Review Article
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Therapeutic potential and epigenetic alterations of plant phytochemicals (as epi-drugs) for the treatment of type 2 diabetes mellitus: a systematic review

Abstract

There has been a significant escalation of type2 diabetes mellitus(T2DM), all over the world in particular more recently, secondary to population, age, obesity in addition to the sedentary life styles stranges. The determination as per the projections has been that 230 million people would be diabetic by the year2030. The properties of T2DM are dysfunctional pancreatic β cells function in addition to insulin liberation, hyperglycemia along with insulin resistance as well as recently, the epigenetics control pancreatic β cells differentiation has got emphasized as being implicated. Currently it is clear that various bioactive molecules, that are in plenty of amounts in plants that get utilized as foods or infusions, possess crucial part in histone modifications as well as DNA methylation, thus make up potential agents to work as epidrugs. Having earlier reviewed the epigenetic modes seen in DiabeticNephropathy so here we conducted a systematic review utilizing search engine pubmed, google scholar ;web of science; embase; Cochrane review library utilizing the MeSH terms like phytochemicals ;epidrugs; T2DM; epigenetics alterations inDM;Resveratrol; polyphenols; licorice; fenugreek;citrus fruits; green tea;ginger from 1990'still date in 2021. We found a total of 3050 articles out of which we selected 151 articles for this review. No meta-analysis was done. Thus we have summarized the epigenetic alterations seen in T2DM per se We have tried to review drugs like polyphenols, garlic, tea, resveratrol, anthrocyanins, liquorice, fenugreek that possess he capacity of avoidance or treatment of T2DM both *in vivo*, awa *in vitro* studies. The major observations, despite certain contradictory outcomes seem that these epidrugs possess roles to act either as complementary/replacement treatment for the usual oral hypoglycemic agents with negligible adverse actions. Actually these natural epidrugs seem to avoid or postpone the generation of disease, in addition to the morbidity that is correlated with the impairment of blood vessels, eyes as well as kidneys secondary to sustenance of hyperglycemia in case of patients with T2DM.

Keywords: T2DM, hyperglycemia, epidrugs, epigenetics alterations, phytochemicals

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Introduction

Type2 Diabetesmellitus (T2 DM) represents a metabolic condition that is correlated with greater morbidity to mortality rates, besides implicating a higher economic burden with regards to the healthcare system all over the world.[1] Basically the etiopathogenesis that is implicated is the deficiency of insulin that gets stimulated by the impairment, of the pancreatic β cells in addition to the insulin resistance in the target organs.[2] At the time of 2014, the World Health Organization(WHO) documented, that 8. 5% of the adults (≥18yrs) possessed this disease, while in2015, 1. 6 million people had a demise directly in association with T2 DM. Simple hyperglycemia perse accounted for 2. 2 million deaths in2012.[3] Enhancement in addition to. The global escalation of obesity besides marked reduction in physical activity, and the high energy containing diets[4] have been responsible for the direct along with epigenetics alterations in the phenotype that ultimately result in the generation of thedisease.[5] These environmental alterations have got associated with, marked escalation of the T2DM. More recently, it has been appreciated that T2DM occurs secondary to the impairment of the controlling modes at genetics along with epigenetics levels. At present it is realized that epigenetics plays a significant part in insulin liberation, and actions along with in the generation of T2 DM.[6] The differentiation of pancreatic β cells is regulated by various genes, like glucagon like peptide 1(GLP-1), that results in insulin liberation besides hampering glucagon liberation, paired box gene4(PAX4; (for generation of pancreatic islets, ii)pancreatic as well as duodenal homeobox1(PDX1;i for the generation of pancreas; ii) differentiation of pancreatic β cells, iii) sustenance, of the mature β cellsfunction) receptor, with control of all these genes manifested at the epigenetics levels. Additionally, certain factors that are implicated In insulin resistance (IR), like the nuclear factor κB(NFκB), osteopontin, as well as toll like receptors (TLRs)are further controlled epigenetically.[7] The case controlled studies along with in intervention studies in case of non diabetic subjects in humans demonstrated epigenetics alterations in PDX1, CDKN1A(cyclin –based kinase inhibitors1; for cell cycle control, glycine receptor alpha1(GLRA1; for down regulation of neuronal excitability) genes that appear to aid in diabetes.[6] An escalation of the DNA methylation of PDX1 has been associated with reduction, in pancreatic islets action along with iimpairment of pancreatic β cells in T2DM.[8] Over expression of CDKN1A results in reduction of insulin liberation in addition to proliferation,[9] besides silencing of GLRA1 in clonal β cells reduction in insulin liberation.[10] Additionally, physical activity results in changes in DNA methylation of T2DM candidate genes like FTO(Fat mass and obesity correlated protein correlated with energy consumption) in addition to TCF7L2(transcription, factor 7 like2; for blood glucose homeostasis, in adipose tissue (AT).[6] In case of obese human beings, subsequent to metabolic surgery, epigenetics

and metabolic alterations were documented in skeletal muscle at the time of enhancement of insulin sensitivity.[11] The maximum signs of uncontrolled T2DM is hyperglycemia, and on sustenance for long duration causes damage of the blood vessels which as a consequence, results in injury to the heart, eyes kidney, and the central nervous system(CNS).[12] Secondary, to that macrovascular(Atherosclerosis) along with microvascular (retinopathy, nephropathy). These complications represent the major cause of mortality in case of T2DM subjects. For these extensive lifestyle modifications have been advocated, along with pharmacotherapy or both, in view of their capacity of postponement and reversal or resulting in delaying of the complications.[2] An escalation of utilization of natural products had been documented by certain studies, in patients, with T2DM.[13] This is in view of longterm utilization of oral hypoglycaemic drugs in addition to insulin which resulted in various adverse actions that is inclusive of hypoglycaemia, gastrointestinal problems(nausea, vomitting, diarrhea, besides hepatological conditions as well.[14] The treatment effect of these plants on utilization as food or infusions is based on the crosstalk of different types of phytochemicals . There is existence of greater than 1200 species of medicinal plants that possess antidiabetic action of which about 200 pure bioactive compounds have hypoglycaemic activity, [15] and possess significant part in histone modifications and DNA methylation.[16] Earlier we had reviewed the role of epigenetic alterations in T2DM, besides prospective management, and role of Resveratrol; polyphenols, anthrocyanins, fenugreek, monoterpenes InDM.[17–20] In this context here our objective was to detail the epigenetic mode that is implicated in diabetes along with protein targets, besides highlighting the *in vivo*, as well as *in vitro* studies along with clinical trials on which work that had been conducted on this topic with regards to phytochemicals that have the potential to act as epidrugs in T2DM.

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 phytochemicals; epidrugs; T2DM; epigenetics alterations inDM; Resveratrol; polyphenols; licorice; fenugreek; citrus fruits; green tea; ginger from 1990'still date in 2021.

Results

We found a total of 3050 articles out of which we selected 151 articles for this review. No meta-analysis was done.

Epigenetic modes of type2 diabetes mellitus

The hyperglycemia that takes place in T2DM, reflects a systemic change which influences all the tissues resulting in long term disease.[21] Specifically, hyperglycemia possesses the capacity of changing the expression of genes that are implicated, in insulin resistance(IR), low grade systemic inflammation, and renal fibrosis.[22] The biological events that are behind the alterations in expression of genes is constituted by epigenetic controlling of genomes of various tissues that is inclusive of skeletal muscle, liver, pancreas, blood along with adipose tissue(AT) for T2DM.[23] The physical reason with regards to epigenetic controlling are alterations in the chromatin structure without any alterations in the DNA sequence, of which certain of these might be transmitted via generations. The epigenetic modifications can get clubbed into three are i) DNA methylation, ii) post-translational histone modifications, iii)non coding RNAs.[24]

General modes of epigenetics

Methylation of DNA was the initially detailed mode which got invented, besides being correlated with transcriptional silencing of genes whose promoter has got methylated. Basically it implies the covalent attachment of the methyl group at the 5' carbon of cytosine residues in a promoter area that is rich in cytosine-phosphate-guanosine (CpG), alias CpG island.[25] The existence, of these modifications of nucleotide possesses the capacity of recruitment of methyl binding protein which facilitates chromatin condensation as well as thus limit the accessibility of the transcription factors, besides the usual transcription machinery to the promoter.[25] The DNA methyltransferases(DNMT) represent a family of enzymes which catalyze the methyl(CH3)grouptransfer from S-adenosyl methionine (SAM)to the 5-carbon of the cytosine, cmprising of DNMT1, DNMT3a, DNMT3b. The elimination of the methyl groups is achieved by demethylases of the Ten –eleven translocation(TET) family proteins that modulates oxidation of the methyl group that results in a 5hydroxy methyl cytosine (5hmc) which later gets replaced by cytosine at the time of the DNA healing . The demethylation of the DNA counters the compacting of chromatin that is mediated by methyl marks, besides being in general associated with transcriptional stimulation.[26] DNMT3a was documented to be an epigenetic modulator of adipose IR in mouse as well as humans.[27]

ii) Post-translational histone modifications, represent a varied group of covalent modifications, which usually resides at the N-terminal. In brief, the acetylation, methylation, phosphorylation as well as ubiquitination, of particular residues are the ones that have received maximum evaluation, however, almost 67 or more newer discovered histone modifications that possess the capacity of controlling gene expression are existent.[28] 1stly histone acetylation takes place in lysine residues that results in gene transcription via chromatin decondensation, working as a binding region for the transcriptional activators. Histone acetylases(HAT's), catalyze the acetylation, thus result in gene transcription, while Histone deacetylases result in elimination of acetyl group from histones, that facilitates the repression of transcription.[29] Methylation of histone takes place, in lysine(Lys) as well as arginine(Arg)residues of histones, with each residue possessing the capacity of presentation of various methylation states that is inclusive of, mono, di as well as trimethyl lysine, whereas arginine might be symmetric/asymmetrically mono or, dimethylated. Based on the particular residue in addition to the state ofmethylation, transcriptional action might get stimulated or repressed. Like the mono, di as well as trimethylation, of histone H3 (H3)at Lys4(H3K4m1/2/3) have got correlated with transcriptionally active genome areas, whereas trimethylation of H3 at Lys9 or at Lys27((H3K9m3/(H3K27m3) and trimethylation of H4 at Lys20((H4K20m3are existent in case of silenced DNA controlling elements.[30] ii) Methylation of histone occurs by histone methyltransferases (HMTs), that possess different ion specificities, with regards to lysine(Lys) and arginine(Arg)residues with elimination of methyl group being based on the action of demethylases that possessed particular capacity of binding as well . The other newer histone modifications are comprised of crotonoylation as well as β-hydroxy butyrate(BHB), both of which impact the lysine residues[31] iii)Lastly gene expression, can further get controlled transcriptionally as well as non transcriptionally by noncoding RNA molecules. Of these, miRNAs are classically made up of 21-23 nucleotide(nt)that are long as well as mediate posttranscriptional repression via binding with the complementary areas of particular target miRNAs that result in the break down by the RISC complex.[32] A separate noncoding RNA with regards to T2DM are the long noncoding RNAs(lnc RNAs) that are implicated in the recruiting of DNMTs, apart from histone modifiers towards their target genes, specifically of eRNAs, promote promoter-enhancer looping, hence escalation of the transcription rates of the adjacent genes.[33]

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Epigenetic changes in T2DM

ADNA methylation

T2DM represents a complicated disease of the metabolism where there exist a lot of interconnected modes that get initiated . Earlier studies evaluated DNA methylation of candidate genes for T2DM like the INS(insulin), PDX1, PPARGC1A(PGC1α; transcriptional coactivator), GLP1R(GLP1receptor)in human pancreatic islets from donors with T2DM as well as non diabetic controls.[23,34] The observation in these studies was that an escalation of DNA methylation existed in the islets from T2DM donors, with reduction in expression of the crucial genes that were correlated with dysfunctional insulin liberation.[23] Additionally, the escalation of DNA methylation of these genes appeared to possess a direct correlation with escalation of glucose as well as glycated haemoglobin(HbA1c) amounts. In case of pancreatic islets early molecular changes takes place, as well as result in modulation of islets impairment, prior to the initiation of T2DM.[35] DNA methylation patterns of β cells are dynamic at the time of maturation in addition to T2DM initiation prior to the onset of overt T2DM as well as evolution.[36] Certain differentially methylated controlling elements have got correlated with the crucial function genes like PDX1, TCF7L2, as well as NKX6-1(homeobox protein Nkx-6. 1; controlling of islets transcription factors as well as genes implicated in glucose as well as insulin homeostasis) in case of islets of langerhans from obese mice that varied in their extent of hyperglycemia, besides liver fat amount a semi exploration strategy isolated 497 genes that were differentially expressed along with methylated that was correlated with insulin liberation along with extracellular matrix[ECM)- receptor crosstalk.[37] Additionally, contrasting of mouse data with the DNA methylation amounts of patients who took part in the European Prospective Investigation Cancer(EPIC)Potsdam cohort documented 105 genes that possessed changed DNA methylation at 605 cytosine phospho-guanine (CpG)dinucleotide areas that were correlated with future T2DM generation. The 1st epigenome wide association studies(EWAS) of DNA methylation markers of obesity and T2DM are aiding in getting a detailed insight in the epigenetic changes correlated with T2DM onset. From blood samples of 5387 persons alterations in methylation markers of genes implicated in lipid metabolism, substrate transfer along with inflammatory pathways have been documented. Intriguingly despite the observation of these alterations have been visualized in tissues not associated with metabolic significance like in adipose tissue, liver and skeletal muscle tissue from a small subset of patients who took part. Intriguingly the DNA methylation that gets stimulated by obesity possess the capacity of anticipation of the generation of T2DM in the coming future.[23,38]

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Modifications of Tail of Histone

Changes in a lot of types of histone modifications have been documented in case of modes beneath the inflammation seen in T2DM. Studies that basically got generated in cellular modes documented alterations in histone marks within the regulatory elements of the genes responsible for inflammation secondary to hyperglycemia. Like Miao and Gonzalo[43] in their observation documented an escalation of histone acetylation at the nuclear factor κB(NFκB) promoter in THP1 monocytes that was stimulated by a momentary exposure to an escalation of glucose amount . The greater acetylation was associated with an escalated recruitment of p300/CBP associated factor to (PCAF) NFκB promoter and over expression of the proinflammatory target genes like the cyclooxygenase(COX2) and tumor necrosis factor alpha(TNFα).[43] Intriguingly akin alterations in histone modifications of NFκB have been revealed in monocytes from T2DM subjects that demonstrated an *in vivo* association of the epigenetic alterations.[43] IL-8 represents one more proinflammatory gene whose over expression gets stimulated by hyperglycemia in human primary vascular cells by an epigenetic mode that implicated hyperacetylation of its promoter area.[44] Ibarra Urizar and Prause[45] posited that continuous exposure of β cells to IL-1β stimulated β cells differentiation having the properties of dysfunctional glucose liberation, stimulated expression of crucial β cell genes and alterations in histone modifications. That study of theirs revealed that IL-1β in low amounts stimulated epigenetic alterations that was correlated with the elimination of β cell identity the way it is visualized in T2DM. The epigenetic action is not restricted to the stimulation of hyperacetylation, however it further induces H3K4 hyper methylation as well as H3K9 hypo methylation in the NFκB p65 that results in continuous upregulation of endothelial cells at the time of hyperglycemic situations. These alterations in histone methyl marks get modulated by the recruitment of SET domains containing 7 histone lysine methyl transferase(SETD7) as well as lysine specific demethylase 1(LSD1) to the NFκB promoter, besides being correlated

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with a greater expression of genes that are controlled by NFκB, like vascular cell adhesion molecule(VCAM), MCP1.[46] Additionally, the ex vivo methylation alterations of NFκB p65 in endothelial cells has further been demonstrated in blood mononuclear cells of the T2DM patients, where this imbalance is further associated with an escalation of expression of MCP1, intercellular cell adhesion molecule protein 1(ICAM1), along withCOX2.[47] Akin to that escalated expression of IL-8 in endothelial cells, besides being mediated by greater histone acetylation, however, takes place, byH3H4 methylation that gets stimulated ion by SETD7 methylase.[48] These highlight that, hyperglycemia results in over expression of the proinflammatory genes by the dispensable epigenetics histone marks, which with regards to NFκB, is further implicated in acetylation of lysine residues of the transcription factor itself.[49] The other overexpression states of the proinflammatory genes that gets mediated by methylation alterations correlated with the hyperglycemic stimulation, are IL-6 and MCP1, in vascular smooth muscle cells(VSMC), IL-6 in rat cardiomyocytes, IL-12 subunitβ(IL-12 β), macrophages inflammatory protein(MIP)-1α, MIP-1β, besides, IL-6 in THP1 monocytes.[50]

Noncoding RNAs

Post transcriptional repression that gets mediated by miRs further aid in impairment of proinflammatory genes expression in T2DM, in general that gats mediated by the exaggeration, of decay ofmiRs. An escalation of expression of miR125b, in the VSMC has further been documented in a T2DM mouse model.[51] The greater amount of miR125b stimulates a reduction in the SUV39H1 histone methylase marks, that results in a decrease of the H3K9 activation signal in the promoter of IL-6 as well as MCP1.[51] The other miRs that are up regulated in T2DM that influence the proinflammatory genes expression are miR146a stimulates a reduction in the TNFα receptor associated factor(TRAF) in addition to interleukin-1 receptor associated kinase 1(IRAK1), miR200c family members, causing escalation of, expression of COX2 as well as MCP1, along with miR504 resulting in escalation of IL-6, COX2 as well as MCP1.[50] Aberrations, of lncRNA have been seen in T2DM correlated inflammation. Like the E33 lncRNA amounts were escalated in macrophages of a mouse model of T2DM along with the human homolog MIR143HG.[52] Nevertheless, just part data is available with regards to the mode of impairment, nevertheless stimulation of a lot of proinflammatory gene, like IL-6, COX2 and TNFα, while the down regulation of MCP1 along with the anti-inflammatory IL-10 has been documented. [52] Satishkumar and Prabhu,[53] correlated that Metastasis associated lung adenocarcinoma transcript1(MALAT1), represents another lncRNA that might control the T2DM, associated inflammation via up regulation of serum amyloid antigen(SAA), that finally results in IL-6, and TNF in human Umbilical vein endothelial cells(HUVEC).

Role of Phytochemicals in . Control of Protein Targets With Regards To T2DM, Treatment

The therapy of T2DM is in general concentrated on the control of protein target actions.[7] Variety of Phytochemicals derived from vegetables, spices, teas in addition to medicinal plants might control the epigenome, besides,[54–56] display low adverse actions on chronic supplementation.[57] The applications, of the main phytochemical groups like polyphenols, terpenoids, organosulfur and alkaloids in the form of epidrugs have been proven with the aid of experimental studies.[55] Here the usual protein targets for the T2DM, treatment and phytochemicals that result in modulation of the actions of these proteins that possess, capacity of exertion of antidiabetic action, in silico, *in vivo*, *in vitro* studies are detailed.

Reduction in insulin resistance through hampering of 11 β - hydroxysteroid dehyrogenase

Cortisol possesses a, significant part in metabolism in addition to T2DM, along with the hampering of hepatic glucocorticoid receptor was seen to result in reduction in the glucose in mice, besides enhancement of insulin resistance.[56] Actually an aberration in glucocorticoid metabolism has got correlated with T2DM.[57] In particular 11 β-hydroxysteroid dehyrogenase (11 β—HSD) represents an oxidoreductase enzyme, which catalyzes the transformation of the inert 11keto products(cortisone, deoxycorticosterone) to the active glucocorticoids(cortisol, corticosterone). The control of cortisol by 11 β—HSD occurs in AT, hepatic and brain tissues.[58] In short 11 β—HSD possesses different isoforms in case of human beings where 11 β—HSD1is a NADPH- based isoform that gets significantly expressed in crucial metabolic tissues like AT, liver, pancreas and skeletal muscle,[59] where 11 β—HSD1 is a robust target for therapy, whose hampering might work for the treatment of T2DM, IR, MetS, in addition to other diseases mediated by escalation of cortisol generation.[58] The capacity of hampering 11 β—HSD1 was contrasted amongst flavonoids as well as iso flavonoids by Zhu and Ge.[60] In brief their observation was that apigein, quercetin and genistein along with(±)-equol possess the capacity of hampering human 11 β—HSD1 with IC values of 2. 2, 5. 4. 11. 0 as well >100mM respectively. Nevertheless, apigein, as well as (±)-equol could not hamper 11 β—HSD2 at doses as high as100mM, however genistein and quercetin hampered by 60%and50% at doses of 100 mM respectively.[60] In streptozocin(STZ)- nicotinamide stimulated diabetic rats, quercetin possessed antidiabetic, capacity by working as a 11 β—HSD1 inhibitor.[61] Furthermore, genistein caused repression of 11 β—HSD1 in AT and glucocorticoid amplification.[62] Nevertheless, in maleob/ob micea diet that was high in genistein(600jmg/kg) for4wks resulted in reduction of hyper corticosteronism that resulted in reduction of protein expression of renal 11 β—HSD2 without any alterations in hepatic 11 β—HSD2.[63] Teich and Pivovarov,[64] evaluated the hampering action of 11 β—HSD1 of curcumin in the preservation of metabolic health in addition to restriction of AT growth subsequent to omission of exercise/day along with reduction of calories (50-65% of ad libuitum consumption) in Sprague Dawley rats. In the form of the significant observation, Teich and Pivovarov (64), documented that curcumin (200mg/kg) resulted in significant reduction of insulin homeostasis model assessment - insulin resistance(HOMA-IR), and C Reactive Protein(CRP), in addition to illustrated hampering action against human and rat 11 β—HSD1 in case of intact cells(IC_{50}=2. 3 and 5. 8μM respectively) and on 11 β—HSD2(IC_{50}=14. 56 and 11. 92μM respectively).[65] Moreover, curcumin (200mg/kg) resulted in reduction of serum glucose, triglycerides, cholesterol, low density lipoprotein (LDL) cholesterol, high fat diet(HFD) induced obese rats.[65]

Resveratrol represents a plant obtained polyphenolic agent with robust anti oxidative action. The action of resveratrol on11 β—HSD1 in case of rodent adipose tissue, was evaluated by Tagawa and Kubota.[66] Here resveratrol caused hampering action on 11 β—HSD1((IC_{50} value =35. 2 μM), however resveratrol was unable to influence the action of the 11 β—HSD2 and hexose -6phosphatedehydrogenase. Various teas (Camellia sinensis (L)Kuntze), tea particular polyphenolic agents were investigated for human liver microsomes and human purified 11 β—HSD1 for their probable antidiabetic action through reduction of cortisone by hampering action on 11 β—HSD1.[67] The polyphenol(-_ epigallocatechin gallate(EGCG) demonstrated, maximum robust hampering action on 11 β—HSD1((IC_{50} value =57. 99 μMfor reduction; IC_{50} value =131. 2 μMfor Oxidation).

Zhu etal.,[68] at the time of a systematic review and meta-analysis of 10short and small sized randomized controlled trial(RCT), ginger (Zingiber officianale Roscoe) further illustrated a great mitigating action on fasting blood glycaemia(FBS), insulin, HOMA-IR, and HbA1c(1-3g/day for4-12wks, n<40) controls as well as fasting insulin sensitivity.[68] Specifically, in case of 2 studies, T2DM patients had a reduction of FBG, HbA1c, insulin and, HOMA-IR subsequent to receipt of a capsule /day that had 1. 6or1g/day of ginger respectively. 33 subjects got the treatment in the first study, whereas 30 acted as controls,[69] in the mean time in the second study, there were39 subjects with 31 controls.[70] Furthermore, in particular, the3 gingerol derivatives known as paradol, (E)-shogol, and (5R)acetoxy gingerol possessed the capacity of hampering human and mouse 11 β—HSD1action((IC_{50} value =1. 09-1. 30μM range.[71] Licorice (Glycyrrhiza glabraL) represents a plant which has been escalatingly investigated with regards to its antidiabetic capacity,[72] besides, which has demonstrated, pre translational hampering action on 11 β—HSD1action in vitro(rat pituitary GH3 cells) and *in vivo*(rats75mg/kg/day Glycyrrhizic for5days).[72]

Gumy and Thurnbichler,[73] further evaluated the capacity of certain, medicinal plant extracts for hampering 11 β—HSD1 in transfected HEK-293 cells. Their major observations were that leave extracts of loquat (Eriobotrya japonica)(Thunb)(Lindl.) and extracts of roasted but not coffee beans possessed the capacity of hampering 11 β—HSD1 . Simultaneously, a lot of clinical studies have tried to evaluate the actions of the natural hampering agents of 11 β—HSD1 in T2DM, mainly soy isoflavones, although certain of these are still going on . Generally the outcomes were not consistent in view of small sample size, various properties of the population that was enrolled, sources and dosages of delivery or the utilization of a combination of other molecules.

A variety of meta-analysis of clinical studies that have been associated with the advantages of flavones, lignans and isoflavones consumption in reduction of T2DM risk or enhancement of bio chemical parameters of the glucose metabolism.[74] Like a consumption of soy product with 9g protein for 1yr in case of 323 overweight postmenopausal women(controls39062 women) caused a reduction in glycosuria.[75] Furthermore, the consumption of10mg of s-equol for12wks in 49 women and men(controls, n=49) caused a reduction in HbA1c.[76] Akin actions were illustrated subsequent to delivery of 360mg/day of flaxseed obtained lignan supplement in 37 T2DM patients, (control n=36)in2 time duration of 12wks for each one.[77] With regards to genistein, the supplementation of54mg/day for2yrs in 198 postmenopausal women (control n=191) reduction in fasting insulin amounts along with enhancement of FBG and HOMA-IR.[78] Furthermore, isoflavones consumption demonstrated, advantageous action in postmenopausal women at dosages of 40 as well as 80mg x1year that caused a reduction in FBG to 5. 2 and 3. 3mg/dl respectively(n=68 in each experimental group, control n=67).[79]

Furthermore, long longitudinal studies are existent which had investigation for the advantages of soy foods, flavones, phytoestrogens isoflavones, and lignans intake. A small study carried out in 468 men that were stratified based on the phytoestrogens consumption for2 yrs illustrated that lignans consumption resulted in reduction of Cpeptide amounts, however isoflavones were devoid of that action.[80] In the other study conducted on 299 pregnant women that continued for 2yrs of the National Health and Nutrition Examination Survey, US observed an inverse correlation amongst isoflavones consumption and insulin, FBG in addition to HOMA-IR.[81] Goodman-Gruen and Kritz-Silverstein,[82] evaluated genistein consumption in postmenopausal women for 1yr, where they observed an inverse correlation with fasting insulin . Utilization of results from6 cohort studies was done for evaluation, of the actions of soy foods, flavonoids, phytoestrogens iso flavones, and lignans. The observation of Zamora-Ros and Forouhi,[83] was a lesser risk of T2DM that was correlated with a greater consumption of flavonoids and lignans in 1558 men and women of the EPIC-Interact study that was followed for a yr. In case of the Nurses Health Study (NHS) I and II, lignans consumption for6 yrs was correlated with a lesser risk of T2DM that correlated in 1107 women in contrast to 1107 controls.[84] Furthermore, on evaluation, of soy foods, consumption in, 43176 men and women from Singapore Chinese Health Study that were followed for 5. 7yrs just isoflavones and nonsweet soy foods were observed to have a correlation with a lesser risk of T2DM, whereas sweetened soy foods had a higher correlation with T2DM.[85] Data from the Japan Public Health Centre Based Prospective Study, in 58791 men and women that were followed for 5yrs consumption of soyproducts and isoflavones, caused a reduction in the risk of T2DM in overweight, obese women.[86] Lastly in case of 64191 postmenopausal women of the Shanghai women's Health Study, soy foods, resulted in reduction in the risk of T2DM that was taken for 4. 6yrs.[87]

Summarizing, case controls in addition to prospective cohort studies pointed that there exists an inverse correlation amongst total flavonoids, isoflavones and lignans consumption with T2DM risk in addition to enhancement of the control of disease propagation with variable effectiveness . In toto these observations pointed that there are other agents in soy like lipids and fibers which might possess, glycaemic actions or propagation possess the capacity of crosstalk with flavones and that is essential for the estimation of particular phytoestrogens Biomarkers for evaluation for its association with T2DM risk.

Occasional clinical trials are existent with regards to curcumin in T2DM. In a small meta-analysis 3/5 randomized controlled trial(RCT), it was demonstrated, that a decrease in FBG, HOMA-IR and HbA1c in dosages amongst 250 and 1000mg, besides therapy amongst10days or 9mths.[74] In the longest study, (9mth, n=120patiens and n=120 controls), curcuminoids –receipt in case of prediabetic patients(1. 5gdaily) no generation of T2DM occurred, whereas in the placebo group, 16% generated T2DM.[90] The group that was in receipt of treatment further demonstrated lesser C peptides in addition to greater HOMA-β, that demonstrated, an enhancement of pancreatic β cells function. Furthermore, in case of T2DM patients, (n=50 treatment, n=50, controls) curcuminoids 500mg/day x3mths resulted in reduction of FBG, C peptides as well as HbA1c.[91] The other meta-analysis,[90] illustrated that on delivery of curcumin, in nano micelles (300mg/dayx3 mths)caused a reduction of FBG, by 18% and HbA1c by 11%.[84] Akin outcomes were delivered if30mg /day supplementation, x3mths(n=35for treated as well as control diabetic group).[92] Additionally, in, 1/3 studies which evaluated renal function in T2DM patients an observation, of advantageous action of curcumin was seen.[90] There is lower amount of absorption from intestine of curcumin besides fast metabolism, in which micelles, nanoparticles, liposomes in addition to lipolipid complex, utilization has been done in certain studies for enhancement of its bioavailability along with, biological effectiveness.[74] Furthermore, variation in gender bioavailability has got demonstrated, that is associated with a greater hepatic metabolisation of, curcumin in men, besides action of body fat in women, that could be taken into account in future studies.[93]

Lastly certain preclinical studies as well as clinical studies investigated the action of green along with black tea in T2DM. The studies were conducted amongst 12wks and 18mths with dosages

amongst, 200mg/day and 2. 5g/3times for day.[94] Like a clinical trial for12wks, conducted on 32 T2DM patients and 28 controls, 1gm of green tea infusion led to a reduction of HbA1c.[95] However in other 4 studies no alterations were seen subsequent to green tea supplementation, for 4wks in case the intervention was lesser like in toolsee, Aruoma[96] study(4wks, 3 cups/day, n=65control, n=58).[94] Nevertheless, when 3(n=24)or 4(n=25)cups of green tea were supplemented for4wks in T2DM, for4wks(controls n=14), systolic & diastolic BP were reduced, with other 4 studies illustrated significant enhancement in both BP along with anthropometric data subsequent to green tea supplementation, in T2DM patients.[97] Noticably inspite of studies that documented conflicting outcomes that were associated with action of tea in T2DM, with a significant proof of the time period of intervention, needs to be highlighted that green tea further possesses flavonols, which by themselves possesses certain advantages in certain clinical trials with hypertensive, diabetic along with, over weight subjects.[98] Ultimately occasional studies that were correlated with EGCG with consumption in T2DM has got obtained, just a single Clinical trial was over(n=25treated, n=25 controls T2DM patients) observed that 300mg of EGCG/day for8wks resulted in significant reduction in FBG.[99]

Enhancement of insulin action through protein tyrosine phosphatase 1B inhibiton

The enhancement of insulin sensitivity represents a crucial approach with regards to therapy. T2DM protein tyrosine phosphatase 1B inhibiton(PTP1B) result in enhancement of insulin receptor sensitivity in addition to in last few yrs targeting PTP1B inhibiton is being believed to be a promising target with regards to treatment of T2DM patients.[20,100] Binding of the type1 insulin like growth factor (IGF1) to its tetrameric receptor results in stimulation of the auto phosphorylation of the receptor, the downstream activation of protein kinase B(PKB), mitogen activated protein kinase(MAPK) pathway that triggers the translocation of the GLUT4 transporter to the plasma membrane.[101]

Natural products that possess, hampering actions against PTP1B got summarized by Jiang, eral[102]. They initially, detailed about 300 secondary metabolites whose Identification was conducted by them from different natural sources or obtained, via synthetic events. Of these the phytochemicals that possessed the capacity of targeting PTP1B were inclusive of phenolics, terpenes, Steroids, N orS possesing compounds along with miscellaneous phytochemicals.

Like resveratrol(dose equivalent at2. 5 mg/kg orally delivered through drinking water) resulted in enhancement of peripheral insulin resistance that was independent of Sirt1 in case of Diabetic mice which was correlated with inhibition of PTP1B.[103] Sirt1 represents one of the 7 mammalian orthologs of the yeast proteins along with has been pointed to be implicated, in the event of glucosehomeostasis in addition to insulin liberation.[104] A lot of studies have demonstrated how the actions of both proteins namely Sirt1 and PTP1B are correlated with each other.[105]

Chuang and Martinez[106] illustrated that quercetin possesses, greater effectiveness, in contrast to resveratrol in hampering PTP1B in primary cultures of human adipose tissue that received treatment with TNFα. Actually, the treatment with quercetin resulted in reduction in mRNA amounts of PTP1B, whereas no action of resveratrol was seen in PTP1B expression amounts.[106] The observation was that Curcumin and cinnamaldehyde resulted in reductionof PTP1B enzymatic action in breast cancer MCF-7cell line,[107] although, greater effectiveness, of curcumin was seen In contrast to cinnamaldehyde. Like Curcumin hampering of PTP1B was initiating from 1μM(IC_{50} =100 μM).[107] In case of fructose fed rats curcumin consumption led to hampering of PTP1B in addition to that of enhancement of insulin along with leptin sensitivity in the liver of rats . Furthermore, they conferred protection from hypertriglyceridemia as well as hepatic steatosis that got stimulated by fructose diet.[108] Moreover, it has been pointed that curcumin results in stimulation of miR206, thus results in enhancement of insulin sensitivity.[109]

Papaverine from Papaver somniferum 1 represents an isoquinolone alkaloid that possesses the capacity of hampering PTP1B in humans.[142] Papaverine demonstrated, a robust *in vitro* hampering action against recombinant –h-PTP1B(IC_{50}=1. 20 μM), whereas *in vivo* it resulted in significant hampering action against FBG amounts in Balb/c mice.[110] The antidiabetic action of bis(2, 3) dibromo-4, 5-dihydroxyl) ether(BDDE), that is a bromophenol that has been isolated from the red alga(Odontholia Corymbifera) was evaluated by Xu &Wang.[111] The *in vitro* treatment with2. 5, 5, or 10 μM of BDDE for16h dose based resulted in hampering action against over expression, of PTP1B in insulin resistant HepG2 cells. In case of db/db mice models the action of BDDE was contrasted against that of metformin, where a significant reduction in blood glucose amounts and HbA1c were documented subsequent to BDDE treatment without any discernible weight accrual was seen.[111]

The hampering action of lipophilic agents derived from Salvia miltiorrhiza Bunze roots against PTP1B were further evaluated,[112] where it was illustrated PTP1B hampering action with the utilization of cryptotan shinone(IC_{50} =5. 5±0. 9 μM)tanshinolB(IC_{50} =4. 7±0. 4 μM) and dehydrodanshinol(IC_{50} =8. 5±0. 5 μM).[112] *In vivo* studies conducted in diabetic rats that received treatment with a polyphenolc fraction of S. miltiorrhiza, further demonstrated a lesser fasting glucose.[113] This way the active constituent tanshinolIIA caused a reduction in glycemia in case of fasted mice subsequent to an acute injection of a bolus of glucose.[114] Restricted data is existent from humans assays that investigated particular, targeting PTP1B inhibitors, besides what is available, evaluated the action of resveratrol. The initially, detailedclinical trial that was comprised of an extremely small sample (full19, 10 intervention and 9 controls) where the observation was that 10mg/day of a capsule of resveratrol delivered for a mth, resulted in enhancement of HOMA-IR,[115] while in others, that was conducted in case of 28 T2DM patients that received the medicine, as 250mg/day of resveratrol for 3 mths resulted in enhancement of HbA1c amounts(controls[n=29].[116] Nevertheless, no action of resveratrol was seen in three studies, in 15 postmenopausal women(controls[n=14], 10 over weight men with non alcoholic fatty liver disease(controls[n=14], and 12 obese men(controls[n=12], that on delivery of 75g/day x12wks,[117] 3000mg/day,[118] and 300mgdaily for4wks[119] respectively . In the initial data from the PREDIMEDstudy(Prevention with Mediterranean Diet)1000 obese T2DM patients that were followed for 2yrs an enhancement of FBG[120] occurred. Usually the advantageous, avoidance or curative actions of resveratrol in T2DM patients is based on dosages, time of intervention, besides the properties of population, however like other phytochemicals, need consumption in form of a supplement in view that dosages taken with diet are very low. Furthermore, urinary metabolites required to be regulated.[121]

Controlling Estradiol through 17 β--Hydroxysteroid Dehyrogenase

Estradiol(E2) is known to cause stimulation of metabolic homeostasis, besides its collections in serum might be a pointer of estrogen resistance, metabolic deficits, besides T2DM.[122] In case of postmenopausal women the observation was that, escalation of,

circulating estradiol were correlated with T2DM,[123] however it did not point that it was the cause of the same. A crucial part is played by 17 βHSD with regards to both break down in addition to stimulation of androgens as well as estrogens. In particular17 βHSD1 promotes the reduction of estrone towards E2, whereas 17 βHSD2 results in oxidation of E2 to estrone.[124] Expression of 17 βHSD1 in case of humans occurs in placenta, ovary, breast epithelial cells, whereas 17 βHSD2 expression takes place in placenta, lung, kidney liver, pancreas, prostate, colon, small intestine, endometrium as well as breast epithelial cells.[124]

The capacity of complicated phenols derived from olive oil of hampering human hepatic microsomes was evaluated for reduction and of T2DM,[149] however it did not point that it was the cause of the same. A crucial part is played by 17 βHSD with regards to both break down in addition to stimulation of androgens as well as estrogens. In particular17 βHSD1 promotes the reduction of estrone towards E2, whereas 17 βHSD2 results in oxidation of E2 to estrone[124] expression of 17 βHSD1 in case of humans occurs in placenta, ovary, breast epithelial cells, whereas 17 βHSD2 expression takes place in placenta, lung, Kidney liver, pancreas, prostate, colon, small intestine, endometrium and breast epithelial cells.[124] Oxidation action was documented by Stupans and Stretch,[125] in particular, dihydroxy benzoicacid, gallic acid, hydroxysterol and oleuropein resulted in hampering of the reduction action of 17 βHSD1, however not the oxidation action . Actually, gallic acid resulted in stimulation action by 30%.[125]

Certain molecules like epicatechin might further result in stimulation of 17 βHSD1 in rat testicular leydig cells.[126] Akin to that resveratrol also controls protein along with, mRNA expression, of 17 βHSD in rat.[127] Curcumin in addition to quercetin escalated the action of 17 βHSD, however curcumin illustrated a little greater action in contrast to quercetin.[128] Conversely, soy isoflavones treatment in female rats resulted in reduction of 17 βHSD amounts.[129] That way a prior report documented that genistein possesses the capacity of hampering the17 βHSD enzyme in both human and rat testis microsomes.[130] Occasional studies that are correlated with the extra virgin olive oil consumption in addition to T2DM.[98] In case of 2 intervention studies, 500mg of leaf extract resulted in insulin resistance factors. The 1st study that was conducted in 21 over weight men that received therapy for21wks in contrast to 22 control men resulted in enhancement of pancreatic β cells function in addition to insulin amounts. A greater enhancement of these parameters, were the observations once 36 subjects received treatment with those with hypolipaemia or under antihypertensive therapy were excluded.[131] The consumption of one capsule /day (with 51. 1mg oleuropein and 9. 7mg hydroxysterol for12 wks) resulted in enhancement of pancreatic β cells function and insulin sensitivity in T2DM patients was seen in another study . This other study was conducted in 41 T2DM male patients for14wks (control, n=38) and demonstrated enhancement of HbA1c in addition to insulin sensitivity amounts.[132] The utilization of dosages of olive oil leaf extract delivered possessed 51. 1mg oleuropein and 9. 7mg hydroxysterol. In contrast to that in the other study, nothing was documented with regards to the delivery of 2 polyphenol high olive oil(20m//day with 6mg hydroxysterol) for6wks in case of 63 healthy controls(group1, n=39, group2, n=29, control n=9).[133] In another study that was conducted in 11 over weight T2DM adult patients, the observation was that the delivery of 25 ml of high phenol olive oil for4wks resulted in reduction of HbA1c along with, FBG.[134] Lastly, PREDIMED(Prevention with Mediterranean Diet)trial demonstrated that Mediterranean Diet which had received supplementation, of extra virgin olive oil resulted in reduction of the incidence, of T2DM by 40% whereas enhancement of glucose metabolism took place in 50% of the recruited patients who possessed greater risk of cardiovascular disease.[135,136] Furthermore, 50ml of of extra virgin olive oil caused an enhancement of expression of correlated candidate genes in the peripheral blood mononuclear cells.[137] Actually, besides possessing greater amounts of polyphenols it is further rich in flavonoids, isoflavones and, lignans, which can get deducted from these effects with regards to glucose metabolism, that might be believed on assessment of the result from interventional experimental studies.

Controlling of the glucose consumption to hexosamineggeneration via glutamine –fructose-6 phosphate aminotransferase

Glutamine –fructose-6 phosphate aminotransferase(GFAT) represents a rate limiting enzyme in the hexosamine bio generation pathway which has a key part in T2DM generation.[138] The enzyme GFAT causes transformation of fructose-6 phosphate into Glutamine –6 phosphate in mammals, the integration of glucose via the hexosamine biogeneration pathway isbelieved to be a cell nutrient sensor, besides this pathway being one of the modes by which hyperglycemia induces peripheral IR,[139] in addition to diabetic complications.[140] In that respect the escalation of human GFAT is believed to be responsible for insulin resistance in case of cellular and animal models.[141]

In case of Wistar rats fenugreek(Trigonella foenum –graecimL.) was documented, to possess the capacity of regulation of the escalation of GFAT action that was induced by corn starch diet in addition to reduction in kidney injury.[142]

Akin to that in silico Coriandrum sativum L, fruits along with its phyto components assessment in silico model revealed that the agent limonene possessed the capacity of hampering GFAT. Actually, a meta-analysis that is inclusive of 10 clinical trials demonstrated, that consumption of fenugreek amongst, 1 as well as 100g/day for 10-84days caused a reduction in FBG by-17. 93mg/dl, 2h post load glucose -39. 46mg/dl in addition to HbA1c by-8. 5%. Fenugreek delivery was in the form of powder, alcoholic extract or capsules.[143] Furthermore, the highlighting of alterations were observed in T2DM in addition to over weight patients (n=20 patients, n=20 controls, 1g/day for2wks)[143] and T2DM with coronary artery disease (CAD n=30 patients, n=30 controls, 25g twice a week).[144] It has been pointed that larger double blind randomized, placebo controlled trials are needed to get conducted as per severe standardis with regards to herbal intervention in view that the trials that have been evaluated and are existent till now possess low sample size (≤25 subjects).[144] The other meta-analysis that evaluated the same articles was conducted later with akin conclusions that emphasized that lower quality of the studies with further highlighting the advantageous actions of fenugreek in pre diabetes patients.[146]

In a separate study that was conducted later 60 patients received therapy with metformin in case of T2DM patients the observation was that delivery of fenugreek in dosages of1g t. i. d. for12wks resulted in correction of FBG, postprandial(PP) glucose, and HbA1c in greater percentage in contrast to the group that received therapy with metformin (n=30in every group), that pointed that the utilization of fenugreek can be done in the form of a complementary treatment for the regulation of T2DM.[147] Simultaneously, the observation in one more longitudinal study was that in case of T2DM patients where men with hyperglycemia and in case of various therapies, 25g/day of fenugreek for24wks resulted in reduction of glucosuria and HbA1c(n=60in treated, n=10in controls.[148]

Controlling of insulin liberation, the uptake of glucose, Besides Gluconeogenesis via Mono-ADP-Ribosyl transferase-Sirtuin6

Sirtuin6 possessess both NAD^+ based fatty deacetylase.[149] in addition to Mono-ADP- Ribosyl transferase activity,[150] besides getting targeted by the antidiabetic epidrugs that display hampering or stimulatory modes. In brief, the lack of SIRT 6 action has been correlated with an escalation of uptake of glucose by tissues in addition to reduction of glucose amounts,[151] via hampering the expression of the resistance transcriptional factor hypoxia inducible factor 1 alpha(HIF 1-α), that is implicated in the transcription of glucose transporters.[152] Furthermore, SIRT 6 enhances the deacetylation of peroxisome proliferator activated receptorγ (PPARγ)coactivator(PGC)-1α, that causes potent stimulation of hepatic gluconeogenesis.[153]

The crosstalk, amongst the major bioactive agents of ginger (namely 4- gingerol, 6- gingerol, 8- gingerol, 10- gingerol, 6- shogal, in addition to β-bisabolol) along with protein targets(GFAT, SIRT6, GLUT4, 11 βHSD1 and glycogen phosphorylases) were evaluated with the utilization of computational crosstalk, approaches, molecular docking, besides pharmacophore.154. SIRT 6 along with GFAT demonstrated greater affinity for binding ranges which were lesser in contrast to 11 βHSD1 as well as glycogen phosphorylases, however possessed greater stability in addition to robust crosstalk with GLUT4, . Thus as conclusions the study documented that the synergistic mixing of ginger phytochemicals might possess a functional action for the therapy with regards to T2DM patients.

Euphorbia thymfolia L. represent a medicinal plant that possesses documented anti hyperglycemic action.155 A study with the objective of assessment of the antidiabetic mode that implicated molecular crosstalk amongst Phytochemicals in E. thymfolia in addition to protein targets (11 βHSD1, GFAT, SIRT6, PTP1B) were evaluated.156 The major observation was that 7 active agents that possessed greater binding affinities (<-8. 0 kcal/mol)toward all the 4 targeted proteins were seen, like βamyrine, taraxerol, 1-O-galloyl-β-D-glucose, corilagin, cosmosin, quercetin -3 galactoside as well as quercetin . Till date there are no clinical outcomes that are existent with regards to the clinical trials that have tried to conduct particular targeting SIRT6, inhibitors thus this needs to be the field where higher evaluation is required in the coming future.

Conclusions

Epidrugs represent another different approach for the avoidance or postponement of the initiation of T2DM via epigenetic modes. The utilization of these innovative drugs has illustrated a greater capacity in view of their ability of genetic modulation, of diseases, whereas other therapies work via other biochemical modes. A lot of plants that we utilize on daily basis(like ginger, tea, as well as fenugreek) in addition to phytochemicals(Curcumin as well as Resveratrol) that possess the capacity of influencing T2DM have been demonstrated, to crosstalk, with various protein targets with regards to T2DM. Nevertheless, in certain cases contradictory outcomes are obtained . The existent data emphasize that certain compounds that have bioactivity possess epigenetic controlling actions and seem to possess the capacity of treatment and /or as complementary agents in addition to pharmacological hypoglycemic agents that present a lot of adverse actions . The modes that have been implicated, with regards to the treatment actions of these epidrugs that are considered as potential treatment agents that have been detailed here are the reduction of insulin resistance through hampering11 β—HSD, the escalation of insulin actions via hampering PTP1B, controlling of estradiol through the 17 βHSD hampering, the glucose that is getting consumed into hexosamine biogeneration controlling through GFAT that gets hampered in addition to the part played by SIRT 6in insulin liberation, uptake of glucose, besides control of gluconeogenesis. Furthermore, escalation of greater in depth studies with regards to natural along with synthetic agents, in addition to newer protein targets are required to be conducted . Additionally, newer pre clinical studies further need to get conducted for estimation of the efficacy of these epidrugs.

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Conflicts of interest

The authors declare that they have no competing interests.

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References

1. ZhouB, LuY, Hajifthalian K, Bet al.Worldwide trends in Diabetes since 1980:a pooled analysis of 751 population – based studies with 4.4 million participants. *Lancet*. 2016;387(10027):1513–1530.
2. Chatterjee S, Khunti K, Davies MJ. Type2 Diabetes. *Lancet*. 2017;389(10085):2239–51.
3. WHO Diabetes.
4. Haslam DW, JamesWPT. Obesity. *Lancet*. 2005;366(9492):1197–1209.
5. Fradin D, Bougneres P. T2dm;Why Epigenetics. *J Nutr Metab*. 2011:2011:647514.
6. LingC. Epigenetic regulation of insulin action and secretion–role in the pathogenesis type2 Diabetes mellitus. *J Int Med.* 2020;288(2):156–157.
7. Shanak S, Saad B, Zaid H. Metabolic and Epigenetic action of antidiabetic medicinal plants. *Evidence Based Complement Alter Med*. 2019:18.
8. Liu J, Lang G, Shi J. Epigenetic regulation of PDX–1 in type2 Diabetes mellitus. *Diabetes Metab Syndr Obes.* 2021;14:431–42.
9. Dayeh T, Volkov P, Salo S, et al. Genome Wide DNA methylation Analysis of human pancreatic islets from type2 Diabetes mellitusand nonDiabetic Donors Identifies candidate genes that influence insulin secretion. *PLoS Genet*. 2014;10(3):e1004160.
10. Hall E, Dekker Nitert M, Volkov P, et al. The effects of high glucose exposure on global gene expression and DNA methylation in human pancreatic islets. *Mol Cell Endocrinol*. 2018;472:57–67.
11. Gancheva S, Ouni M, Jelenik T, et al. dynamic changes of muscle insulin sensitivity after Metabolic surgery. *Nat Commun.* 2019;10(1):4179.
12. Alkhalidy H, WangY, LiuD. Dietary flavooids in the prevention of T2D:an overview. *Nutrients*. 2018;10(4):1–33.
13. Salehi B, Ata A, Vak N, et al. Antidiabetic potential ofmedicinal plants andtheir active compounds. Biomolecules. 2019;9(10):551.
14. Mahomoodally MF, Mootoosamy A, Wambugu S. Traditional therapies used to manage Diabetes and related complications in Mauritius:A comparative ethnoreligious study. Evidence Based Complement. *AlterMedeCAM*. 2016:4523828.
15. TeohSL, DasS. Phytochemicals and their effective role in the treatment of Diabetes mellitus:a short review. *Phytochem Rev.* 2018;17(5):1111–1128.
16. Ortega A, Berna G, Rojas A, et al. Gene–diet interactions in type2 Diabetes:the chicken and egg debate. *IntJ Mol Sci.* 2017;18(6):1188.

17. Kochar Kaur K, Allahbadia GN, Singh M. Importance of Simultaneous Treatment of Obesity andDiabetes Mellitus:A Sequelae to the Understanding of Diabesity–A Review. *Obes Res Open J*. 2019;6(1):1–10.

18. Kochar Kaur K, Allahbadia GN, Singh M. Potential role of Epigenetic Modulation in prevention or therapy for Diabetic Kidney Disease–still a dream or a reality –A Systematic Review. *J Diab Nephro Diab Mgmt*. 2021;1:1(1–26)

19. Kochar Kaur K, Allahbadia GN, Singh M. Role of *Trigonella foenum–graecim* Extract along with Ursolic Acid a Pentacyclic Triterpenoid as Newer Plant Productsfor the Therapy of Diabetes Mellitus – A Short Communication". *Acta Scientific Nutritional Health.* 2021;5(6):(12–15) .

20. Kulvinder Kochar Kaur, Allahbadia GN, Singh M. Development of protein tyrosine phosphatase 1B (PTPIB)Inhibitors from marine sources and other natural products–Futureof Antidiabetic Therapy:A Systematic Review. *Korean Journal of Food & Health Convergence.* 2019;5(3):21–33.

21. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type2 Diabetes: perspectives on the past , present and future. *Lancet*. 2014;383(9922):1068.

22. Martinez–Moreno JM, Fontecha –Barriuso M, Martin – Sanchez D, et al. Epigenetic modifiers as potential therapeutic targets in Diabetic Kidney Disease. *Int J Mol Sci*. 2020;21:4113.

23. Ling C, Ronn T. Epigenetics in human obesity and type2 Diabetes. *Cell Metab*. 2019;29(5):1028–1044.

24. Allis CD, Jenuwein T. The molecular hallmarks of Epigenetic controls. *Nat Rev Genet*. 2016;17(8):487–500.

25. Bonev B, Cavalli G. Organization and function of the 3D Genome. Nat RevGenet. 2016;17(11):661–78.

26. CavalliG, Heard E. Advances in Epigenetics link genetics to the environment and disease. *Nature*. 2019;571(7766):489–499.

27. You D, Nilsson E, Tenen E, et al. Dnmt3a is an Epigenetic mediator of adipose insulin resistance. *Elife*. 2017;6(1):661–20.

28. Tan M, Lou ZH, Lee S, et al. Identification, of 67 histone marks and histone lysine crotonoylation as a new type of histone modifications. *Cell*. 2011;146(6):1016–1028.

29. Alamdari N, Aversa Z, Castillero E, et al. Acetylation and de Acetylation–novel factors in muscle wasting. *Metabolism*. 2013;62(1):1–11.

30. Hyun K, Jeon J, Park K, et al. Writing, erasing and reading histone lysine methylations. *Exp Mol Med*. 2017;49(4):e324–e.

31. Martinez–Moreno JM, Fontecha –Barriuso M, Martin – Sanchez D, et al. The contribution of Histone crotonylation to tissue health and disease :focua on kidney health. *Front Pharmacol*. 2020;11:393.

32. Kim M, Zhang X. The profiling and role of miRNAs in Diabetes mellitus. *J Diabetes Clin Res*. 2019;1(1):5–23.

33. Mongelli A, Martelli F, Farsetti A, et al. The dark that matters :long noncoding RNAs as master regulators of cellular metabolism in Non Communicable Diseases. *Front Physiol.* 2019;10:369.

34. Hall E, Dayeh T, Kirkpatrick CL, et al. DNA methylation of the glucagon like peptide 1 receptor in human pancreatic islets. *BMC Med Genet.* 2013;14:76.

35. Prentki M, Nolan CJ. Islets β cell failure in type2 Diabetes. J CI Insight. 2006;5:1802–1812.

36. Avraham D, Kaestner KH. The dynamic methylome of islets in health and diseases. *Mol Metab*. 2019;27S(Suppl):S25–32.

37. Ouni M, Sausethaaler S, Eichelmann F, et al. Epigenetic changes in islets of langerhans preceding theonset of *Diabetes*. Diabetes. 2020;69(1):2503–2517.

38. Wahl S, Drong A, Lehne B, et al. Epigenome wide association studiesof body mass index and the adverse outcomes of adiposity. *Nature*. 2017;541(7635):81–86.

39. Chambers JC, Loh M, Lehne B, et al. Epigenome wide association of DNA .methylation markers in peripheral nested case controlled study. Lancet Diabetes *Endocrinol*. 2015;3(7):526–534.

40. Liu ZF, Chen LI, Deng XL, et al. Methylation status of the CpG sites in the MCP1 promoter is controlled by serum MCP1 in type2 Diabetes. *J Endocrinol*. 2012;35(6):585–589.

41. RoshanzamirN, Hassan–ZadehV. Methylation and Epigenetic sites in IL–1β and IL–1R1 genes is by hyperglycemia in type2 Diabetes patients. *Immunol Invest*. 2020;49(3):287–298.

42. Barres R, Osler ME, Yan J, et al. Non CpG methylation of thePGC1alpha promoter through DNMT3B controls mitochondrial density. *Cell Metab*. 2009;10(3):189–198.

43. Miao F, GonzaloI G, Lanting N, et al. In vivo chromatin remodeling events leading to inflammatory gene transcription underDiabetic conditions. *J BiolChem.* 2004;279(17):18091–18097.

44. Pirola L, Balcerczyk A, Tothill RW, et al. Genome wideanalysisdisti nguishes hyperglycemia regulated Epigenetic signatures of primary vascular cells. *Genome Res*. 2011;21(10):1601–15.

45. Ibarra Urizar A, Prause M, Wortham M, et al. Beta cell dysfunctioninduced by non cytotoxic Concentrations of interleukin–1β is associated with changes in expression of Beta cell maturity genes and associated histone modifications. *Mol Cell J Endocrinol*. 2019;496:110524.

46. El–Osta A, Brasacchio D, Yao D, et al. Transient high glucose Concentrations causes persistent epigenetics changes and altered Gene expression during subsequent normorglycemia. *J Exp Med*. 2008;205(10):2409–2417.

47. Paneni F, Costantino S, Battista R, et al. Adverse Epigenetic signatures by histone methyltransferase Set7 contribute to vascular dysfunction in patients with type2 Diabetes mellitus. *Circ Cardiovasc Genet*. 2015;8:150–158.

48. Okabe J, Orlowski C, Balcerczyk A, et al. Distinguishing hyperglycemic changes by Set7 in vascular endothelial cells. *Circ Res*. 2012;110(8):1067–1076.

49. Huang B, YangXD, Zhou MM, et al. Brd4 coactivates transcriptional activation of nuclear factor κB via specific binding to to acetylated Rel A. *Mol CellBiol*. 2009;209(5):1375–1387.

50. AkbariM, Hassan–ZadehV. The inflammatory effects of Epigenetic factors and modifications in type2 Diabetes. *Inflammo Pharmacology*. 2020;28(32):345–362.

51. Villeneuve LM, Kato M, Reddy MA, et al. Enhanced levels of microRNA 125b in vascular smooth muscle cells of Diabeticdb/dbmice lead to increased inflammatory Gene expression by targeting the histone methyltransferase Suv39h1. *Diabetes*. 2010;59(11):2904–2915.

52. Reddy MA, ChenZ, Park JT, et al, regulation of inflammatory phenotype in macrophages by Diabetes induced long noncoding RNAs. *Diabetes*. 2014;63(12):4249–4261.

53. Satishkumar C, PrabhuP, Bala Subramanyam M. Linking a role of lncRNA(long noncoding RNAs)with insulin resistance accelerated Senescence and inflammation inpatients with type2 Diabetes. *Hum Genet.* 2018;12(1):41.

54. Jayasinghe CD, Udalamaththa A, Imbulana IBPS, et al. Dietary Phytochemicals as epidrugs :role in modulating the Epigenetic mechanisms of human diseases. *Int J Curr PharmRev Res*. 2016;7:50–58.

55. ProshkinaE, Shaposhnikov M, Moskalev A. Genome, protecting compounds as gero protectors. *Int J Mol Sci*. 2020;21(12):4484.

Citation: Kaur KK, Allahbadia G, Singh M. Therapeutic potential and epigenetic alterations of plant phytochemicals (as epi-drugs) for the treatment of type 2 diabetes mellitus: a systematic review. *Adv Obes Weight Manag Control.* 2021;11(6):195–206. DOI: 10.15406/aowmc.2021.11.00355

56. Zinker B, Mika A, NguyenP, et al, Liver selective glucocorticoid receptor antagonism decrease glucose production and increases glucose disposal, ameliorating insulin resistance. *Metabolism– ClinExp*. 2007;56(3):380–387.

57. Cabrera–PerezLC, Padilla MII, CruzA, et al. Design, synthesis, molecular docking and in vitro evaluation, of benzothiazole derivatives of 11 β—hydroxysteroid dehyrogenase 1 inhibitors. *Mol Divers*. 2020;24(4):1–14.

58. Bailey MA. 11 β—hydroxysteroid dehyrogenase s and hypertension in the Metabolic Syndrome. *Curr Hypertens Rep*. 2017;19(12):100.

59. MortonNM. Obesity andcorticosteroids:11 β—hydroxyssteroid dehyrogenase 1 as a cause andtherapeutic target in Metabolic disease. *Mol CellEndocrinol*. 2010;316(2):154–164.

60. ZhuQ, GeF, DongY, et al. Comparison of flavonoids and isoflavonoids to inhibit rat and human11 β—hydroxyssteroid dehyrogenase 1 and2. *Steroids*. 2018;132:25–32.

61. Torres–PiedraM, Ortiz– Andrarde R, Villalobos–Molina R, et al. A comparative study on flavonoid analogues on streptozocin– nicotinamide induced Diabetic rats:quercetin as a potential anti diabetic agent acting via 11 β—hydroxyssteroid dehyrogenase 1 type inhibition. *Eur J Med Chem*. 2010;45(6):2606–12.

62. Takawa N, Kubota S, Kobayashi Y, et al. Genistein inhibits glucocorticoid amplification in Adipose tissue by suppressionof 11 β—hydroxyssteroid dehyrogenase 1. *Steroids*. 2015;93:77–86.

63. Rockwood S, Broderick TL, Al–Nakkash L. Feeding obese Diabetic mice a Genistein diet induced thermogenic and Metabolic change. *J Med Food*. 2018;21(4):332–339.

64. Teich T, PivovarovJA, Porras DP, DunfordEC, RiddellMC. Curcumin limits weight gain, adipose tissue growth , and glucose intolerance following cessation of exercise and caloric restriction in rats. *J Appl Physiol*. 2017;123(6):1625–1634.

65. Hu GX, Lin H, Lian Q, et al, Curcumin as a potent and selective inhibitor of 11 β—hydroxyssteroid dehyrogenase 1:improving lipid profiles in high fat diet treated rats. *PLoSONE*. 2013;8(3):e49976.

66. Takawa N, Kubota S, Kato I, et al. Resveratrol inhibits 11 β—hydroxyssteroid dehyrogenase 1activity in rat adipose microsomes. *J Endocrinol*. 2013;218(3):311–20.

67. Hintzpeter J, Stapelfeld C, Loerz C, et al. Green tea and one of its constituents epigallocatechin gallate, are potential inhibitors of human 11 β—hydroxyssteroid dehyrogenase type 1. *PLoSONE*. 2014;9(1):e84468.

68. Zhu J, Chen H, Song Z, et al. Effects of ginger (Zingiber officianale Roscoe) on type2 Diabetes mellitus and components of the Metabolic Syndrome:a systematic review and, meta–analysis of randomized controlled trials. *Evidence Based Complement AlterMedeCAM.* 2018;2018:5692962.

69. Arablou T, Aryaeian N, Valizadeh M SharifiF, et al. The Effects of ginger consumption on glycaemic status , lipid status and inflammatory markers in patients with type2 Diabetes mellitus*. Int JFood SciNutr*. 2014;65(4):515–20.

70. Shidfar F, Rajab A, Rahideh T, et al. Effects of ginger (Zingiber officianale)on glycaemic markers in patients with type2 Diabetes. *J Complement Alter Med.* 2015;12(2), 165–70.

71. Feng T, SuJ, Ding ZH, ZhengYT, LiY, LengY, et al. chemical constituents and their bioactivities of to ngling white ginger (Zingiber officianale Roscoe). *J AgricFood Chem*. 2011;59(21):11690–11695.

72. Whirlwooed CB, Sheppard MC, Stewart PM. Licorice inhibits 11 β—hydroxysteroid dehyrogenase type1 messengr ribonucleic acid levels and potentiates glucocorticoid hormone action. *Endocrinolog.*y 1993;132(6):2287–2292.

73. GumyC, ThurnbichlerC , Aubry EM, et al. Inhibition of 11 β—hydroxysteroid dehyrogenase 1by plants extracts used as traditional antidiabetic medicine. *Filotrapia*. 2009;80(3):200–205.

74. Pivari F, Mingione A, Brasacchio C, et al. Curcumin and type2 diabetes mellitus, prevention and treatment. *Nutrients*. 2019;11(8):1837.

75. Yang G, ShuX O, Jin F, et al. Soy foods consumption and risk of glycosuria:a cross–sectional study within the Shanghai women's HealthStudy. *EurJ ClinNutr.* 2004;58(4):615–620.

76. Usui T, Tochiya M, Sasaki Y, et al. Effects of natural S–equol supplements on over weight or obesity and Metabolic Syndrome in theJapanese based on sex andand equol status. *Clin Endocrinol(Oxf).* 2013;78(3), 365–372.

77. Pan A, Sun J, Chen Y, et al. Effects of a flaxseed derived lignan supplement in type2 diabetics patients, :a randomized, double blind crossover trial . *PLoSONE.* 2007;2(11):e1148–e.

78. Atteritano M, Marini H, Minutoli II, et al. Effects of thePhytoestrogen genistein teritae on some predictors of cardiovascular risk in osteopenic postmenopausal women :a2year a randomized, double blind, placebo controlled study. *J Clin Endocrinol Metab*. 2007;92(8):3068–3075.

79. Ho SC, Chen Y–m, HoSSS, et al. Soy isoflavones supplementation and Fasting serum glucose andlipid profile among postmenopausal Chinese women:a randomized, double blind, placebo controlled trial. *Menopause*. 2007;14(5):905–912.

80. Van der Schow YT, Sampson I, Willett WC, et al. The usual intake of lignans but not that of isoflavones may be to cardiovascular risk factors in US men. *J Nutr*. 2005;135(2):260–266.

81. Shi L, Ryan HH, Jones E, et al. Urinarysoflavone Concentrations, are inversely associated with cardio metabolic risk markers in pregnantUS women. *J Nutr*. 2014;144(3):344–351.

82. Goodman–Gruen D, Kritz–Silverstein D. Usual dietary isoflavones intake is associated ion with, cardiovascular disease risk factors inpostmenopausal women. *J Nutr*. 2001;131(4):1202–1206.

83. Zamora–Ros R, Forouhi NG, Sharp SJ, et al. The association between dietary flavonoid and lignan intake and incident type2 diabetes in European population:the EPIC–Interact study. *Diabetes Care.* 2013;36(12):3961–3970.

84. Sun Q, Weddick NM, PanA, et al. gut microbiota metabolites of dietary lignans and risk of type2 diabetes: a prospective investigation, in two cohorts of US women. *Diabetes Care*. 2014;37(5):1287–1295.

85. Mueller NT, Odegaard AO, GrossMD, et al. Soy intake and risk of type2 diabetes in Chinese Singaporean*. Eur J Clin Nutr.* 2012;51(8):1033–1040.

86. Nanri A, Mizoue T, Takahashi Y, et al. Soy products and isoflavones intake are associated with, a lower and risk of type2 diabetes in overweight , obese Japanese women. *J Nutr*. 2010;140(3):580–6.

87. Villegas R, Gao YT, Yang G, et al. Legumes and soy foods, intake and the incidence of type2 diabetes in the Shanghai women's HealthStudy. *AmJ ClinNutr*. 2008;87(1):162–167.

88. Chuengsamarn S, Rattanamonkolgul S, Leuchapudiporn R, et al. Curcumin extract for prevention of type2 diabetes. *Diabetes Care.* 2012;35(11):2121–2127.

89. Panalu Y, Khalili N, Sahebi E, et al. Effects of curcuminoidsplus piperine on glycaemic , hepatic and inflammatory biomarkers in patients with type2 diabetes:a randomized, double blind, placebo controlled trial. *Drug Res(Stuttg).* 2018;68(7):403–409.

90. Rivera– Mancia S, Trujillo J, