Indonesian Journal of Pharmaceutical Science and Technology
Journal Homepage : http://jurnal.unpad.ac.id/ijpst/
Review Article

Biomolecular Mechanism of Herbal Medicine on Muscle Atrophy in Type 2 Diabetes Mellitus Rats: Systematic Review

Asep Kuswandi[1], Nur K. K. Ikram[2], Muchtaridi Muchtaridi[3]

[1]Pharmacology Division, Department of Community Clinical Pharmacy, Diploma 3 Pharmacy Education Program, Poltekkes Kemenkes Tasikmalaya, 46115, Indonesia

[2]Institute of Biological Sicences, Facultu of Science, Universiti Malaya, Kualalumpur, Malaysia

[3] Department of Pharmaceutical Analysis and Medcinal Chemistry, Faculty of Pharmacy, Universitas Padjadjaran, Jatinangor, 45363, Indonesia

Submitted 03 November 2023; Revised 15 November 2023; Accepted 15 November 2023; Published 01 February 2024
*Corresponding author: asep18006@mail.unpad.ac.id

Abstract

Elevation in proinflammatory phenotype, oxidative damage, and advanced glycation end products are brought on by musculoskeletal atrophy and can result in both micro- and macrovascular problems. Sarcopenia may result from this loss of skeletal muscle mass, strength, and function. Herbal remedies have the capacity to build skeletal muscle mass and have been shown to be effective in treating a variety of human ailments. Herbal remedies have been shown to stimulate a number of different genes to stop muscular atrophy in chronic illnesses. The molecular processes by which herbal remedies prevent chronic disease-related muscle atrophy must be explained. In T2DM mice, the routes of inflammation, protein synthesis, apoptosis, autophagy, and glucose uptake are used to investigate the biomolecular mechanisms of each herbal remedy. The findings of the study indicate that 81 gene expressions may be triggered by herbal medicine in T2DM animals, thus avoiding muscular atrophy.

Keywords: Biomolecular, Herbal medicine, Musculoskeletal atrophy, Type 2 diabetes.

Mekanisme Biomolekular Obat Herbal terhadap Atrofi Otot pada Penyakit Diabetes Melitus Tipe 2: *Review*

Abstrak

Atrofi muskuloskeletal menyebabkan peningkatan produk akhir glikasi lanjut, fenotip proinflamasi dan stres oksidatif, yang dapat menyebabkan komplikasi mikro dan makrovaskular. Hal ini dapat menyebabkan hilangnya massa, kekuatan, dan fungsi otot rangka, yang berpotensi menyebabkan sarkopenia. Obat-obat herbal telah terbukti mampu mengatasi berbagai penyakit pada manusia, obat herbal mempunyai potensi untuk meningkatkan massa otot rangka. Ada berbagai gen yang telah diinduksi oleh obat herbal untuk mencegah atrofi otot pada penyakit kronis. Perlu dijelaskan mekanisme molekuler peran obat herbal dalam mencegah atrofi otot akibat penyakit kronis. Studi ini mengeksplorasi mekanisme biomelokular masing-masing obat herbal berdasarkan jalur inflamasi, sintesis protein, apoptosis, autofagi, dan ambilan glukosa pada tikus diabetes melitus tipe 2 (DMT2). Hasil penelitian menunjukkan bahwa obat herbal berpotensi mengaktifkan 81 ekspresi gen yang dapat mencegah terjadinya atrofi otot pada model tikus DMT2.

Kata Kunci: Biomolekular, Obat herbal, Atrofi muskuloskeletal, Diabetes tipe 2

ABBREVIATIONS :

2-DG : 2-deoxyglucose
4-HNE : 4-hydroxy2-neonatal
Ache : acetylcholinesterase
Akt : Protein kinase
ALT : Alanine transaminase
AMP : Adenosinemonophosphate
AMPK : AMP kinase
AP : Activator protein
APS : Astragalus polysaccharide
AST : Aspartate transaminase
ATG : Antithymocyte globulin
ATP : Adenosinetriphosphate
AUC : Area under the curve
BALF : Bronchoalveolar lavage fluid
BAX : Bcl2- associated X protein
BCL-XL : B-cell lymphoma extra large
BG : Blood glucose
BNIP : BCL2/adenovirus E1B 19 kDa interacting protein
CCK-8 : Cell counting kit-8
CD : Chow diet
C/EBP : CCAAT/enhancer-binding protein
CKD : Chronic kidney disease
COPD : Chronic obstructive pulmo nary disease
DMT2 : diabetes mellitus type 2
DNM : Deoxynojirimycin
DPPH : 1,1-diphenyl-2-picrylhydra zyl
DTNB : 5,5-dithiobisnitrobenzoic acid
DRP1 : Dynamin-related protein 1
F6P : Fructose-6-phosphate
F-1,6-BP : Fructose-6-phosphateintof rcutose-1,6-bisphosphate
FBG : Fast blood glucose
FBPase : Fructose-1,6-Bisphosphatase
FM : Fermetedmaize
Fbxo32 : F-box only protein 32
Fn-14 : Fibroblast growth factor-inducible 14
FoxO : Forkhead box protein O
GADPH : Glyceraldehyde-3-phosphate dehydrogenase
GAE : Galic acid equivalent
GLUT-4 : Glucose transporter type4
GOD : Gegen qinlin decoction
GPx : Glutathione peroxidase
Grb2 : Growth factor receptor-bound protein 2
GS : Grb2–SOS complex
GSH : Glutathione
GSH-Px : Glutathione peroxidase
GSP : Glycated serum protein
GST : graphene-silica-trypsin
HbA1C : Glycated hemoglobin
HDAC2 : Histone deacetylase2
HDL : High density lipoprotein
HFD : High fat diet
HK : Hexokinase
HOMA-IR : Homeostasis model assess ment insulin
HRP : Horseradish peroxidase
IFM : Intermyofibrillar mitochin dria
IGF-IR : Insulin-like growth factor-1 receptor
IL-6 : Interleukin-6
IPGTT : intraperitoneal glucose toler ance test
IRS1 : Insuin receptor substrate 1
ITT : Insulin tolerance test
LC3B : Light chain 3B
LDLc : Low density lipoprotein cho lesterol
LDL : Low density lipoprotein
LKB1 : Liver kinase B1
LWDH : Liuwei dihuang
MAFbx : Muscle atrophy F-box
MAPK15 : mitogen-activated protein kinase15
MCT : Medium-chain triglyceride
MDA : Malondialdehyde
MG : Methylglyyoxal
MEP : Molecular electrostatic po tential
MHC : Myosin heavy chain
MIP : Macrophage inflammatory protein
MSK : mitogen and stress-activated protein.
MQC : Mitochondrial quality
mTOR : Mammalian target of rapa mycin
mtTFA : Mitochondrial transcription factor A
MuRF1 : Muscle RING finger 1
MWM : Morris water maze

MyHC : Myosin heavy chin
NAC : N-acetyl-L-cysteine
NADPH : Nicotinamide adenin dinu cleotide phosphate
NE : No effect
NF : Nuclear factor
NF-Kb : Nuclear factor kappa B
N-FM : Non-fermentedmaize
NO : Nitric oxide
Nox : NADPH oxidase
NRF : Nuclear respiratory factor
Nox : NADPH oxidase
OCR : Oxigen consumtion rate
OGTT : Oral Glucose tolerance test
OSI : Oxidative stress index
PA : Palminate acid
Pax : peptide-antimicrobial-Xenorhabdus
PBS : Phosphate-buffered saline
PFK : phosphofructokinase
PFK-1 : Phosphofructokinase-1
PGC-1α : Peroxisome proliferator-activated receptor-α coacti vator control 1- α
PI3K : Phosphoinositide 3-kinase

1. Introduction

Muscle atrophy occurs due to various causes, including lack of activity, old age, type 2 diabetes mellitus, and chronic disease causing difficulty in movement, such as stroke, and paralysis.[1] Muscle atrophy gene expression in chronic diseases such as diabetes involves several factors including FoxO, ubiquitin-proteosome, and autophagy changes categorized by amplified LC3-3, and increased stages of phosphorylase ULK1, Fbxo32 (Atrogin1), Trim63 (MuRF1), Bnip3L, and LC3.[1] Musculoskeletal atrophy causes T2DM due to insulin resistance, increased advanced glycation end-products, a proinflammatory phenotype and oxidative stress, which can lead to micro- and macro-vascular complications. These can lead to losses in skeletal muscle mass, strength, and function, potentially leading to sarcopenia.[2]

The first line of treatment for muscle atrophy in chronic disease is synthetic drugs such as metformin. However, there are several obstacles, including a long period of time that can lead to glucose intolerance . Prevention of systemic complications cannot be controlled due to failure to maintain blood sugar levels. Synthetic drugs have some adverse side effects for patients such as diarrhea, nausea, and vomiting with a prevalence of 2%-63%.[3]

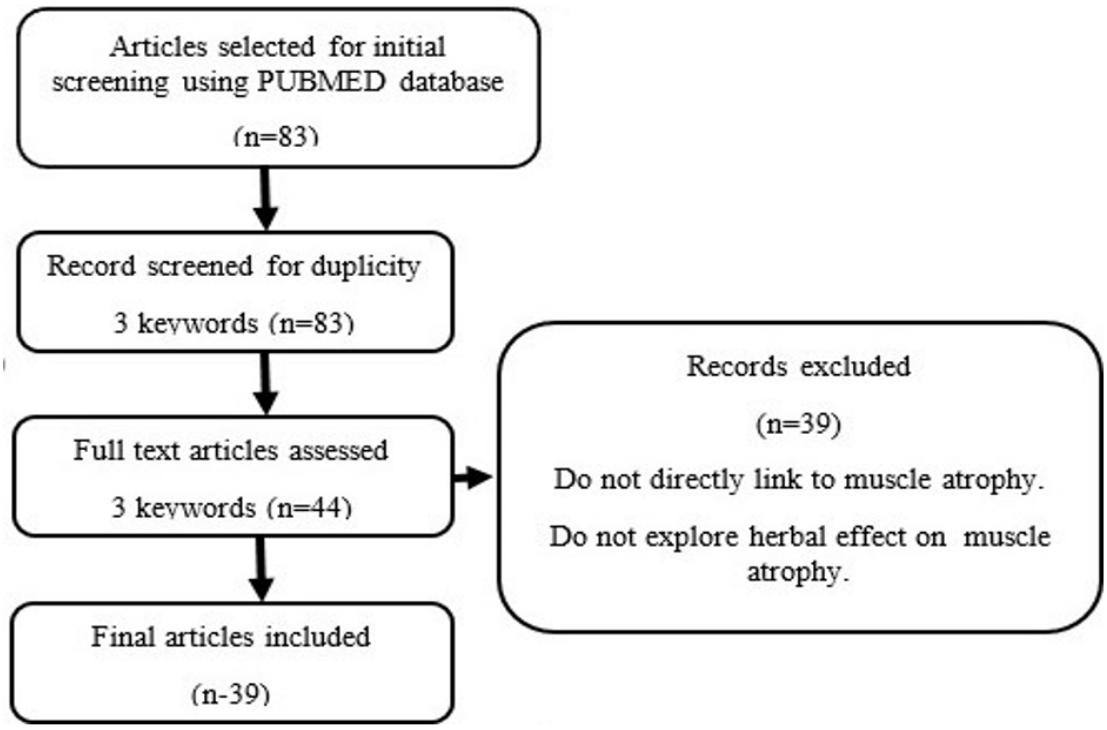

Figure 1. Flowchart of the article screening procedure via PRISMA Diagram. Out of 83 articles screened, only 39 articles were included in this review.

As a result of these side effects, approximately 5% of the patients discontinue their treatment in the world.[4] Therefore, herbal medicines for long-term chronic disease treatment are crucially needed. Herbal medicine such as phytomedicine or botanical medicine, is a treatment using various plant parts including flowers, fruits, seeds, leaves, stems, and roots.[5] The advantages include minimal side effects, adaptability of the body, and safety if used in the long term.[6]

This review article aims to describe several types of herbal medicine that focus on muscle atrophy in diabetes mellitus using experimental animal media to see various gene expressions that are activated in skeletal muscle.

2. Method

This review's literature material was obtained from Scopus, PubMed, and Google Scholar using the keywords "herbal", "diabetes", "atrophy", and "metabolic". Articles that do not match the review title and/or keywords, review journal articles are excluded. The article that was the inclusion criteria was an original article regarding herbal medicines for T2DM mice with musculoskeletal atrophy. The article selection process uses PRISMA screening. The procedure flow diagram is shown in Figure 1.

3. Result and Discussion

3.1. Signal of Atrophy in Skeletal Muscles

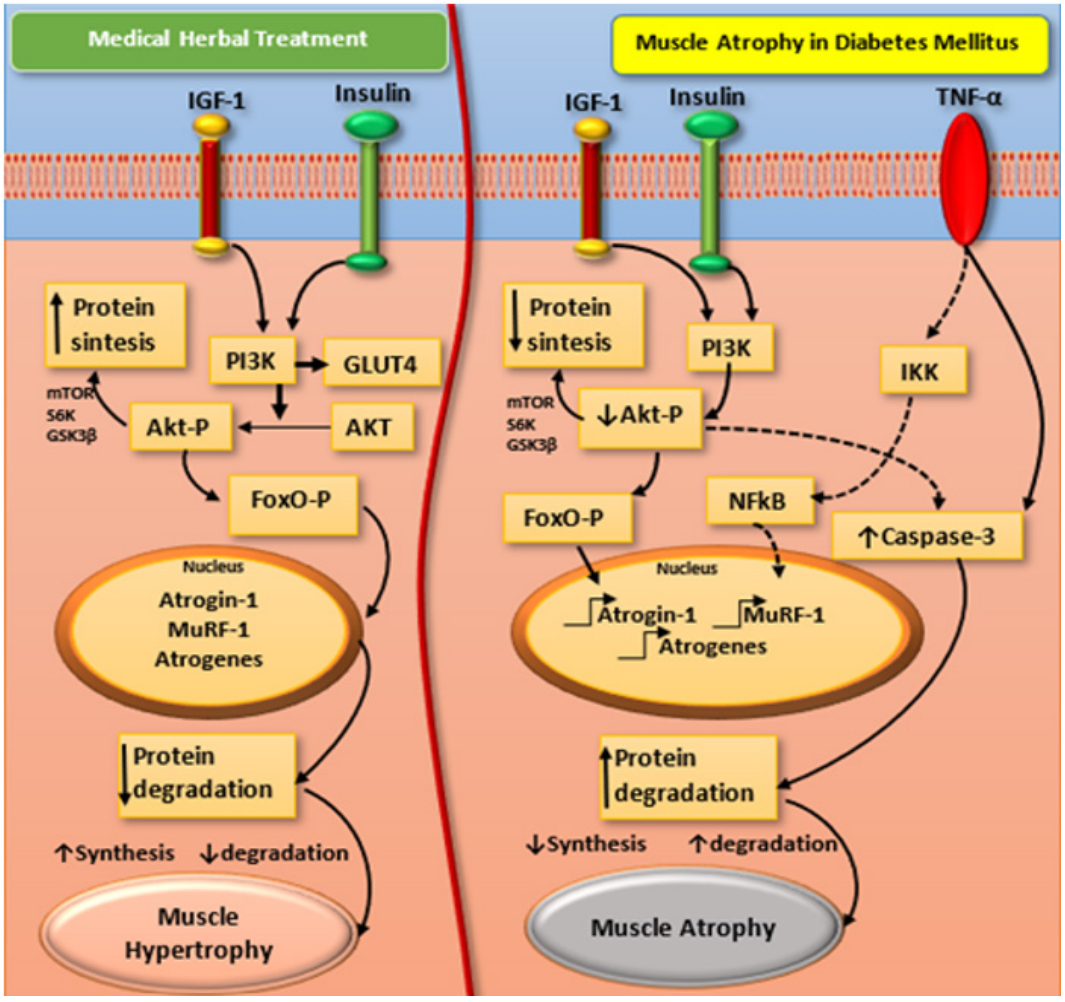

Figure 2. Differences in muscle gene expression that received medical herbal treatment versus those without medical herbal treatment in diabetes mellitus conditions. PI3K (phosphoinositide 3-kinase); GLUT4 (glucose transporter 4); AKT-p = protein kinase P); FOXO (forkhead box transcription factors); MuRF (muscle-specific RING finger-1); IGF-1 (insulin-like growth factor 1); TNF-α (tumor necrosis factor- α); IKK (IkappaB kinase); NF-kB (nuclear factor kappa B).

Muscle atrophy occurs due to several factors, including the absence of muscle activity, old age and chronic diseases including diabetes mellitus.[7] In catabolic situations, muscle degenerate can reduce its ability to live, the quality of life and may lead to death.[8] The ubiquitin-proteosome, autophagy-lysosome and caspase-3-mediated proteolytic paths are responses due to protein deprivation (Figure 2). Deprivation of healthy muscle is necessary in maintaining cellular homeostasis.[9] Inactive muscles in chronic disease will increase muscle atroph y[10] which then causes reduced protein production and skeletal muscle inactivity and declined activation of the mammalian target of rapamyacin pathway (Figure 2).[11,12]

Musculoskeletal atrophy due to T2DM can be treated with herbs containing a combination of vitamins C, D and E with the mechanism of increasing insulin secretion, and herbs containing zinc can increase the sensitivity of insulin receptors.[13] Both conditions of increasing insulin secretion and increasing receptor sensitivity to insulin can improve the condition of hyperglycemia on T2DM.

The dynamism of this mechanism can increase IRS-1, increase PI3K signaling, activate AKT and activate mTor so that protein synthesis occurs, so muscle mass increases.[14] Herbs as shown in table 1 are proven to be able to activate genes that can increase gene expression to increase muscle mass and lower blood glucose levels biomolecularly.

3.2. Herbal Medicine

Herbal medicine is a substance derived from natural plants to treat a disease. Recently, people have been consuming more and more herbal medicines compared to synthetic medicines. This is because the advantages of herbal medicines are that they have minimal side effects, the body is more adaptable, safe for long-term use and can biomolecularly increase the genes needed to prevent T2DM and reduce blood glucose levels.[15] Table 1 shows various herbs that play an important role in preventing or treating T2DM and musculoskeletal atrophy. Based on the results of the review, it was found that these herbs have an effect on blood glucose, repair pancreatic beta cells, improve musculoskeletal atrophy in chronic diseases and lower cholesterol, and so on.[12]

3.3. Potential Role of Herbal Medicine for Muscle Atrophy

The results of research related to herbal medicine have been proven to be able to treat musculoskeletal atrophy in the gastrocnemius muscle. For example, Tinospora cordifolia extract can prevent musculoskeletal atrophy by biomolecular mechanisms by reducing TNF-α, IL-6, MuRf-1, Atrogen-1, Beclin-1, and Foxo. Meanwhile, Tinospora cordifilia can increase PI3K gene expression.[12] Other herbs that can increase muscle mass include: Jamu Jian-Pi-Yi-Shen16, Schisandra chinesis (SC), Lycium chinense Mill and Eucommia ulmoides Oliv (EU),[17] Catalpol extract, Hot water Extract of juzentaihoto,[18] Hot water Extract of juzentaihoto,[19] Dioscorea nipponica extracts (DNM),[20] Resverartol,[21] tomato,[22] whole grain cereal,[23] Brazilian propolis,[24] Rhodiola rosea,[25] extract annatto and green tea polyphenol,[26] and red bean extract.[27] These herbs can be considered given to patients who have a high risk of musculoskeletal atrophy due to lying down too much in cases of chronic diseases, for example T2DM.

3.4. Anti-inflammatory potential of herbal remedies for muscle atrophy

Herbals works by inhibiting pro-inflammatory genes (34%) that prevent protein degradation and increase protein synthesis. Protein deprivation is facilitated by ubiquitin proteasome pathway.[54] The appearance of MAF-box/ atrogin-1 and MuRF1 is controlled by FOXO family.[55] FOXO plays a role in proliferation, cell cycle, and cellular defense, and is expressed in all human cells.[56] FOXO in skeletal muscle contributes to muscle size by regulating the production of atroggenes, such as muscle-specific ligase E3 ligases.[57] Overexpression of FOXO1 or FOXO3a can cause muscle atrophy in vivo.[58]

Systemic inflammation is the cause of muscle disorders due to amplified appearance

of pro-inflammatory cytokine genes such as TNF-α, IL-1β, and IL-6 which contribute to a decrease in skeletal muscle mass and function. Several research had shown that increased levels of TNF- is caused by limb immobilization or denervation. Inflammatory cytokine mRNA levels were increased after immobilization for 14 days.[59]

3.5. Protein synthesis potential of herbal medicine

Muscle atrophy consist of the AMP-activated protein kinase (AMPK) pathway and the Akt pathway60. Genes that act as activators of protein synthesis include: mTOR, Myo D, Myogen, p70, AKT, PI3K, IRS1, IGF-IR, PGC-1α, and vascular endothelial growth factor (VEGF). mTOR is the main signalling pathway that stimulates muscle hypertrophy and protein synthesis.[61] It can be initiated by herbal medicine leading to an increase protein synthesis.

Herbal medicine ameliorate muscle atrophy by stimulating the extracellular-signal-regulated kinase 1/2 (ERK1/2) and PI3K-Akt-mTOR pathways which further activate muscle mTOR complex 1 (mTORC1).[61,62] The mTORC1 pathway activates the phosphorylation of proteins vigorous for continued protein production and hypertrophy, such as ribosomal S6 kinase 1 and 4E-BP1.[63] Chronic disease patients is associated with inhibition of protein synthesis by inhibition of 4E-BP1 phosphorylation in the muscle in reaction to protein and insulin intake.[64] This condition causes insulin and protein resistance that can increase ubiquitin-proteosum activation resulting a decreased muscle mass in chronic disease.[65] Herbal medicines can activate mTORC1 and prevent muscle atrophy. mTOR activates Akt, hence the ubiquitin-proteosum system is activated as well.[66]

3.6. Apoptotic potential of herbal medicine

Apoptosis is a highly programmed process of cell death. It is important for replacement of damaged cells, improved immune system growth and function, hormone-dependent atrophy, embryonic growth and biochemical induction of cell death.[67] Apoptotic disorders could be a factor in human disturbances in the form of neurodegenerative disease, ischemia, autoimmune and cancer. Therefore, it must be controlled in the body.[68]

Control of apoptosis can be performed by pharmacological and non-pharmacological management. Pharmacologically, it can be done using herbal medicines that have been tested both in vivo, in vitro and clinically. The herbal medicine having synergistic properties in controlling apoptosis presented in Table 1 are catalpol extract, rattan tea, dokhwalgisaeng-tang, nigella sativa oil, brazilian propolis, and moringa concanensis. Herbal medicines have active compounds that can maintain balanced apoptosis with apoptotic gene expression pathways. Gene expressions activated by these herbal medicinal compounds include Bax, BCL (B-cell lymphoma), BCL-XL, GSH (glutathione) and BCL-W, p50-p105, TGF-β1 (transforming growth factor beta 1), TSP-1 (thrombospondin-1), and SREBPs (Sterol regulator element binding proteins) (Table 1). Activation of these genes can prevent muscle atrophy by destroying dead cells.[70]

Bax/Bcl gene expression is a ratio that determines the prognosis of a disease such as cancer. Several studies showed an increase in the Bax/Bcl ratio after given the herbal medicine: catalpol, rattan tea, and dokhwalgisaeng-tang. The proapoptotic expression gene SREBPs, which play a role in cell growth, can be activated with moringa herbal medicine. The TGF-β1 gene plays a role in the apoptotic process, especially in terms of muscle granulation. The gene can be activated by the herbal medicine pterostilbene, and resveratrol.[71]

3.7. Autophagy potential of herbal medicine

The autophagy or 'self-eating', is a process to removes unwanted molecules and non-functioning parts and recycle it into new components.[72] At the cellular level, autophagy remove toxic proteins and recycled residual proteins, that will provide energy and building materials for cells.[73] Autophagy can be maintained with regular exercise and by

Table 1. Several names of herbs that work biomolecularly and their musculoskeletal effects

NO	HERBALS NAME	BIOMOLLECULAR MECHANISM	EFFECTS	REF.
1	Tinospora cordifolia Extract	Target: gastrocnemius muscle. TNF-α↓, IL-6↓, MuRf1↓, Atrogin-1↓, Level of Beclin-1↓, PI3K↑, Akt ↑, FoxO↓.	FBG ↓. Regenerated pancreatic islets. Reversed the skeletal muscle atrophy in chronic desease, TC↓	12
2	Jian-Pi-Yi-Shen decoction.	Target: quadriceps muscles ubiquitin ↓, Atrogin-1↓, MuRF1↓, FoxO3a↓.	BW loss↓, muscle loss↓, muscles fiber decline↓, muscles protein deprivation↓, and muscle protein synthesis↑.	16
3	Rehmannia glutinosa	Target: gastrocnemius tissue. MuRF1↓ , FoxO↓, SOD↑, CAT↑, MDA↓.	inhibition of FOXO-mediated ubiquitin-proteasome pathway.	28
4	Schisandra chinesis (SC), Lycium chinense Mill and Eucommia ulmoides Oliv (EU).	Target: gastrocnemius, soleus. TNF-α ↓, Myo D ↑, Myogen ↑, Akt ↑, .Mtor ↑, Ubiquitin-protesum ↓	BW ↑, muscle mass↑ hold power↑, muscle strength mass↑, muscle fiber type atpase stain↑	17
5	Methanol extract of Centella asiaticabax	Target: gastrocnemius. Muscle glycogen↑, HK↓ PFK↓, FBPase↑, GS↑, GP↑	Blood glucose↓, polyphagia↓, polyuria↓, polydipsia↓, body weight↑, ALT↓, AST↓	29
6	Catalpol extract	Target: gastrocnemius, AChE↑, MEP↑, LC3II↓, Bax/BCL-2↑, LC3II/LC31↑, -mTOR ↑	Muscle atrophy↓.	18
7	Hot water Extract of juzentaihoto	Target: Gastrocnemius muscle, liver, spleen and thymus gland, SIRT1↑, SOD↑.	Juzentaihoto can prevent atrophy by decreasing oxidative stress.	19
8	Liuwei dihuang water extracts	Target: skeletal muscle, Nox↓, ROS↓, IGF-1R↑, Akt↑, mTOR ↑, FoxO3↓, Atrogin-1↓, Murf-1↓, acetyltransferase↑	Body weight↑, muscle strength↑, insulin muscle↑, grip strength↑	30
9	Rattan tea	Sample: gastrocnemius muscle. MDA↓, PGC-1α↑, Atrogin-1↓, MAFbx↑, MuRF1 (not affected). Bax/BCL-2↑, AMPK-2 ↑, SIRT1↑, Akt↑	Fiber diameter of gastrocnemius muscle↑ Dose 100 mg/ kg bw is better than 200 mg/k g bw	31
10	Water extract of Dokhwalgisaeng-tang (DGT).	Sample: gastrocnemius muscle. Bax/BCL-2↑	Protecting special effects against neglect muscle atrophy, potentially through changed bax and Bcl-2 protein appearance in the gastrocnemius muscle.	32
11	Astragalus polysaccharide	Sample: gastrocnemius muscle. Atrogin-1↓, Ubiquitin↓	Delay the development of muscle cell atrophy related with starvation in CRF, possibly by targeting the UPP and its downstream effector atrogin 1	33

NO	HERBALS NAME	BIOMOLLECULAR MECHANISM	EFFECTS	REF.
12	Dioscorea nipponica extracts (DNM)	Sample: gastrocnemius muscle. MyoD↑, MyiG↑, TNFα↓, MuRF1↓, Atrogin-1↓, MAFbx↓, NF-kB↓	DNM significant for preventing and treating the various causes of muscle atrophy	20
13	Resverartol	Sample: gastrocnemius muscle. MuRF-1↓, LC3-II/ LC3-I↓, Cleaved caspase-3↓, PGC-1α↑, NRF-1↑, mtTFA↑, E3 ubiquitin↓, MAFbx↓	Muscle mass↑, Physical activity↑ UPS↓, Blood glucose, reatinine not affected, Ureum NA, Albumin NA, ALT NA, AST NA	21
14	Licorice flavonoid oil.	Sample: femoral and soleus muscle. mTOR↑, P70 S6K↑, P38/FoxO3a↑, Akt/FoxO3a↑, MuRF1↓, Atrogin-1↓	Femoral muscle↑ Prevent muscle atrophy	34
15	Wushenziye formula	Sample: soleus muscle. p-IRSI↑, p-Akt↑, GLUT4↑, PTPIB↓	FBG↓, Glycosylated serum protein↓, HbA1C↓. Insulin concetration↓, Insulin resistence index↓.	35
16	Cassia occidentalis L	Sample: gastrocnemius muscle. Atrogin-1↓, MuRF-1↓, IL-1β (no effect)	CSE-BUF prevented muscle atrophy caused by metiprednislon.	36
17	Formononetin, Soybean, katuk leaves, red clover	Sample: gastrocnemius SIRT1↑	Plasma glucose↓ at 40 mg/kg bw. Glucose acceptance↑, Insulin HOMA-IR↓, Fat profile, Hepatic glycogen content↑. HbA1C↓	37
18	Nutmeg extract	Sample: gastrocnemius muscles, Pax↑, MyoD↑, Myogenin↑, MHCI↑, IGF1↑.	Soleus mass↑, Gastrocnemius mass↑	38
19	Nigella Sativa Oil[39]	Sample: blood, skeletal muscle, pancreas, liver. Pancreatic catalase↑, Hepatic catalase↑. Pancreatic GSH↑ Hepatic GSH↑, AMPK↑	Blood glucose↓, Serum insulin↑, Hepatic glycogen↑, Gluconeogenesis↓.	40
20	Carica papaya seed extract	Sample: gastrocnemius muscle. GLUT4↑, mTOR↑, PI3K↑, Akt↑	Sample: soleus and gastrocnemius, GLUT4↑, AMPK↑, SIRT1↑, PGC-α↑.	41
21	Berberin	Sample: soleus and gastrocnemius, GLUT4↑, AMPK↑, SIRT1↑, PGC-α↑.	Cholesterol↓, TG↓ATP↑, ROS↓.	42
22	Hot water extract of Juzentaihoto (JTT)	Sample: gastrocnemius muscle. TNF-α↓, IL-6↓, mRNA Atrogin1↓ MuRF1↓, Sirt1↑, IGF-1↑.	Muscle mass↑	43

NO	HERBALS NAME	BIOMOLLECULAR MECHANISM	EFFECTS	REF.
23	Zanthoxylum alkylamides	Sample: skeletal muscle and liver. Insulin receptor↑ , IGF1↑, PI3K↑. Insulin like growth↑ factor 1 receptor↑. PKB↑, mTOR ↑, atrogin-1↓, muscle ring finger1↓, FoxO↓	Muscle weight↑, BUN↓, Total protein↑, Albmin↑.	44
24	Leucin supplementation	Sample: soleus muscle.. Just histopathological study : leucine supplemented rats showed an increase in mean cross-sectional area.	Soleus muscle mass↑	45
25	Silybum marianum L. Gaertn	Sample: serum, liver. MDA↓, TOS↓, OSI↓, TAC↑, TTM↑, In liver : PGC-1α↑, FNDC5↑, Serum : Irisin↑	Bw↑, FBG↓, Insulin level, HOMA-IR↓, ALT↓, AST↓, ALP↓. Billrubin total↓	46
26	Mangiferin	Sample: soleus muscle, plasma, IFN-α↓, IL-6↓, IL-10↓	Body weight↑, LDLc↓, FGF21↓, HDLc↑	47
27	Resverartol	Sample: soleus, gastrocnemius and tibialis aterior muscle. PKA↑, LKB1↑, AMPK↑, PGC-1α↑, ROS↓, mTOR↑, FoxO3a↑, MHC↑.	Bw↑, Grip strength↑	48
28	Tomato	Sample: blood, gastrocnemius and soleus.C2C12↑, MyHC I↑, MyHCIIb↓, MyHC I↓	Skeletal muscle mass↑ Fiber-type composition↑, TG↓	22
29	Aqueous extract of Syzygium paniculatum Gaertn	Sample: liver, kidney, muscle. Thiobarbituric acid reactive substrate (TBARS) ↓, Malondialdehyde (MDA) ↓ GPx↑, SOD↑, GST↑.	FBG↓, Muscle glycogen↑, HbA1C↓, TC↓, TG↓, HDL↑, AST↓, ALT↓, ALP↓, TP↑, Vitamin C↑, GSH↑, Repair in the exocrine acinar cell, silets of langerhand and cellular of β–cell in pancreatic cells.	49
30	Panax notoginseng saponins	Sample: skeletal muscle, IRS1↑, GLUT4↑, PI3K↑, AKT↑.	TC↓, LDL↓, FBG↓.	50
31	Whole grain cereal	Sample: gastrocnemius. PI3K↑, Akt↑, mTOR↑, MyoD↑, Myogenin↑, FoxO3a↑, Atrogin-1↑, MuRF1↑	Muscle mass↑, Muscle strength↑, LDL↓, TG↑	23
32	Pterostilbene and resveratrol (PTS)	Sample: gastrocnemius muscle and bloods. SIRT1↑, TGF-β1↓, Acetyl histone H3↓	Mix dose more effective for blood glucose and bw. 40 mg/ kg bw more efektiv for decreasing MDA level.	51
33	Brazilian propolis	Sample: soleus muscle. P53↓, TSP-1↓, VEGF↑	Body weight↑, Muscle weight↑.	24

NO	HERBALS NAME	BIOMOLLECULAR MECHANISM	EFFECTS	REF.
35	Extract annatto and green tea polyphenol	Sample: soleus, gastrocnemius muscle, pancreas, and blood. IRS-1↑, Akt↑, GLUT4↑.	Muscle mass↑, Body weight↑ Blood glucose↓, Lipid peroxidation↓.	26
36	Extract of synsepalum	Sample: blood, liver, pancreas, kidneys Catalase↑, SOD↑, GST↑, GPx↑.	Blood glucose↓, Total protein↑, AST↓, ALT↓, TG↓, HDL↑.	26
37	Red bean extract	Sample: gastrocnemius and soleus, tibialis anterior, and extensor digitorum longus muscle. MuRF1↓, FoxO3↑, Atrogin-1↓, PI3K/Akt↑, mTOR↑, NF-kB↓, TNF-α↓, IL-6↓.	Grip strength↑, Running time↑, Running distance↑, Muscle mass↑	27
38	Moringa concanensis	Sample: Gastrocnemius muscle. PPAR-γ↑, C/EBP-α↑, t-SREBPs↑, FAS↑ GLUT-4↓, Adipogenin↑, DAG↑, LPL↑, Akt↑.	Bw↑, Insulin level↓, BG↓, HbA1c↓, amylase↓, cholesterol↓, TG↓, HDL↑, LDL↓, VLDL↓.	52
39	Extract rambutan peels phenolic	Sample: liver, kidney, pancreas. Hepatic glicogen↑, SOD↑, GSH-Px↑, MDA↓.	Bw↑ , BG↓, FBG↓, TC↓, TG↓, Total protein↑, creatinin↓, HbA1c↓.	53

↑ : increase; ↓ : decrease.

eating foods containing herbal medicine, it can activate normal autophagy.[74]

There are several herbal medicines that can activate autophagy and gene expression of the autophagy pathway preventing muscle atrophy. Such gene expression pathways includes: MAPK15 (mitogen-activated protein kinase15), ULK1,2 (UNC-51-like kinase 1 and 2), AMPK (AMP protein kinase), Beclin1, and ATG (autophagy-related proteins 7).[75]

3.8. Antioxidant potential of herbal medicine

Antioxidants are molecular substances that can neutralize free radicals or prevent the oxidation of other components. Besides, it can prevent fats and oils in food via oxidative degradation. Some herbal medicines can activate anti-oxidant enzymes, thus avoiding oxidative stress that leads to muscle atrophy.[76]

Food ingredients with high levels of antioxidants (Table 1) include: Catalpol Extract, Rattan tea, Dokhwalgisaeng-tang, Nigella Sativa Oil, Brazilian propolis, and Moringa concanensis. It can be induced by herbal medicines include SOD (superoxide dismutase), catalase, MDA (Malondialdehyde), NADPH (Nicotinamide adenine dinucleotide phosphate) GST (Glutathione-S-Transferase), GPX (glutathione peroxidase).[77]

3.9. Glucose utilization potential of herbal medicine

GLUT-4 is the central glucose carrier, located in muscle and fat cells. GLUT-4 is

different from other glucose carriers because it is generally located at the intracellular which is lack of insulin stimulation.[78] Furthermore, there is a decrease in glucose transport into cell. Intracellular movement of GLUT-4 begins with sufficient insulin in the blood to the transmembrane insulin receptor and sufficient GLUT-4 translocatoan to the cell membrane for glucose uptake into the cell.[79]

GLUT-4 translocation to cell membranes can be activated by herbal medicines other than exercise.[80,81] Drugs that significantly activate glucose utilization include *Centella asiatica/ gotu kola extract, wushenziye formula, carica papaya seed, berberine, panax ginseng, saponins, extract annatto and green tea polyphenols,* and *moringa concanensis.* These herbal medicines have target genes such as HK (Hexokinase), GLUT4, PFK (phosphofructokinase), HK (hexokinase) FBPase (fructose 1,6-bisphosphatase), GS (glycogen synthase) and GP (glycogen phophorylase).[82] Activation of glucose utilization can improve muscle atrophy, and insulin concentration in the blood, which is followed by an increase in GLUT-4. Herbal medicine can activate IRS-1 and Akt in chronic disease. In addition, these herbal medicines can increase mitochondrial biogenesis by activating SIRT1, SIRT3 and AMPK in diabetic muscle.[83]

5. Conclusion

Herbal medicine significantly improved muscle strength and muscle mass in chronic diseases, especially T2DM. Pharmacologically, these herbs suppressed inflammation, increased protein synthesis and apoptosis, activated antioxidants, suppressed autophagy, and increased glucose utilization. Therefore, this review demonstrates that herbal medicine is suitable as adjuvant therapy for muscle atrophy conditions in various chronic diseases.

Reference

1. O'Neill BT, Bhardwaj G, Penniman CM, Krumpoch MT, Beltran PAS, Klaus K, et al. FoxO transcription factors are critical regulators of diabetes-related muscle atrophy. 2019;68(3):556-70.
2. Mesinovic J, Zengin A, De Courten B, Ebeling PR, Scott D. Sarcopenia and type 2 diabetes mellitus: a bidirectional relationship. Diabetes, metabolic syndrome and obesity: targets and therapy. 2019:1057-72.
3. Siavash M, Tabbakhian M, Sabzghabaee AM, Razavi NJJoripp. Severity of gastrointestinal side effects of metformin tablet compared to metformin capsule in type 2 diabetes mellitus patients. 2017;6(2):73.
4. Kim CH, Han KA, Oh HJ, Tan KEK, Sothiratnam R, Tjokroprawiro A, Klein MJJod. Safety, tolerability, and efficacy of metformin extended-release oral antidiabetic therapy in patients with type 2 diabetes: An observational trial in Asia. 2012;4(4):395-406.
5. Choudhury H, Pandey M, Hua CK, Mun CS, Jing JK, Kong L, et al. An update on natural compounds in the remedy of diabetes mellitus: A systematic review. 2018;8(3):361-76.
6. Tran DNH, Hwang I-H, Chen F-J, Tseng Y-P, Chang C-M, Tsai S-J, et al. Core prescription pattern of Chinese herbal medicine for depressive disorders in Taiwan: a nationwide population-based study. 2021;10(3):100707.
7. Hirata Y, Nomura K, Senga Y, Okada Y, Kobayashi K, Okamoto S, et al. Hyperglycemia induces skeletal muscle atrophy via a WWP1/KLF15 axis. 2019;4(4).
8. Giglio J, Kamimura MA, Lamarca F, Rodrigues J, Santin F, Avesani CMJJoRN. Association of sarcopenia with nutritional parameters, quality of life, hospitalization, and mortality rates of elderly patients on hemodialysis. 2018;28(3):197-207.
9. Khalil RJMA. Ubiquitin-proteasome pathway and muscle atrophy. 2018:235-48.
10. Sartori R, Romanello V, Sandri MJNC. Mechanisms of muscle atrophy and hypertrophy: Implications in health and disease. 2021;12(1):1-12.
11. Chen L, Chen L, Wan L, Huo Y, Huang

J, Li J, et al. Matrine improves skeletal muscle atrophy by inhibiting E3 ubiquitin ligases and activating the Akt/mTOR/FoxO3α signaling pathway in C2C12 myotubes and mice. 2019;42(2):479-94.
12. Yadav A, Singh A, Phogat J, Dahuja A, Dabur RJJoE. Magnoflorine prevent the skeletal muscle atrophy via Akt/mTOR/FoxO signal pathway and increase slow-MyHC production in streptozotocin-induced diabetic rats. 2021;267:113510.
13. Jeddi S, Gheibi S, Carlström M, Kashfi K, Ghasemi A. Long-term co-administration of sodium nitrite and sodium hydrosulfide inhibits hepatic gluconeogenesis in male type 2 diabetic rats: Role of PI3K-Akt-eNOS pathway. Life Sciences. 2021;265:118770.
14. Jin D, Tian J, Bao Q, Zhang H, Ding Q, Lian F, Xiao-Lin T. Does Adjuvant Treatment with Chinese Herbal Medicine to Antidiabetic Agents Have Additional Benefits in Patients with Type 2 Diabetes? A System Review and Meta-Analysis of Randomized Controlled Trials. Evid Based Complement Alternat Med. 2019;2019:1825750.
15. Wang D, Chen J, Liu X, Zheng P, Song G, Yi T, Li SJSR. A Chinese herbal formula, Jian-Pi-Yi-Shen decoction, improves muscle atrophy via regulating mitochondrial quality control process in 5/6 nephrectomised rats. 2017;7(1):1-12.
16. Cho S, Hong R, Yim P, Yeom M, Lee B, Yang WM, et al. An herbal formula consisting of Schisandra chinensis (Turcz.) Baill, Lycium chinense Mill and Eucommia ulmoides Oliv alleviates disuse muscle atrophy in rats. 2018;213:328-39.
17. Wang Y, Shao Y, Gao Y, Wan G, Wan D, Zhu H, et al. Catalpol prevents denervated muscular atrophy related to the inhibition of autophagy and reduces BAX/BCL2 ratio via mTOR pathway. 2019;13:243.
18. Ishida T, Iizuka M, Ou Y, Morisawa S, Hirata A, Yagi Y, et al. Juzentaihoto hot water extract alleviates muscle atrophy and improves motor function in streptozotocin-induced diabetic oxidative stress mice. 2019;73(1):202-9.
19. Park K-S, Kim HJ, Hwang JT, Ko BSJJoFF. Dioscorea nipponica extracts enhance recovery from skeletal muscle atrophy by suppressing NF-κB expression. 2020;73:104109.
20. Wang D, Sun H, Song G, Yang Y, Zou X, Han P, et al. Resveratrol improves muscle atrophy by modulating mitochondrial quality control in STZ-induced diabetic mice. 2018;62(9):1700941.
21. Liu S, Yang D, Yu L, Aluo Z, Zhang Z, Qi Y, et al. Effects of lycopene on skeletal muscle-fiber type and high-fat diet-induced oxidative stress. The Journal of Nutritional Biochemistry. 2021;87:108523.
22. Lee S, Kim M-B, Kim C, Hwang J-K. Whole grain cereal attenuates obesity-induced muscle atrophy by activating the PI3K/Akt pathway in obese C57BL/6N mice. Food Science and Biotechnology. 2018;27(1):159-68.
23. Tanaka M, Kanazashi M, Maeshige N, Kondo H, Ishihara A, Fujino HJTJoPS. Protective effects of Brazilian propolis supplementation on capillary regression in the soleus muscle of hindlimb-unloaded rats. 2019;69(2):223-33.
24. Huang Z, Fang Q, Ma W, Zhang Q, Qiu J, Gu X, et al. Skeletal muscle atrophy was alleviated by salidroside through suppressing oxidative stress and inflammation during denervation. 2019;10:997.
25. Chung E, Campise SN, Joiner HE, Tomison MD, Kaur G, Dufour JM, et al. Effect of annatto-extracted tocotrienols and green tea polyphenols on glucose homeostasis and skeletal muscle metabolism in obese male mice. 2019;67:36-43.
26. Kim C, Kim M-B, Hwang J-KJJomf. Red bean extract inhibits immobilization-induced muscle atrophy in C57BL/6N mice. 2020;23(1):29-36.
27. Ou L, Kang W, Zhang J, Liang Z, Li M, Gao F, Chen LJACB. Effects of Rehmannia glutinosa polysaccharides on bone tissue structure and skeletal muscle atrophy in rats with disuse. 2021;36.
28. Oyenihi AB, Langa SO, Mukaratirwa S,

Masola BJB, Pharmacotherapy. Effects of Centella asiatica on skeletal muscle structure and key enzymes of glucose and glycogen metabolism in type 2 diabetic rats. 2019;112:108715.
29. Tseng Y-T, Chang W-H, Lin C-C, Chang F-R, Wu P-C, Lo Y-CJP. Protective effects of Liuwei dihuang water extracts on diabetic muscle atrophy. 2019;53:96-106.
30. Kou X, Li J, Liu X, Yang X, Fan J, Chen NJB, Pharmacotherapy. Ampelopsin attenuates the atrophy of skeletal muscle from d-gal-induced aging rats through activating AMPK/SIRT1/PGC-1α signaling cascade. 2017;90:311-20.
31. Gong HM, Lee YK, Lee BH, Kim JS, Lee H-JJJoAR. The Effects of Dokhwalgisaeng-tang against disuse muscle atrophy in gastrocnemius of rats. 2018;35(4):207-13.
32. Geng Z, Wei L, Zhang C, Yan XJE, medicine t. Astragalus polysaccharide, a component of traditional Chinese medicine, inhibits muscle cell atrophy (cachexia) in an in vivo and in vitro rat model of chronic renal failure by activating the ubiquitin-proteasome pathway. 2017;14(1):91-6.
33. Yoshioka Y, Yamashita Y, Kishida H, Nakagawa K, Ashida HJLs. Licorice flavonoid oil enhances muscle mass in KK-Ay mice. 2018;205:91-6.
34. Tian C, Chang H, La X, Li J-aJE-BC, Medicine A. Wushenziye formula improves skeletal muscle insulin resistance in type 2 diabetes mellitus via PTP1B-IRS1-Akt-GLUT4 signaling pathway. Hindawi. 2017;2017.
35. Pal S, Mittapelly N, Husain A, Kushwaha S, Chattopadhyay S, Kumar P, et al. A butanolic fraction from the standardized stem extract of Cassia occidentalis L delivered by a self-emulsifying drug delivery system protects rats from glucocorticoid-induced osteopenia and muscle atrophy. Scientific Reports. 2020;10(1):195.
36. Oza MJ, Kulkarni YAJFip. Formononetin treatment in type 2 diabetic rats reduces insulin resistance and hyperglycemia. 2018;9:739.
37. Pratiwi YS, Lesmana R, Goenawan H, Sylviana N, Setiawan I, Tarawan VM, et al. Nutmeg extract increases skeletal muscle mass in aging rats partly via IGF1-AKT-mTOR pathway and inhibition of autophagy. 2018;2018.
38. Grant SJ, Chang DH, Liu J, Wong V, Kiat H, Bensoussan A. Chinese herbal medicine for impaired glucose tolerance: a randomized placebo controlled trial. BMC Complement Altern Med. 2013;13:104.
39. Abdelrazek H, Kilany OE, Muhammad MA, Tag HM, Abdelazim AMJOm, longevity c. Black seed thymoquinone improved insulin secretion, hepatic glycogen storage, and oxidative stress in streptozotocin-induced diabetic male wistar rats. 2018;2018.
40. Wulansari DD, Wulandari DD, Risthanti RR, Kirtishanti AJMPI. Ameliorative Effect of Carica papaya Seed Extract on Diabetic Rat Model with Muscle Atrophy. 2019;2(4):208-15.
41. Yu Y, Zhao Y, Teng F, Li J, Guan Y, Xu J, et al. Berberine improves cognitive deficiency and muscular dysfunction via activation of the AMPK/SIRT1/PGC-1a pathway in skeletal muscle from naturally aging rats. 2018;22(6):710-7.
42. Morita Y, Ishida T, Morisawa S, Jobu K, Ou Y, Fujita H, et al. Juzentaihoto Suppresses Muscle Atrophy and Decreased Motor Function in SAMP8 Mice. 2021;44(1):32-8.
43. Ren T, Zhu Y, Xia X, Ding Y, Guo J, Kan JJJome. Zanthoxylum alkylamides ameliorate protein metabolism disorder in STZ-induced diabetic rats. 2017;58(3):113.
44. Gawada NK. The effect of leucine supplementation on the skeletal muscles of streptozotocin (STZ)diabetic rats %J Records of Pharmaceutical and Biomedical Sciences. 2018;2(1):22-5.
45. Kheiripour N, Karimi J, Khodadadi I, Tavilani H, Goodarzi MT, Hashemnia MJIjoms. Hepatoprotective effects of silymarin on liver injury via irisin upregulation and oxidative stress reduction in rats with type 2 diabetes. 2019;44(2):108.
46. Acevedo LM, Raya AI, Martinez-Moreno JM, Aguilera–Tejero E, Rivero J-LLJPo.

Mangiferin protects against adverse skeletal muscle changes and enhances muscle oxidative capacity in obese rats. 2017;12(3):e0173028.
47. H, Zhang Y, Hou P, et al. Resveratrol prevents sarcopenic obesity by reversing mitochondrial dysfunction and oxidative stress via the PKA/LKB1/AMPK pathway. 2019;11(8):2217.
48. Konda PY, Dasari S, Konanki S, Nagarajan PJH. In vivo antihyperglycemic, antihyperlipidemic, antioxidative stress and antioxidant potential activities of Syzygium paniculatum Gaertn. in Streptozotocin-induced diabetic rats. 2019;5(3):e01373.
49. Guo X, Sun W, Luo G, Wu L, Xu G, Hou D, et al. Panax notoginseng saponins alleviate skeletal muscle insulin resistance by regulating the IRS 1–PI 3K–AKT signaling pathway and GLUT 4 expression. 2019;9(5):1008-19.
50. Tastekin B, Pelit A, Polat S, Tuli A, Sencar L, Alparslan MM, et al. Therapeutic potential of pterostilbene and resveratrol on biomechanic, biochemical, and histological parameters in streptozotocin-induced diabetic rats. 2018;2018.
51. Balakrishnan BB, Krishnasamy K, Choi KCJB, Pharmacotherapy. Moringa concanensis Nimmo ameliorates hyperglycemia in 3T3-L1 adipocytes by upregulating PPAR-γ, C/EBP-α via Akt signaling pathway and STZ-induced diabetic rats. 2018;103:719-28.
52. Ma Q, Guo Y, Sun L, Zhuang YJN. Anti-diabetic effects of phenolic extract from rambutan peels (Nephelium lappaceum) in high-fat diet and streptozotocin-induced diabetic mice. 2017;9(8):801.
53. Okamoto T, Machida SJBR. Changes in FOXO and proinflammatory cytokines in the late stage of immobilized fast and slow muscle atrophy. 2017;38(6):331-42.
54. Miyawaki A, Rojasawasthien T, Hitomi S, Aoki Y, Urata M, Inoue A, et al. Oral Administration of Geranylgeraniol Rescues Denervation-induced Muscle Atrophy via Suppression of Atrogin-1. 2020;34(5):2345-51.
55. Rajendran NK, Kumar SSD, Houreld NN, Abrahamse HJJocc, signaling. Understanding the perspectives of forkhead transcription factors in delayed wound healing. 2019;13(2):151-62.
56. Zhiyin L, Jinliang C, Qiunan C, Yunfei Y, Qian XJB, Pharmacotherapy. Fucoxanthin rescues dexamethasone induced C2C12 myotubes atrophy. 2021;139:111590.
57. Li J, Chan MC, Yu Y, Bei Y, Chen P, Zhou Q, et al. miR-29b contributes to multiple types of muscle atrophy. 2017;8(1):1-15.
58. Kazemi FJC. Myostatin alters with exercise training in diabetic rats; possible interaction with glycosylated hemoglobin and inflammatory cytokines. 2019;120:99-106.
59. Chiu CY, Yang RS, Sheu ML, Chan DC, Yang TH, Tsai KS, et al. Advanced glycation end-products induce skeletal muscle atrophy and dysfunction in diabetic mice via a RAGE-mediated, AMPK-down-regulated, Akt pathway. 2016;238(3):470-82.
60. Perry BD, Caldow MK, Brennan-Speranza TC, Sbaraglia M, Jerums G, Garnham A, et al. Muscle atrophy in patients with Type 2 Diabetes Mellitus: roles of inflammatory pathways, physical activity and exercise. 2016;22:94.
61. Jacobs BL, You JS, Frey JW, Goodman CA, Gundermann DM, Hornberger TAJTJop. Eccentric contractions increase the phosphorylation of tuberous sclerosis complex-2 (TSC2) and alter the targeting of TSC2 and the mechanistic target of rapamycin to the lysosome. 2013;591(18):4611-20.
62. Green CJ, Pedersen M, Pedersen BK, Scheele CJD. Elevated NF-κB activation is conserved in human myocytes cultured from obese type 2 diabetic patients and attenuated by AMP-activated protein kinase. 2011;60(11):2810-9.
63. Patsouris D, Cao J-J, Vial G, Bravard A, Lefai E, Durand A, et al. Insulin resistance is associated with MCP1-mediated macrophage accumulation in skeletal muscle in mice and humans. 2014;9(10):e110653.

64. Bassil MS, Gougeon RJCOiCN, Care M. Muscle protein anabolism in type 2 diabetes. 2013;16(1):83-8.
65. Liu GY, Sabatini DMJNRMCB. mTOR at the nexus of nutrition, growth, ageing and disease. 2020;21(4):183-203.
66. Elmore SJTp. Apoptosis: a review of programmed cell death. 2007;35(4):495-516.
67. Favaloro B, Allocati N, Graziano V, Di Ilio C, De Laurenzi VJA. Role of apoptosis in disease. 2012;4(5):330.
68. Wang Y, Shao Y, Gao Y, Wan G, Wan D, Zhu H, et al. Catalpol prevents denervated muscular atrophy related to the inhibition of autophagy and reduces BAX/BCL2 ratio via mTOR pathway. Drug Design, Development and Therapy. 2018:243-53.
69. D'arcy MS. Cell death: a review of the major forms of apoptosis, necrosis and autophagy. Cell biology international. 2019;43(6):582-92.
70. New J, Thomas SMJA. Autophagy-dependent secretion: mechanism, factors secreted, and disease implications. 2019;15(10):1682-93.
71. Fan Y, Wang N, Rocchi A, Zhang W, Vassar R, Zhou Y, He CJA. Identification of natural products with neuronal and metabolic benefits through autophagy induction. 2017;13(1):41-56.
72. Rocchi A, He CJCpr. Regulation of exercise-induced autophagy in skeletal muscle. 2017;5(2):177-86.
73. Colecchia D, Dapporto F, Tronnolone S, Salvini L, Chiariello MJJoBC. MAPK15 is part of the ULK complex and controls its activity to regulate early phases of the autophagic process. 2018;293(41):15962-76.
74. Yashin A, Yashin Y, Xia X, Nemzer B. Antioxidant Activity of Spices and Their Impact on Human Health: A Review. 2017;6(3):70.
75. Assefa B, Mahmoud AM, Pfeiffer AF, Birkenfeld AL, Spranger J, Arafat AMJOm, longevity c. Insulin-like growth factor (IGF) binding protein-2, independently of IGF-1, induces GLUT-4 translocation and glucose uptake in 3T3-L1 adipocytes. 2017;2017.
76. Jaldin-Fincati JR, Pavarotti M, Frendo-Cumbo S, Bilan PJ, Klip AJTiE, Metabolism. Update on GLUT4 vesicle traffic: a cornerstone of insulin action. 2017;28(8):597-611.
77. Flores-Opazo M, Boland E, Garnham A, Murphy RM, McGee SL, Hargreaves MJPr. Exercise and GLUT4 in human subcutaneous adipose tissue. 2018;6(22):e13918.
78. Rachmani EPN. Effect flavonoid enriched fractio increase GLUT-4 translocat 2018.
79. Lee H, Lim YJTJonb. Tocotrienol-rich fraction supplementation reduces hyperglycemia-induced skeletal muscle damage through regulation of insulin signaling and oxidative stress in type 2 diabetic mice. 2018;57:77-85.