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AN UPDATE ON THE THERAPEUTIC POTENTIAL OF HERBAL PREPARATIONS WITH REGARDS TO MOLECULAR & BIOCHEMICAL MECHANISMS IN THE MANAGEMENT OF DIABETES MELLITUS: A SYSTEMATIC REVIEW

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ABSTRACT

Evaluation of Diabetesmellitus (DM)kinds has demonstrated significant patterns. Of these the ones of maximum importance are inclusive of Oxidative stress,inflammation in addition to cellular demise .Till date drug treatments for DM are not optimal,hence need for innovative therapy has assumed great significance that is key for trying to discover the same. In the past decades medicinal plants have got thoroughly explored as well as their utilization is being escalatingly done in the form of alternative ones as natural product s with the idea of curing the disease. We had reviewed various phytochemical therapiesearlier that were inclusive of Dietary polyphenols, like resveratrol,curcumin, proteintyrosine phosphatase1 B (PTP1B) inhibitors, plant terpenes (specifically monoterpenes), flavonoids (quercetin, kaempherol), ursolic acid, besides epigenetic modes of certain plant agents. Our aim was to extensively evaluate the modes of biochemical actions in control of DM, to be able to utilize them clinically. Here we conducted a systematic review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms likeDM; Plant preparations from Nigella Sativa(NS**);** Berberine(Ber); curcumin(CUR); Moringa Olifera(MO); Portulaca Oleracea(PO); Punica Granatum(PG); typeIIID Mor Alzheimer'sdisease; 5'AMP-activatedprotein kinase(AMPK); STAT3, PI3K/Akt; PTP1BInhibiors; IRS1;2; NADPH Oxidase; AGE; RAGE; NFκB,; proinflammatory cytokines; COVID19 from 2010 till date. Although main idea was to include human studies, we did include animal studies for validation of biochemical mode to help in their utilization with oral hypoglycaemic agents infuture if not alone. We found a total of 3600 articles out of which we selected 168 articles for this review. No meta-analysis was done. It was observd that most of these 6 major plants studied(NS,Ber, CUR, MO, PO, PG,targeted 5'(adenosine monophosphate (AMP)-activated protein kinase(AMPK) actionthat was followed by down stream actions of ACC,Akt as well as PI3K by which they ameliorated the disease. Thus with least toxicity, economical, easy access it is warranted to get over whatever bioavailability, problems we have faced with drugs like curcumin sothat they can get easily used singly or for reduction of oral antidiabetics.

KEYWORDS: DM;herbal plants; NS, Ber; CUR; MO; PO; PG; AMPK; DM complications.

1. INTRODUCTION

Type II Diabetes mellitus(DM) represents a chronic endocrinology aberration, with its harmful action has become a big challenge with regards to its avoidance in addition to treatment.[1] It gets classified into 3 major types, type I, type II, type III DM.[2] The one that gets acquired is characterized as typeII, in view of it being, basically an insulin resistance(IR) syndrome.[3] The different fatal harmful actions are inclusive of Diabetic retinopathy, Nephropathy end stage renal Disease(ESRD), Diabetic cardiomyopathy, Diabetic gastroenteropathy, Heart failure (HF; HF with conserved

(≥50%) ejection fraction(HFpEF), with HF with decreased (<40%) ejection fraction(HFrEF),Diabetic myonecrosis, erectile dysfunction[[reviewed byus]diabetic foot,[4] ii) diabetic bone disease,[5] iii) diabetic neuropathy,[6] along with reduction in resistance to bacterial as well as viral infections through having an influence on innate immunity.[7] The molecular mode of action occurs secondary to abnormalities in the kinase molecular signaling pathways,namely phosphatidyl inositide 3 -kinase(PI3K) / protein kinase B(AKT), p38 mitogen activated protein kinase(p38 MAPK), calmodulin kinase,that impact glucose metabolism along with insulin effects.[8]

Numerous synthetic anti diabetic therapeutic agents like Sodium –glucose cotransporter 2(SGLT2) inhibitors,[9] dipeptidyl peptidase -4 (DPP-4) inhibitors.[10] glucagon like peptide 1(GLP-1)-analogs,[11] Sulfonylureas,[12] thiazolidenediones.[13] along with biguanides,[14] are existent. Nevertheless,for last 2 decades,the innovative science that implicates treatment with natural product has been emphasized for reduction of certain chronic diseases that are inclusive of typeII DM.[15] The active constituents, in this natural treatment might possess antidiabetic action,like nonflavonoid polyphenols like curcumin,tannins,lignans as well as resveratrol.[16] or flavonoids like anthrocyanins, epigallocatechin gallate(EGCG),quercetin,naringin,rutin along with kaempherol.[17]

Briefly maximum polyphenols along with flavonoids display their anti diabetic action through enhancement of glucose regulation insulin sensitivity,[16] hampering oxidative stress(OS),[17] resulting in reduction of proinflammatory cytokines amounts,[18] hampering α-amylase along with α-glucosidase action,besides escalation of tyrosine phosphorylation of insulin as well as insulin receptor.[20] Earlier we had reviewed various phytochemical therapies that were inclusive of Dietary polyphenols, like resveratrol,curcumin, proteintyrosine phosphatase1 B(PTP1B) inhibitors, plant terpenes (specifically monoterpenes), flavonoids (querceetin,kaempherol),ursolic acid, besides epigenetic modes of certain plant agents.Here we tried to extensively evaluate the modes of biochemical actions in control of DM.[21-27]

METHODS

Here we conducted a systematic review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like DM; Plant preparations from Nigella Sativa**;** Berberine; curcumin; Moringa Olifera; Portulaca Oleracea; Punica Granatum; typeIII DM or Alzheimer'sdisease;5'AMP-activatedproteinkinase(AMPK);STAT3,PI3K/Akt;PTP1 BInhibiors;IRS1;2;NADPH Oxidase; AGE;RAGE; NFκB,; proinflammatory cytokines;COVID19 from 2010 till date. Although main idea was to include human studies, we did include animal studies for validation of biochemical mode to help in their utilization with oral hypoglycaemic agents in future if not alone.

RESULTS

We found a total of 3600 articles out of which we selected 168 articles for this review.No meta-analysis was done.

