses multiple biological effects both on muscle and diabetes. In zebrafish, FA regulated muscle development as represented by decreasing fat deposition (Yin *et al.* 2022). In insulin resistance, FA might enhance glycogen synthesis to modulate glucose metabolism of skeletal muscle (Kang and Chiang 2020). Moreover, diabetic muscle atrophy impair fiber size and grip strength in skeletal muscle. We proposed that FA maintained structure and function of muscle in diabetes. In this study, FA relieved pathological damage of skeletal muscle tissues in STZ-mediated diabetic mice, as represented by increasing cross-sectional muscle area and grip strength.

Oxidative stress is a precipitating factor of muscle injury (Aoi and Sakuma 2011). In diabetes, hyperglycemia disturbs oxidative imbalance in internal environment homeostasis (de Carvalho Vidigal *et al.* 2012, Giacco and Brownlee 2010). In diabetic nephropathy, FA decreased MDA level in renal to attenuate oxidative stress (Qi *et al.* 2020). In diabetic wound healing, FA exhibited firm antioxidant activity by increasing SOD level (Ghaisas *et al.* 2014). In addition, oxidative stress was increased in skeletal muscle of diabetic mice. Previous study showed promotion of oxidation resistance can availably mitigate high glucose-induced muscle injury (Al-Shwaheen *et al.* 2022). In this study, FA increased T-AOC, SOD, CAT and decreased MDA to relieve skeletal muscle injury.

Inflammatory response is related to muscle function (Schiaffino *et al.* 2013). Hyperglycemia aggravates the

progression of inflammatory reaction. In diabetic nephropathy, FA restrained sucrose-induced inflammation to improve renal structural (Choi *et al.* 2011). In diabetic neuropathy, FA mitigated STZ-mediated pro-inflammatory mediators in sciatic nerve tissue (Dhaliwal *et al.* 2020). In addition, inflammatory response was increase in skeletal muscle of diabetic mice. Previous study showed alleviation of inflammatory response can effectively mitigate high glucose-induced dysfunction in skeletal muscle (Malardé *et al.* 2015). In this study, FA decreased TNF- α and IL-6 levels to relieve skeletal muscle function in STZ-mediated diabetic mice.

Hyperglycemia intensifies ubiquitin E3 ligase production which results in the alters of protein degradation in skeletal muscle (Rom and Reznick 2016, Svikle *et al.* 2021). Muscle atrophy is characterized by significantly increased in content of Fbxo-32 and MuRF-1. Fbxo-32 and MuRF-1 are important ubiquitin-proteasome system components. Previous study showed that reduction of Fbxo-32 and MuRF-1 is an effective approach for mitigating muscle atrophy in diabetes (Yin *et al.* 2021). In this study, FA alleviated high glucose-induced ubiquitin-proteasome system discords by decreasing Fbxo-32 and MuRF-1 expressions to relieve skeletal muscle atrophy, which showed that FA possessed protective effects on muscle structure and function.

Endoplasmic reticulum stress was involved in development of muscle atrophy (Hunter *et al.* 2021, Kny and Fielitz 2022). In diabetes, endoplasmic reticulum stress was activated to cause organ damage (Bohnert *et al.* 2018). Many investigations implied that FA suppressed endoplasmic reticulum stress. In diabetic retinopathy, FA might be involved in altering hyperglycemic environment to DDIT-3 expression (Zhang *et al.* 2018). In diabetic cardiomyopathy, FA exhibited hypoglycemic effects to mitigate GRP78 level (Chowdhury *et al.* 2016). In addition, amelioration of endoplasmic reticulum stress is beneficial to diabetic muscle atrophy (Reddy *et al.* 2019). In this study, FA decreased DDIT-3 and GRP78 expressions in STZ-associated diabetic mice. These results indicated that FA was involved in inhibition of high glucose-induced endoplasmic reticulum stress to improve muscle atrophy.

Apoptosis dysfunction is harm for muscle mass (Dirks-Naylor and Lennon-Edwards 2011). Hyperglycemia was proved to perturb apoptosis dysfunction (Fiorentino *et al.* 2013). In many disease models, FA boosted anti-apoptosis defenses (Li *et al.* 2021). In gestational diabetes mellitus, FA enhanced BCL-2 expression to protect β cells of female rats (Zhao *et al.* 2020). In db/db mice, FA relieved hyperglycemia-induced apoptosis mediators in retina tissues (Zhu *et al.* 2022). In NRK-52E cell, FA restrained high glucose-induced apoptotic death of cells (Chowdhury *et al.* 2019). Moreover, amelioration of apoptosis-related markers is conducive to improve

muscle-cross sectional area in diabetes (Reddy *et al.* 2019). In this study, FA decreased BAX expression and increased BCL-2 expression in STZ-mediated diabetic mice. These results indicated that FA improved diabetic-associated muscle atrophy via alleviation of apoptosis.

CONCLUSION

Our result displayed FA promoted myofiber size and grip strength to reduce muscle atrophy in diabetic mice. In serum, FA enhanced T-AOC, SOD and CAT levels and reduced MDA, TNF- α and IL-6 levels in high glucose environment. Moreover, FA relieved FBXO-32, MURF-1, DDIT-3, GRP-78 and Bax expressions and elevated BCL-2 expressions in high glucose-mediated skeletal muscle injury. The protective action of FA on muscle atrophy attributed to its biological effect on improvement of ubiquitin-proteasome system, endoplasmic reticulum stress and apoptosis in high glucose environment.

REFERENCES

- Afroze D and Kumar A (2019). ER stress in skeletal muscle remodeling and myopathies. *FEBS J.*, **286**(2): 379-398.
- Al-Shwaheen A, Aljabali AAA, Alomari G, Al Zoubi M, Alshaer W, Al-Trad B and Tambuwala MM (2022). Molecular and cellular effects of gold nanoparticles treatment in experimental diabetic myopathy. *Heliyon.*, **8**(9): e10358.
- Aoi W and Sakuma K (2011). Oxidative stress and skeletal muscle dysfunction with aging. *Curr. Aging. Sci.*, **4**(2): 101-109.
- Bassi-Dibai D, Santos-de-Araújo AD, Dibai-Filho AV, de Azevedo LFS, Goulart CDL, Luz GCP, Burke PR, Garcia-Araújo AS and Borghi-Silva A (2022). Rehabilitation of Individuals With Diabetes Mellitus: Focus on Diabetic Myopathy. *Front. Endocrinol. (Lausanne.)*, **13**: 869921.
- Bohnert KR, McMillan JD and Kumar A (2018). Emerging roles of ER stress and unfolded protein response pathways in skeletal muscle health and disease. *J. Cell. Physiol.*, **233**(1): 67-78.
- Chen X, Guo Y, Jia G, Zhao H, Liu G and Huang Z (2019). Ferulic acid regulates muscle fiber type formation through the Sirt1/AMPK signaling pathway. *Food. Funct.*, **10**(1): 259-265.
- Choi R, Kim BH, Naowaboot J, Lee MY, Hyun MR, Cho EJ, Lee ES, Lee EY, Yang YC and Chung CH (2011). Effects of ferulic acid on diabetic nephropathy in a rat model of type 2 diabetes. *Exp. Mol. Med.*, **43**(12): 676-683.
- Chowdhury S, Ghosh S, Das AK and Sil PC (2019). Ferulic acid protects hyperglycemia-induced kidney damage by regulating oxidative insult, inflammation and autophagy. *Front. Pharmacol.*, **10**: 27.

- Chowdhury S, Ghosh S, Rashid K and Sil PC (2016). Deciphering the role of ferulic acid against streptozotocin-induced cellular stress in the cardiac tissue of diabetic rats. *Food. Chem. Toxicol.*, **97**: 187-198.
- de Carvalho Vidigal F, Guedes Cocate P, Gonçalves Pereira L, and de Cássia Gonçalves Alfenas R (2012). The role of hyperglycemia in the induction of oxidative stress and inflammatory process. *Nutr. Hosp.*, **27**(5): 1391-1398.
- Dhaliwal J, Dhaliwal N, Akhtar A, Kuhad A and Chopra K (2020). Beneficial effects of ferulic acid alone and in combination with insulin in streptozotocin induced diabetic neuropathy in Sprague Dawley rats. *Life. Sci.*, **255**: 117856.
- Dirks-Naylor AJ and Lennon-Edwards S (2011). Cellular and molecular mechanisms of apoptosis in age-related muscle atrophy. *Curr. Aging. Sci.*, **4**(3): 269-278.
- Ghaisas MM, Kshirsagar SB and Sahane RS (2014). Evaluation of wound healing activity of ferulic acid in diabetic rats. *Int. Wound. J.*, **11**(5): 523-532.
- Giacco F and Brownlee M (2010). Oxidative stress and diabetic complications. *Circ. Res.*, **107**(9): 1058-1070.
- Fiorentino TV, Priolella A, Zuo P and Folli F (2013). Hyperglycemia-induced oxidative stress and its role in diabetes mellitus related cardiovascular diseases. *Curr. Pharm. Des.*, **19**(32): 5695-5703.
- Heald AH, Stedman M, Davies M, Livingston M, Alshames R, Lunt M, Rayman G and Gadsby R (2020). Estimating life years lost to diabetes: outcomes from analysis of national diabetes audit and office of national statistics data. *Cardiovasc. Endocrinol. Metab.*, **9**(4): 183-185.
- Hunter RB, Mitchell-Felton H, Essig DA and Kandarian SC (2021). Expression of endoplasmic reticulum stress proteins during skeletal muscle disuse atrophy. *Am. J. Physiol. Cell. Physiol.*, **281**(4): C1285-C1290.
- Kang BB and Chiang BH (2020). Amelioration of insulin resistance using the additive effect of ferulic acid and resveratrol on vesicle trafficking for skeletal muscle glucose metabolism. *Phytother. Res.*, **34**(4): 808-816.
- Khromova NV, Fedorov AV, Ma Y, Kondratov KA, Prikhodko SS, Ignatieva EV, Artemyeva MS, Anopova AD, Neimark AE, Kostareva AA, Babenko AY and Dmitrieva RI (2021). Regulatory action of plasma from patients with obesity and diabetes towards muscle cells differentiation and bioenergetics revealed by the C2C12 cell model and MicroRNA analysis. *Biomolecules.*, **11**(6): 769.
- Kny M and Fielitz J (2022). Hidden Agenda - The Involvement of Endoplasmic Reticulum Stress and Unfolded Protein Response in Inflammation-Induced Muscle Wasting. *Front. Immunol.*, **13**: 878755.
- Li D, Rui YX, Guo SD, Luan F, Liu R and Zeng N (2021). Ferulic acid: A review of its pharmacology, pharmacokinetics and derivatives. *Life Sci.*, **284**: 119921.
- Li X, Wu J, Xu F, Chu C, Li X, Shi X, Zheng W, Wang Z, Jia Y and Xiao W (2022). Use of ferulic acid in the management of diabetes mellitus and its complications. *Molecules*, **27**(18):6010.
- Liu X, Liu M, Chen C, Deng B and Xie J (2021). Sinaptic acid attenuates muscle atrophy in streptozotocin-induced diabetic mice. *Iran J. Basic. Med. Sci.*, **24**(12): 1695-1701.
- Malardé L, Groussard C, Lefeuvre-Orfila L, Vincent S, Efsthathiou T and Gratas-Delamarche A (2015). Fermented soy permeate reduces cytokine level and oxidative stress in streptozotocin-induced diabetic rats. *J. Med. Food.*, **18**(1): 67-75.
- Rom O and Reznick AZ (2016). The role of E3 ubiquitin-ligases MuRF-1 and MAFbx in loss of skeletal muscle mass. *Free. Radic. Biol. Med.*, **98**: 218-230.
- Mustapha S, Mohammed M, Azemi AK, Yunusa I, Shehu A, Mustapha L, Wada Y, Ahmad MH, Ahmad WANW, Rasool AHG and Mokhtar SS (2021). Potential roles of endoplasmic reticulum stress and cellular proteins implicated in diabetes. *Oxid. Med. Cell. Longev.*, **2021**: 8830880.
- Murtaza G, Virk HUH, Khalid M, Lavie CJ, Ventura H, Mukherjee D, Ramu V, Bhogal S, Kumar G, Shanmugasundaram M and Paul TK (2019). Diabetic cardiomyopathy - A comprehensive updated review. *Prog. Cardiovasc. Dis.*, **62**(4): 315-326.
- Ohnishi M, Matuo T, Tsuno T, Hosoda A, Nomura E, Taniguchi H, Sasaki H and Morishita HJB (2004). Antioxidant activity and hypoglycemic effect of ferulic acid in STZ-mediated diabetic mice and KK-A^y mice. *Biofactors*, **21**(1-4): 315-319.
- Perry BD, Caldow MK, Brennan-Speranza TC, Sbaraglia M, Jerums G, Garnham A, Wong C, Levinger P, Asrar Ul Haq M, Hare DL, Price SR and Levinger I (2016). Muscle atrophy in patients with type 2 diabetes Mellitus: Roles of inflammatory pathways, physical activity and exercise. *Exerc. Immunol. Rev.*, **22**: 94-109.
- Qi MY, Wang XT, Xu HL, Yang ZL, Cheng Y and Zhou B (2020). Protective effect of ferulic acid on STZ-mediated diabetic nephropathy in rats. *Food Funct.*, **11**(4): 3706-3718.
- Reddy SS, Shruthi K, Joy D and Reddy GB (2019). 4-PBA prevents diabetic muscle atrophy in rats by modulating ER stress response and ubiquitin-proteasome system. *Chem. Biol. Interact.*, **306**: 70-77.
- Refardt J, Winzeler B and Christ-Crain M (2020). Diabetes insipidus: An update. *Endocrinol. Metab. Clin. North. Am.*, **49**(3): 517-531.
- Richter-Stretton GL, Fenning AS and Vella RK (2020). Skeletal muscle - A bystander or influencer of metabolic syndrome? *Diabetes Metab. Syndr.*, **14**(5): 867-875.
- Roy S, Metya SK, Sannigrahi S, Rahaman N and Ahmed FJE (2013). Treatment with ferulic acid to rats with streptozotocin-induced diabetes: Effects on oxidative

- stress, pro-inflammatory cytokines and apoptosis in the pancreatic β cell. *Endocrine*, **44**(2): 369-379.
- Schiaffino S, Dyar KA, Ciciliot S, Blaauw B and Sandri M (2013). Mechanisms regulating skeletal muscle growth and atrophy. *FEBS J.*, **280**(17): 4294-314.
- Singh A, Phogat J, Yadav A and Dabur R (2021). The dependency of autophagy and ubiquitin proteasome system during skeletal muscle atrophy. *Biophys. Rev.*, **13**(2): 203-219.
- Son MJ, Rico CW, Nam SH and Kang MYJJ (2011). Effect of oryzanol and ferulic acid on the glucose metabolism of mice fed with a high-fat diet. *J. Food. Sci.*, **76**(1): H7-H10.
- Sri Balasubashini M, Rukkumani R and Menon VJAD (2003). Protective effects of ferulic acid on hyperlipidemic diabetic rats. *Acta. Diabetol.*, **40**(3): 118-122.
- Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC, Pavkov ME, Ramachandaran A, Wild SH, James S, Herman WH, Zhang P, Bommer C, Kuo S, Boyko EJ and Magliano DJ (2022). IDF diabetes atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res. Clin. Pract.*, **183**: 109119.
- Svikle Z, Peterfelde B, Sjakste N, Bauman K, Verkauskiene R, Jeng CJ and Sokolovska J (2022). Ubiquitin-proteasome system in diabetic retinopathy. *Peer. J.*, **10**:e13715.
- Wang Y, Chen X, Huang Z, Chen D, Yu B, Chen H, Yu J, Luo Y, Zheng P and He J (2021). Effects of dietary ferulic acid supplementation on growth performance and skeletal muscle fiber type conversion in weaned piglets. *J. Sci. Food. Agric.*, **101**(12): 5116-5123.
- Wen Y and Ushio H (2017). Ferulic Acid promotes hypertrophic growth of fast skeletal muscle in zebrafish model. *Nutrients*, **9**(10): 1066.
- Xiao Q (2010). Intervention of aerobic exercise on metabolism and antioxidant in obese female college students. *J. Hunan Univ. Arts Sci. (Sci. Tech.)*, **22**(4): 88-93.
- Yin L, Chen X, Li N, Jia W, Wang N, Hou B, Yang H, Zhang L, Qiang G, Yang X and Du G (2021). Puerarin ameliorates skeletal muscle wasting and fiber type transformation in STZ-induced type 1 diabetic rats. *Biomed. Pharmacother.*, **133**: 110977.
- Yin X, Liu W, Chen H, Qi C, Chen H, Niu H, Yang J, Kwok KWH and Dong W (2022). Effects of ferulic acid on muscle development and intestinal microbiota of zebrafish. *J. Anim. Physiol. Anim. Nutr. (Berl.)*, **106**(2): 429-440.
- Zhang C, Xu Y, Tan HY, Li S, Wang N, Zhang Y and Feng Y (2018). Neuroprotective effect of He-Ying-Qing-Re formula on retinal ganglion cell in diabetic retinopathy. *J. Ethnopharmacol.*, **214**: 179-189.
- Zhao J, Gao J and Li H (2020). Ferulic acid confers protection on islet β cells and placental tissues of rats with gestational diabetes mellitus. *Cell Mol. Biol. (Noisy-le-grand.)*, **66**(1): 37-41.
- Zhu D, Zou W, Cao X, Xu W, Lu Z, Zhu Y, Hu X, Hu J and Zhu Q (2022). Ferulic acid attenuates high glucose-induced apoptosis in retinal pigment epithelium cells and protects retina in db/db mice. *Peer. J.*, **10**: e13375.