2. Diabetes mellitus

2.1Prevalence Pathophysiology, molecular modes of DM

Having assumed maximum significance at the International platform in the form of Public Health hazard it has generated marked interest amongst scientists. It has been anticipated that by 2030 this silent killer would have escalated so much that the diabetic individuals would assume such high proportions of578 million (besides reaching 700 million by 2045).[28] DM represents a chronic metabolic condition,with 2 isolated kinds, insulin dependent Diabetes mellitus(IDDM) along with non insulin dependent Diabetes mellitus(NIDDM). IDDM is believed to be an autoimmune condition that occurs secondary to damage of βcells of the islets of Langerhans in the Pancreas.[29] Conversely, NIDDM takes place secondary to stress factors,obesity, hormonal disturbances,where over generation of insulin as well as amylin hormones occurs from the βcells of the islets of Langerhans,[30] in addition to reduction in adiponectin, Calcium(Ca^{2+})25 hydroxy Vitamin D.[31] More recently, Alzheimer'sdisease was labeled as typeIIIDM.[32] that is mostly correlated with amyloid β plaques in addition to phosphorylated tau protein collection in hippocampus of the brain.[33] The other kinds of DM are transitory like Gestational Diabetes mellitus(GDM),that takes place in second or third trimester of pregnancy in females,disappearing subsequent to parturition.[34] Moreover, in certain situations DM takes place secondary to total or part dissection of the Pancreas subsequent to certain disease that are associated with tumours or robust inflammation.[35]

Summary

The Pancreatic βcells not possessing the capacity of generation of insulin in IDDM,[36] or insulin resistance(IR),[37] influences the incapacity of insulin to conduct its function, that results in, hyperglycemia, polydipsia, weight reduction, delay with regards to wound repair along with blurring of vision.[38] Hyperglycemia by itself results in the generation of advanced glycation end-products(AGE)along with their receptors, ie receptor advanced glycation end-products (RAGE).[39] In this context in particular NIDDM is correlated with the facilitation of free radicals in the mitochondrial matrix which results in destruction of numerous biomolecules of the cell like deoxy ribonucleic acid(DNA)lipids as well as proteins.[40] Thus as a consequence this causes escalated proneness towards chronic inflammation in addition to apoptosis, besides interfering with the working of different organs.[41]

Conversely, AGE along with their receptors result in escalation of nicotinamide adenine nucleotide phosphate(NADPH)oxidases in addition to their messenger ribonucleic acid(mRNA) besides arachidonic acid pathways.[42] The crosstalk of AGEs with its receptors RAGE causes stimulation of certain Signal transduction pathway like PKC, PI3K/ AKT,[43] p38 MAPK,[44] extracellular signal –regulated kinase (ERK1/2),[45] RhoA/ RhoA kinase that stimulate downstream kinases besides modulates Ca^{2+} sensitization,[46]janus kinase / Signal Transducers and Activators of Transcription(JAK/STATs), in addition to SOCS3(Suppressor of cytokines signaling 3).[47] Moreover, an impairment, of 5' AMP-activated protein kinase(AMPK) action through hampering of gluconeogenesis genes,[48] down regulation of glucose transporter 4 (GLUT4),[49] stimulation of lipogenesis genes via escalation of HMG CoA reductase action.[50] besides start of mitochondrial axonal cell demise.[51] Consequetly the stimulated signals being an escalation of the transcription factors which are nuclear factor κB(NFκB).[52] as well as early growth response -1)Egr-1 protein,that represents a key zinc finger transcription factors[53]ii) changes in cell metabolism iii) stimulation of inflammation, apoptosis along with proliferation of the NOD –like receptor protein(NLRP3) inflammasome.[54] The cytokines, that are generated include tumor necrosis factor alpha(TNFα),MCP1, interleukin-6(IL-6), as well as IL-1β.[55]All these cytokines resulted in impairment of insulin signaling in addition to peripheral glucose uptake that generate insulin resistance, lipolysis along with hepatic glucose generation.[56]

Furthermore, hyperglycemia in NIDDM is a deleterious problem which imbalances the genetic expression that is required for insulin liberation like sirtuin-1 (Sirt-1) in addition to glucose transporter 2(GLUT2) that is existent in βcells.[57] Moreover, it causes activation of the signaling pathway in adipose tissue as well as skeletal muscle like GLUT4,that takes glucose from the cytoplasm to the membrane in addition to Peroxisome Proliferator Activated Receptor γ(PPARγ).[58] or in hepatic tissue like insulin Receptor substrate-1(IRS-1), serine /threonine /Akt as well as phosphoenol pyruvate carboxykinase (PEPCK1).[59] The molecular mode of insulin resistance is shown in figure1.[60]

2.2Complications correlated with DM

If left without treatment DM cause damage to the small blood vessels of certain organs like Kidney heart, eye as well as nervous system.[61] Thus Diabetic Nephropathy,[62] diabetic cardiomyopathy,[63] retinopathy,[64] diabetic foot infection.[65] are some of the most appreciated complications. Moreover, atrophy of the vagus nerve might take place subsequent to neuronal, or autoimmune injury along with oxidative stress(OS).[66] DM is correlated with numerous musculoskeletal problems like joint stiffness, gouty arthritis, osteo arthritis, rheumatoid arthritis, besides myotonic amyotrophy.[67] In certain persons these negative, influences of DM are correlated with the gut with a reduction in the butyrate generating bacteria with of an escalation of opportunistic pathogens.[68] Furthermore, the incidence of cancer might occur subsequent to DM in certain late stages.[69] A reduction in the salivary liberation in addition to elements is also common in case of patients with type2 Diabetes mellitus.[70] Moreover, diabetic ketoacidosis in addition to hyperglycemic hyperosmolar syndrome are believed to be life threatening risks secondary, to insulin deficiency, that takes place subsequent to DM that causes development of ketone bodies, thus metabolic acidosis occurring.[71] Low immunity has been, demonstrated in certain diabetic individuals making them susceptible to invading fungal infections like filamentous fungus Syncephalastrum recemosum which influence the Gastrointestinal Tract(GIT).[72]

Furthermore, in 2020 it was corroborated by the group of Balbaa etal., with regards to diabetic patients possessed greater susceptibility to get COVID infection in view of their dysfunctional immune system.[73] Under normal circumctances angiotensin converting enzyme(ACE2) expression occurs in βcells of Pancreas, as well as SARS CoV2 virus binding occurs basically to ACE2 resulting in injury of βcells of Pancreas.[74] Noticeably DM causes stimulation of oxidation free radicals in addition to Hypoxia inducible factor 1α(HIF 1α). Escalation of viral replication is stimulated by DM.[75] In case of different tissues some NIDDM situations, are shown infig2 &3.

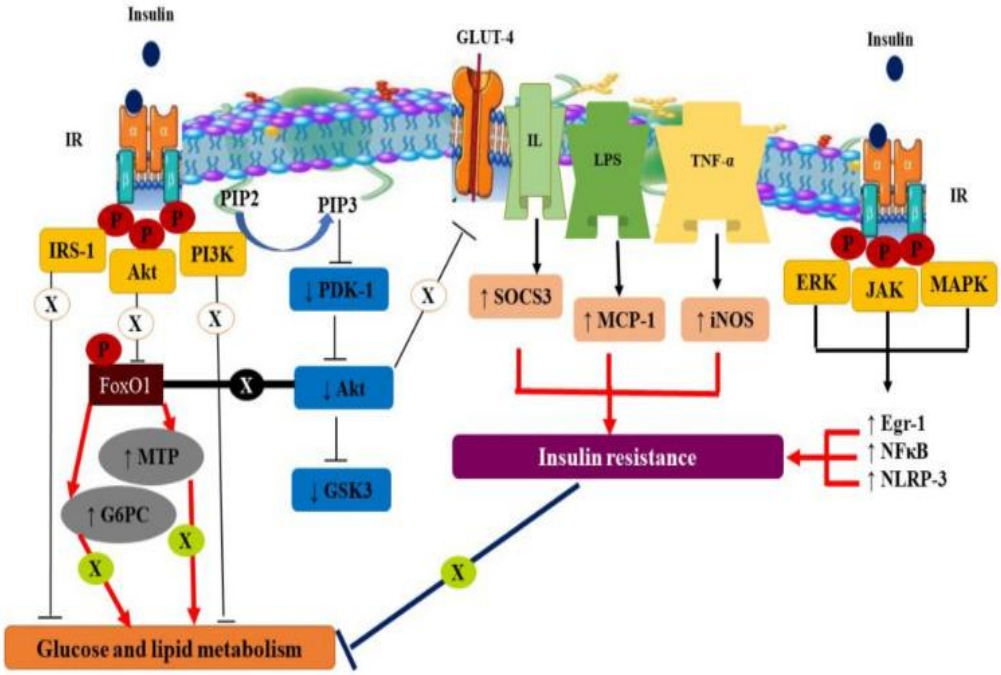


Figure 1: Courtesy refn0-60-Molecular mechanism of insulin resistance. Akt: protein kinase B, IRS-1: insulin receptor substrate-1, PI3K: phosphatidyl inositol-3-kinase, PIP2: phosphatidylinositol 4,5-bisphosphate, PIP3: phosphatidylinositol 3,4,5-trisphosphate, PDK-1: phosphoinositide-dependent protein kinase 1, GSK3: glycogen synthase kinase 3, GLUT-4: glucose transporter-4, IL: interleukin, SOCS3: suppressor of the cytokine signaling, LPS: lipopolysaccharides, MCP-1: monocyte chemoattractant protein-1, TNF-α: tumor necrosis factor-alpha, iNOS: inducible nitric oxide synthase, ERK: extracellular signal-related kinase, JAK: Janus kinase-2, MAPK: mitogen-activated protein kinase, Egr-1: early growth response-1, NF-κB: nuclear factor-kappa B, NLRP-3: NOD-like receptor protein-3, FoxO1: forkhead box O1, MTP: microsomal triacylglycerol transfer protein, G6PC: glucose-6-phosphatase catalytic subunit 1.

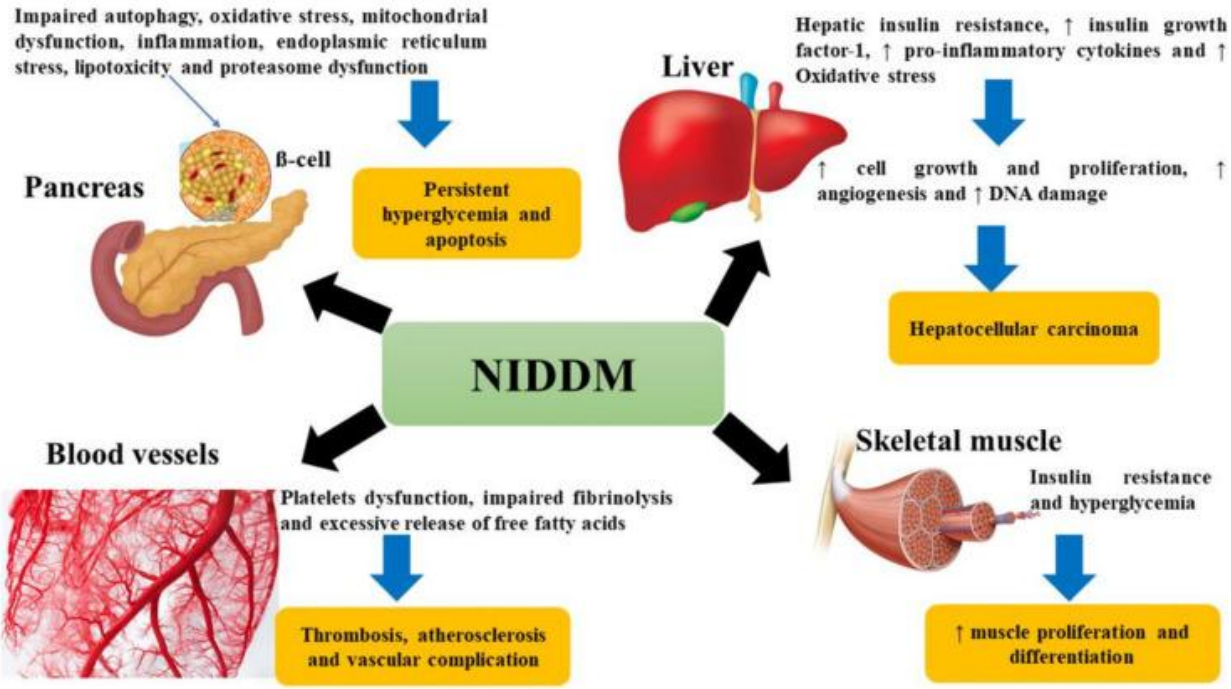
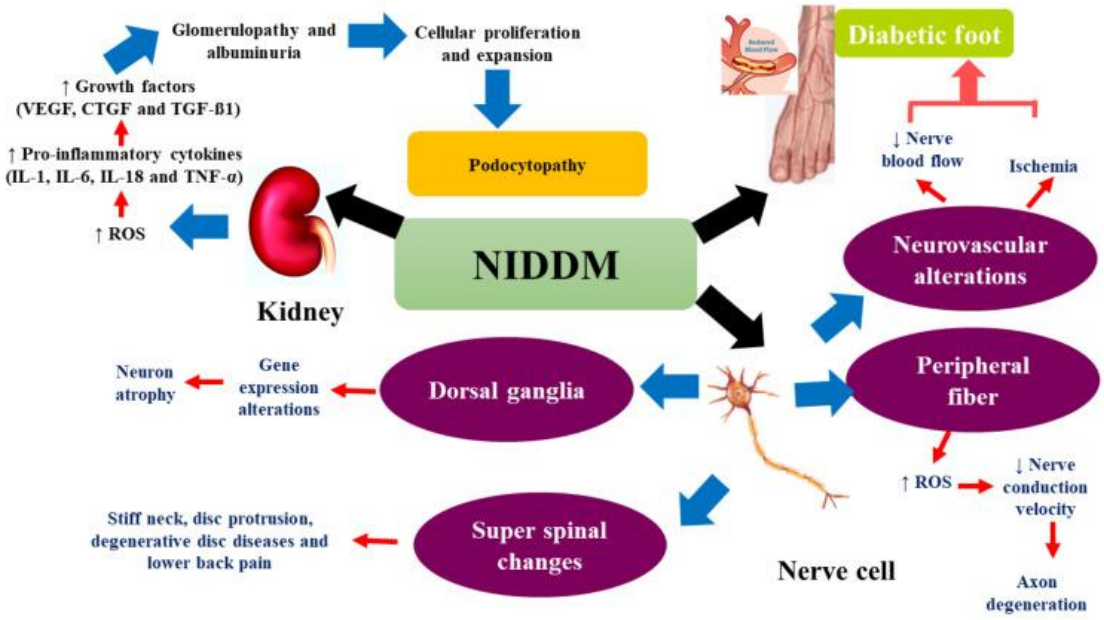
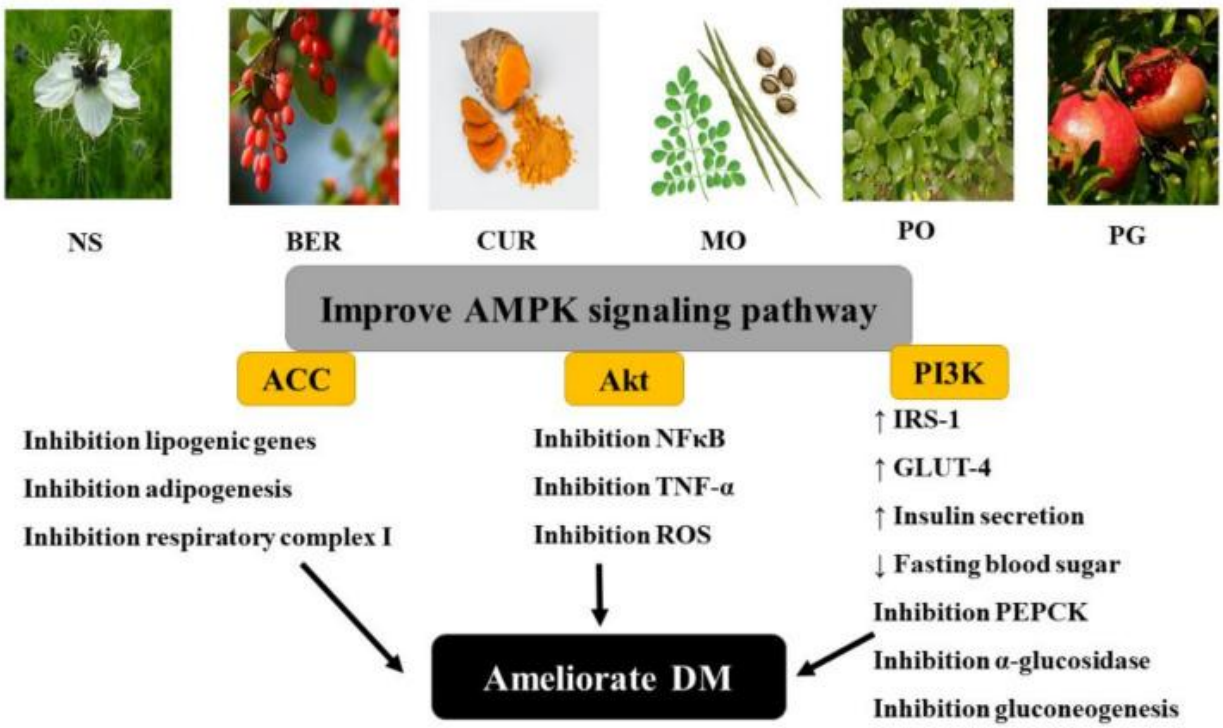


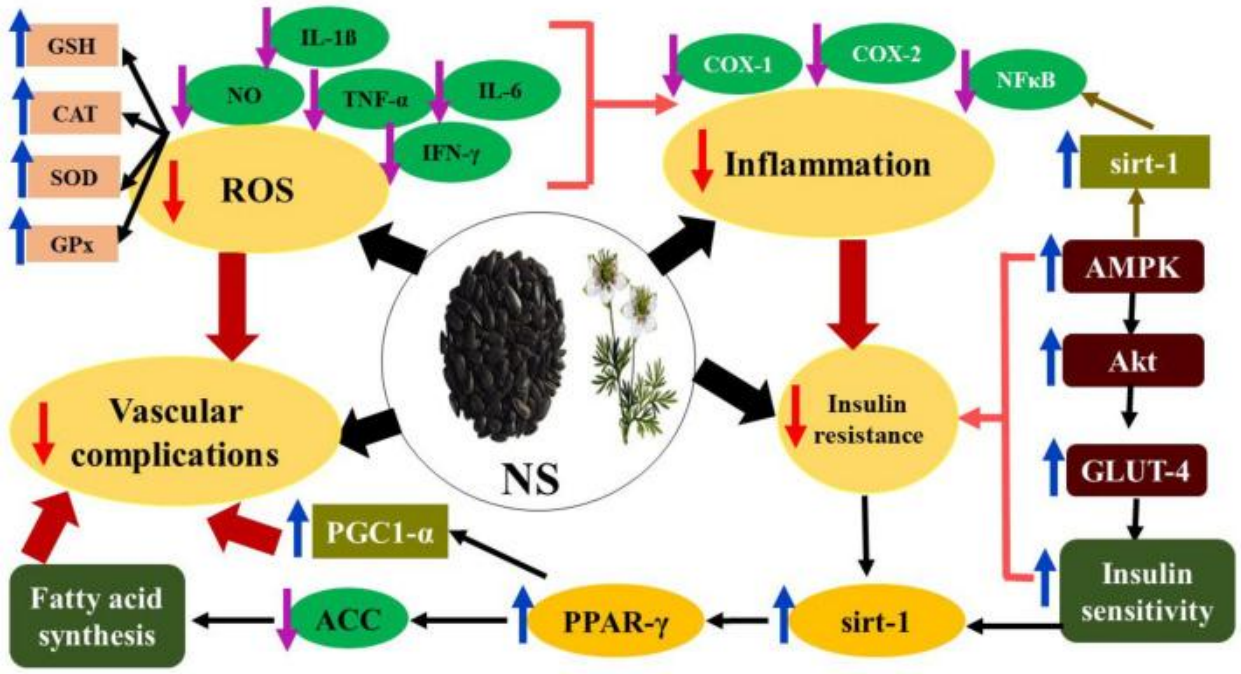
Figure 2: Courtesy ref no-60-Effect of noninsulin-dependent diabetes mellitus (NIDDM) on liver, pancreas, blood vessels, and skeletal muscle. ER: endoplasmic reticulum, DNA: deoxyribonucleic acid.



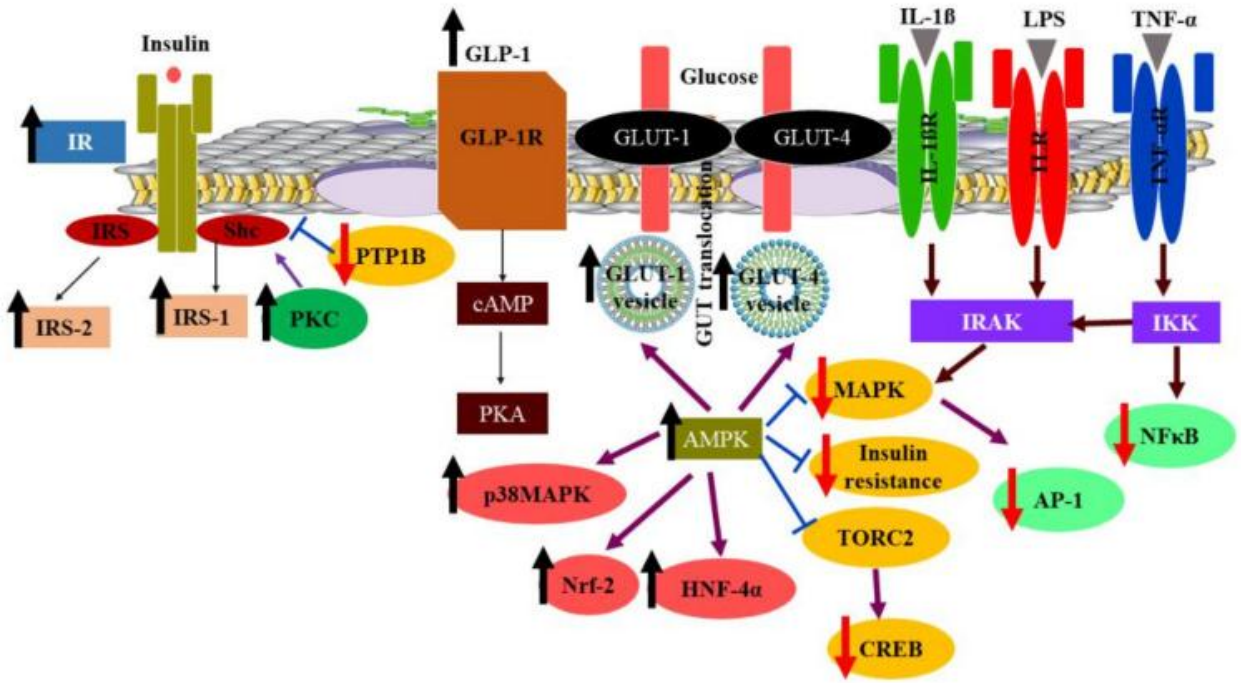
Legend for Figure 3: Courtesy ref no-60-Effect of noninsulin-dependent diabetes mellitus (NIDDM) on kidney, nerve cell, and foot. VEGF: vascular endothelial growth factor, CTGF: connective tissue growth factor, TGF-β1: transforming growth factor-beta 1, IL-1: interleukin-1, IL-6: interleukin-6, IL-18: interleukin-18, TNF-α: tumor necrosis factor-alpha, ROS: reactive oxygen species.



Legend for Figure 4: Courtesy ref no-60-Effect of some natural plants on adenosine monophosphate-activated protein kinase (AMPK) signaling pathway. NS: Nigella sativa, BER: berberine, CUR: curcumin, MO: Moringa olifera, PO: Portulaca oleracea; PG: Punica granatum, ACC: acetyl CoA carboxylase, Akt: protein kinase B, NF-κB: nuclear factor-kappa B, TNF-α: tumor necrosis factor-alpha, ROS: reactive oxygen species, PI3K: phosphatidyl inositol-3-kinase, IRS-1: insulin receptor substrate-1, GLUT-4: glucose transporter-4, FBS: fasting blood sugar, PEPCK: phosphoenolpyruvate carboxykinase, α-glucosidase: alpha-glucosidase, DM: diabetes mellitus.

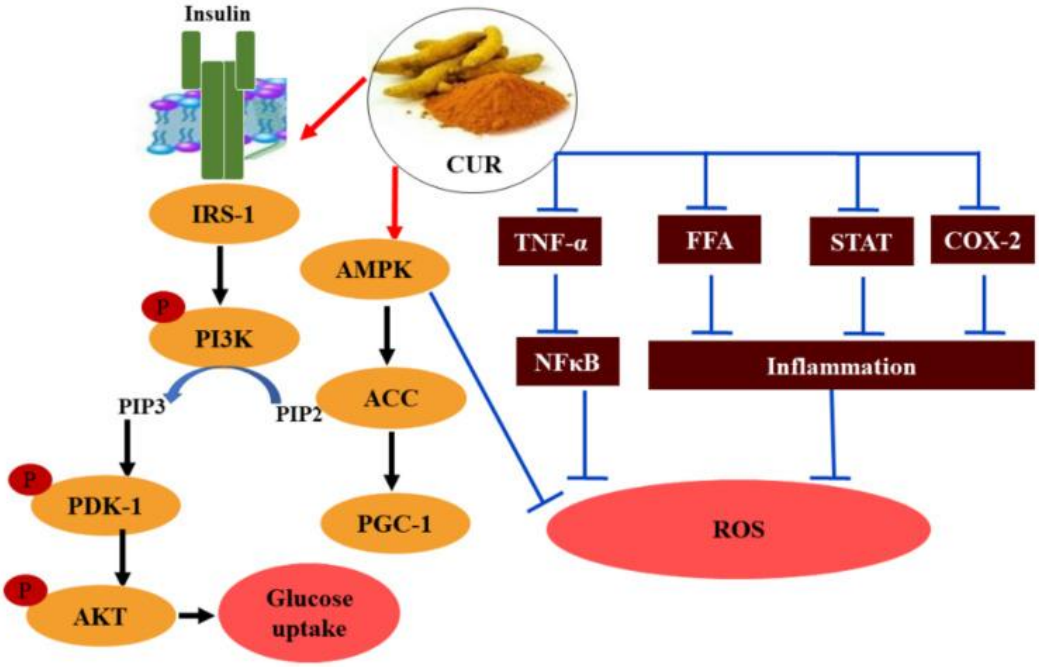


Legend for Figure 5: Courtesy ref no-60-The molecular mechanistic pathways of antidiabetic effect of NS. GSH: reduced glutathione, CAT: catalase, SOD: superoxide dismutase, GPx: glutathione peroxidase, ROS: reactive oxygen species, NO: nitric oxide, IL-1β: interleukin-11 beta, TNF-α: tumor necrosis factor-alpha, IL-6: interleukin-6, IFN-γ: interferon-gamma, COX-I: cyclooxygenase-I, COX-II: cyclooxygenase-II, NF-κB: nuclear factor-kappa B, Sirt-1: Sirtuin-1, AMPK: adenosine monophosphate-activated protein kinase, Akt: protein kinase B, GLUT-4: glucose transporter-4, PPAR-γ: peroxisome proliferator-activated receptor-gamma, ACC: acetyl CoA carboxylase, PGC1-α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha.



Legend forFigure 6: Courtesy ref no-60-Molecular pathways of BER in ameliorating NIDDM. InsR: insulin receptor, IRS: insulin receptor substrate, IRS-1: insulin receptor substrate-1, IRS-2: insulin receptor substrate-2, Shc: mammalian Shc locus encoding three protein variants with molecular mass of 46, 52, and 66 kDa and identical modular structure, PKC: protein kinase C, PTP1B: protein tyrosine phosphatase 1B, GLP-1: glucagon-like peptide-1, GLP-IR: glucagon-like peptide-1 receptor, cAMP: cyclic adenosine monophosphate, PKA: protein kinase A, GLUT-1: glucose transporter-1, GLUT-4: glucose transporter-4, GLUT: glucose

transporter, AMPK: adenosine monophosphate-activated protein kinase, p38 MAPK: p38 mitogen-activated protein kinase, Nrf2: protein regulating the expression of antioxidant proteins that protect against oxidative damage triggered by injury and inflammation, HNF-4α: hepatocyte nuclear factor-4 alpha, MAPK: mitogen-activated protein kinase, TORC2: target of rapamycin 2 kinase, CREB: cAMP response element-binding protein, IL-1β: interleukin-1 beta, IL-1βR: interleukin-1 beta receptor, LPS: lipopolysaccharides, TLR: Toll-like receptor, IRAK: interleukin-1 receptor-associated kinase, AP-1: activator protein-1, TNF-α: tumor necrosis factor-alpha, TNF-αR: tumor necrosis factor-alpha receptor, IKK: IkB kinase (a cytokine-activated protein kinase complex), NF-κB: Nuclear factor kappa B.



Legend for Figure 7: Courtesy ref no-60-Mechanisms of the potential antidiabetic effect of CUR. IRS-1: insulin receptor substrate-1, PI3K: phosphatidyl inositol-3-kinase, PIP2: phosphatidylinositol 4,5-bisphosphate, PIP3: phosphatidylinositol 3,4,5-trisphosphate, PDKI: phosphoinositide-dependent protein kinase 1, Akt: protein kinase B, AMPK: adenosine monophosphate-activated protein kinase, ACC: acetyl CoA carboxylase, PGC-1: peroxisome proliferator-activated receptor-gamma coactivator, TNF-α: tumor necrosis factor-alpha, NF-κB: nuclear factor-kappa B, FFA: free fatty acids, STAT: Signal transducer and activator of transcription, COX-2: cyclooxygenase-2, ROS: reactive oxygen species.

3. Natural treatment: a Tool Considered safe with regards to management of DM

Currenltly –in view of them being economical in addition to prevention of adverse actions of some drugs, utilization of plants that possess medicinal actions might be done with the idea of tackling DM. Fig4 demonstrate the observation of how certain herbal plants resulted in enhancementof hyperglycemia along with insulin resistance through theAMPK signaling pathway.

3.1 Nigella Sativa (NS)

NS is commonly referred to as black cumin,that belongs to the Ranunculaceae family that has exhaustive growth in,numerous countries,that possess numerous classical uses in the form of spices along with food preservatives.[76] Seeds of NS possess numerous biological functions that are inclusive of carminative stimulant,analgesic, antipyretic, along with diuretic functions.[77] A complicated mixing of fatty acids, Vitamins, pigments as well as volatile constituents, comprise NS oil(NSO),that is inclusive of thymoquinone(TQ) along with extra agents,thymol as well as dithymoquinone.It possesses significance with regards to treatment of numerous tumors, GIT disorders,cirrhosis,hepatitis as well as chemical poisoning.[78] Furthermore, NSO demonstrated in vivo anti diabetic along with neuroprotection in an animal model of experimental diabetes.[79,80] Besides that NS seed extracts controller possess advantages actions in liver.[81] It further results in regeneration of βcells of Pancreas at the time of hyperglycemia secondary, to great polyphenol amounts,that results in escalation of metabolic events of carbohydrate as well as lipids.[82] with its capacity of hampering the upregulation of gluconeogenesis enzymes.[83]

Various events that implicate NSO by itself or ita major active compound TQ are the ones that result in antidiabetic actions of NSO.It causes AMPK phosphorylation getting stimulated in case of hepatic as well as muscle tissues, NSO might result in escalation of insulin sensitivity.[84] Moreover, NSO causes

enhancement of GLUT4,IGF1,PI3K.[85] Via hampering Sodium –glucose cotransporters(SGLT) NSO results in reduction of glucose absorption from the intestine.[86] An alternative theory gave clarification with regards to hampering of glucose levels by NSO is secondary to its hampering actions on α-glucosidase.[87] NSO escalates PPARγ in the adipocyte as well as hampers its enzymes which breaks down insulin, that is believed to result in hyperglycemia.[88] In view of its unsaturated fatty acids constituents, besides, downregulation of the 3 hydroxy,3 methyl glutaryl-coenzyme reductase gene, that hampers cholesterol oxidation as well as triacylglycerol lipoproteins, NSO influenced hyperlipidemia that is initiated by DM.[89]

The oxidative stress(OS) existent in DM is subsequent to generation of the reduced state of nicotinamide adenine nucleotide (NADH) which causes imbalance of the equilibrium amongst NADH as well as its oxidative form NAD^+ hence causing OS. Thus it is a NADH: NAD^+ redox imbalance disease.[90] Through the NADH-based redox cycle, TQ in NSO can result in reoxidation of NADH, hence reduction in NADH: NAD^+ ratio. This causes stimulation of glucose as well FF oxidation in addition to Sirt1- based pathway.[91] Furthermore, NAD^+ causes activation of Sirt1,that is a NAD^+ based histone deacetylase, playing a crucial part in regulation of both carbohydrate as well as lipid metabolism, besides liberation of adiponectin as well as insulin, which confers protection to βcells of Pancreas from OS along with inflammation via hampering NFκB action.[92] The antiinflammatory action of NS at the time of DM is noticeably associated with, its repression action on cyclooxygenase along with 5' lipooxygenase pathway that causes reduction of nitric oxide (NO), monocyte chempoattractant protein 1(MCP1), TNFα generation along with hamperingIL-1β, as well as TNFα IL-6.[93] Moreover, NS aids in improvement of certain DM complications like Diabetic Nephropathy,via upregulation of vascular endothelial growth factor-A(VEGFA), transforming growth factor beta(TGF-β).[94] The molecular mode pathways of NS in DM are depicted in fig5.

3.2 Berberine

Berberine(NS Ber) represents a quartenary isoquinoline alkaloid, that is existent in plants families like Berberidaceae, Papaveraceae, Ranunculaceae, Rutaceae as well as Menispermaceae.[95] Ber possesses noticeable greater action in treatment along with avoidance of different metabolic factors like DM, hyperlipidemia, obesity, liver impairment, along with certain diseases that are correlated with aberrations of the nucleic acid metabolism.[96] Here our concentration is on the antidiabetic targets of Ber which possess numerous pathways. Ber facilitates liberation of insulin, glucose uptake as well as glycolysis,[97] besides enhancement of glycogenesis secondary to inactivation of glycogen synthetase kinase enzyme.[98] Conversely, it avoids gluconeogenesis because of decrease in its crucial controlling enzymes glucose-6 phosphate dehyrogenase along with PEPCK.[99] Moreover, Ber causes reduction of insulin resistance by upregulation of PKC-based expression of insulin receptor,[100] via blockade of mitochondrial respiratory complex, the adenosine mono phosphate / adenosine triphosphate(AMP/ATP)ratio escalates, thus causing stimulation of AMPK.[101] Thus AMPK controls transcription of uncoupling protein 1(UCP1) in White Adipose tissue(WAT as well as brown adipose tissue (BAT).[102] that aids in the phosphorylation of acetylCoA carboxylase(ACC) as well as carnitine palmoyl transferase I enzymes, resulting in reduction of lipogenesis in addition to escalation of fatty acid oxidation.[103] Through retinol binding protein4 as well as phosphatase as well as tension homolog(PTEN) down regulation, along with activation of Sirt1, Ber conducts its hypoglycemic, function hence causing enhancement of insulin resistance in skeletal muscles.[104]

Alternative mode of Ber antidiabetic impact is secondary to its capacity of controlling short chain fatty acids (SCFA) as well as branch chain amino acids.[105] thus results in reduction of butyric acid generating bacteria which result in destruction of polysaccharides.[106] An earlier study, demonstrated the part of Ber in avoidance of cholesterol absorption from the intestine via enhancement of cholesterol-7 α hydroxylase as well as sterol 27 hydroxylase gene expression.[107] Furthermore, Ber yields a robust defense against insulin resistance through making protein tyrosine phosphatase-1 B normal,[108] besides PPARγ/Coactivator -1α signaling pathways resulting in escalation of fatty acids oxidation.[109] Moreover, it was demonstrated that Ber causes adjustment of GLUT4 translocation through AS 160 phosphorylation secondary to AMPK activation in the insulin resistant cells.[110]

At the time of DM an association amongst inflammation as well as Oxidative stress that results in the liberation of proinflammatory cytokines like TNFα along with IL-6.[111] There was a documentation that Ber results in repression of certain inflammatory events with amelioration of NADPH Oxidase(NOX) which causes development of Reactive oxygen species(ROS), hence reduction in AGEs as well as escalation of endothelial cells working in DM.[112] It was illustrated that Ber tended to abrogate the inflammation occurring secondary to DM through numerous pathways like repression of phosphorylated toll like receptor(TLR4) along with IκB kinase-β(IKK-β)which is implicated in activation of NFκB, hence Ber influencing serine phosphorylation of IRS along with reduction of insulin resistance.[113] Furthermore, Ber causes activation of p38 which hampers nuclear factor erythroid-2-related factor-2((Nrf2) as well as hemeoxygenase-1(HO1) enzyme blockade resulting in proinflammatory cytokines generation.[114] Additionally, hampering of activator protein 1(AP1), hence repressing generation of COX-2 as well as MCP1.[115] It got revealed that Ber ameliorated certain DM complications in view of its capacity of

amelioration of DNA necrosis in numerous influenced tissues, along with escalation of cell viability.[116] Moreover,it was demonstrated, that Ber confers protection to the lens in diabetic eyes from cataract incidence by enhancement of the polyol pathway via in activation of the aldose reductase enzymes implicated in the transformation of glucose into sorbitol which results in degeneration of the lens fibres.[117] Figure6 illustrates certain hypoglycemic modes of Ber.

3.3 Curcumin (CUR)

Curcumin (CUR) represents a polyphenolic compound that gets obtained from the turmeric rhizomes of Curcuma Longa Lrhizomes,that has got commercial utilization in the form of a spice in addition to a food preservative.[118] It possess advantages actions with regards to robust chronic diseases that are associated with inflammation along with oxidative stress as has been found in DM as well as cancer.[120] More recently it got documented that CUR possesses the capacity of hampering the COVID19 protease enzyme.[121] One of the posited mode of how CUR ameliorated DM is associated with its anti hyperlipidemic action is via repression of the fatty acid synthase, as well as carnitine palmoyl transferase I,3hydroxy-,3methyl glutaryl-coenzyme reductase as well as acetylCoA cholesterol acetyl transferase enzymes.[122] Furthermore, CUR causes reduction of lipogenesis in the insulin resistance syndrome that is correlated with the in activation of the two transcription factors sterol regulatory element binding protein 1c(SREBP1c), in addition to carbohydrateresponse element binding protein.[123] Moreover, possessed the capacity of rectification of escalation of proteintyrosine phosphatase-1 B occurring secondary to insulin resistance substrate-1(IRS-1) as well as JAK2,[124] besides hampering STAT3 as well as SOCS3.[125] Furthermore, CUR causes stimulation, of Akt as well as ERK1/2.[126] in addition to alterations of PI3K/ Akt signaling pathway.[127]

Besides that thecredit of the anti-inflammatory characteristic are given to its capacity of hampering macrophages infiltration along with migration into metabolic organs along with reduction of transcription biomarkers of inflammation,that is inclusive of NFκB in addition to proinflammatory cytokines like TNFα, IL-1β,TLR4 as well as C Reactive Protein(CRP).[128] Other inflammatory pointers like COX,phospholipases, as well as MCP1 might be reduced with the utilization of CUR in DM.[129] Furthermore,the effectiveness of CUR in DM is by blockade of activation of TLR4, besides modulation of caveolin phosphorylation in case of DM subjects.[130]

Moreover, it causes sustenance, of mitochondrial break down along with impairment, whereas, resulting in enhancement of mitochondrial membrane potential as well as genesis.[131] The significance of mitochondria is germane in their part of modulation of metabolic pathway along with preservation of cellular functions like ion homeostasis, Antioxidant defense, fatty acids oxidation,branch chain amino acids biogeneration along with energy generation.[132] CUR augments the mitochondrial action by escalation of1)cytochrome c protein amounts along with 2) mitochondrial as well as carnitine palmoyl transferase 1 enzyme,that causes transportation of long chain fatty acids into the mitochondria for β oxidation.[133]

CUR results in reduction of Hypoxia stimulated cell damage as well as HIF 1α that is an oxygen based activator of transformation, besides intricately associated with oxidative stress particular to diabetic cardiomyopathy.[134] Furthermore, CUR plays a part in enhancement of wound repair in experimental Diabetic rats via escalation of certain granulation tissue growth factors like VEGF,Stromal cell obtained factor--1α(SDF-1α), TGF-β1, Endothelial nitric oxide synthase (eNOS)was further escalated.[135] Improvement in insulin sensitivity along with cardiac complications was resultant of CUR action through upregulation of certain thermogenic genes likeuncoupling protein(UCP)1,2 as well as 3.[136] that are mitochondrial anion carriers besides possess the capacity of adjustment of heart's energy metabolism along with confers protection against ROS by modulation of mitochondrial respiration.[137] Therapy with CUR results in reduction of accumulation of S-phase-kinase correlatedprotein2(S-phase-Skp2) as well as escalation of p27 protein accretion in the pancreatic cancer cells that cause an important abrogation of Diabetic Nephropathy.[138] Fig7 illustrates the probableCUR mode of actions.

3.4 MoringaOlifera (MO)

MoringaOlifera (Ber CUR MO) represents a continued deciduous tropical plant that is affiliated with the genus Moringa from the family Moringaceae,that gets detailed in the form of a marvelous tree in view of all its parts possessing the capacity of medicinal, industrial or functional foods.[139] The flowers,pods leaves along with seeds of MO are believed to be food sources that possess growth promoters since they have the properties of rich in amounts of Vitamins, minerals in addition to proteins.[140] Pharmacologically it possesses antidiabetic, anti cancer as well as anti-inflammatory, anti-microbial, anti hypertensive as well as anti ulcer therapeutic utilization.[141] Numerous modes aid in the hypoglycemic curative effects of MO,that is obtained from its active components Specifically 3 classes of Phytochemicals,phenolic acids (chlorogenic acid), flavonoids (quercetin as well as Kaempherol) along with glucoinolates that possess ric antioxidant foraging effects towards ROS.[142] In this context the observation was that some phytochemicals in MO like quercetin as well as terpenoids resulted in escalation of glucokinase enzyme effects as well as βcells of Pancreas respectively, hence result in reduction of insulin resistance.[143] Secondary to the existence of isothiocyanates in the form of one of its constituents, MO might hamper both gluconeogenesis as well as glycogenolysis in the liver besides absorption of glucose into adipose tissue as well as muscles.[144]

Furthermore, MO controls insulin resistance in the muscle through activation of GLUT4, resulting in an enhancement in the Akt signaling pathway.[145] On one end Sirt1 stimulation that crosstalks with along with resulting in deacetylation of PPAR-1α,the existence of niazrin a phenolic glycoside existent in seeds causes escalation of phosphorylation of AMPKα.[146] It causes reduction of fork head box proteinO1(FOXO1) as well as hepatocyte nuclear factor 4 alpha (HNF-α)that influences PPAR-1α to cause blockade of the gluconeogenesis event. Furthermore, PKC-zeta/Nox4/ROS signaling pathway which probably results in reduction of oxidative stress generated in DM.[147]

Moreover, MO causes enhancement of FA oxidation through theAMPK/ACC as well as or PPAR-1α pathways. Nevertheless, it hampers triacylglycerol as well as cholesterol bio generation via getting controlled by SREBP1.[148] There is an intricate association of MO with the downregulation of α-glucosidase, Pancreatic lipase as well as ipoprotein lipase enzymes that are key rate controlling enzyme which are essential for the hydrolysis of carbohydrate as well as lipids that areexistent in the diet at the time of carbohydrate as well as lipid metabolism.[149]

3.5 Portulaca Oleracea (PO)

Portulaca Oleracea (PO) is affiliated to the Portulaceae family. It represents an annual luscious herb growing in warm climates that is spread in the form of turfgrass weed or field crop.[150] Moreover, it possesses good nutritional, characteristics in view of great amounts of α-linolenic acid,β-carotene as well as VitaminB complex.[151] Furthermore, it displays a wide variety of biological effects like antidiabetic, antiaging, antiulcergenic, anti inflammatory, anti cancer, anti cancer microbial, antiseptic, neuroprotective characteristics besides enhancement of immune system.[152] The various posits with regards to the hypoglycemic effects of PO are i)It causes facilitation of generation of insulin in the βcells of Pancreas through closure of the potassium-ATP channels, membrane depolarization, besides escalation of Ca^{2+} influx.[153] It further accelerates glycolysis as well as causes enhancement of phosphofructokinase, lactate dehydrogenase in addition to pyruvate kinase enzymes.[91]

PO results in reduction of chronic inflammation that gets generated secondary to insulin resistance via hampering of Rho/ROCK/ NFκB pathway,to which is attributed the generation of pro inflammatory molecules.[154] PO further possesses the capacity of avoidance of DM complications by control of lipid metabolism through phosphorylation of ACC at Ser79,that is an AMPK phosphorylation region Hence FA as well as triacylglycerol biogeneration gets hampered along with enhancement of PI3K/Akt as well as AMPK pathways in skeletal muscle,that gets followed by an escalation of glucose uptake in the adipose tissue.[155] Additionally PO possesses a highly abundant green plant source of phenolic acid, flavonoids alkaloids,terpenoids, glutathione in addition to other antioxidants,thus it is a potent antioxidants herb with regards to conferring protection to Pancreas in DM.[156] In view of its phytochemical amounts, specifically terpenoids as well as homoisoflavonoids.PO possesses the capacity of starting GLUT4 translocation.[157]

3.6. Punica Granatum (PG)

Punica Granatum (PG) represents a primitive continuing plant species belonging to the Punicaceae family that is distributed in Africa, America, Europe besides Asia.[158] The utilization of roots barks fruits peels in addition to leaves of PG is done in multiple diseases that is inclusive of therapy of cancer, microbial infections obesity ulcer, inflammation along with Alzheimer's disease.[159]

Generally various precious PG phenolic components like ellagic acid,punicalagin flavonoids anthocyanins along with flavonoids which yield great anti-oxidant action.[160] Polyphenolic compounds that are existent in PG contribute significantly to the hypoglycemic action through numerous, pathway that are inclusive of i) enhancement sensitivity of insulin receptors ii) escalation of the actions of PPAR-γ,[161] as well as Paroxonase 1amounts that represents a high density lipoprotein (HDL) correlated lipolactones which have anti-oxidant properties,[162] iii)manipulating the expression of GLUT4,[163] iv) besides resulting in escalation of glucose uptake by the peripheral tissue as well as hampering gluconeogenesis.[164]

Furthermore, hampering of DPP4 enzyme that is correlated with glucose metabolismby breakdown of the incretin hormones GLP1 as well as glucose dependent insulinotropic polypeptide, hence resulting in insulin liberation.[165] Moreover, PG displayed robust actions in reduction of glucose absorption by hampering pancreatic lipase as well as α-amylase enzymes to which digestion of fat along with carbohydrates can be attributed respectively.[166] Documentation was done with regards to the hypoglycemic impact of PG occurred via hampering of cytochrome P450(CYP)2C9 which is implicated in the metabolisation of certain Sulfonylureas like tolbutamide, hence resulting in escalation of hypoglycemic drugs.[167] Furthermore, avoidance of certain cardiovascular complications of DM is brought about by PG via suppressing lipogenesis in adipose tissue in addition to triacylglycerol bio generation in liver along with hampering of fatty acid synthase enzyme besides SREBP-1c.Exoplorationhas been attempted via numerous studies with regards to the antidiabetic capacity of PG demonstrated a decrease in blood glucose amounts along with escalation of insulin amounts in rats through excitaion of βcells besides escalation of their quantities.One more study illustrated that an IDDM model that received treatment with PG,showed reduction in lipid per oxidation in addition to immune cell infiltration.[168]

4. CONCLUSIONS

The utilization of medicinal plant treatment for diabetes mellitus points to the significance of avoidance along with therapy of the same.Various herbs have demonstrated antidiabetic action through different modes,like ameliorating oxidative stress along with inflammation, escalation of insulin sensitivity besides glucose uptake in addition to insulin modulated signaling in various tissues. Moreover, different kinds of herbs were easy to procure through out the world, being, economical, minimal toxicity a as well as significant phytochemical constituents. However, greater clinical studies are required for validation of the important actions of these plant obtained preparations with regards to the therapy of diabetes mellitus.

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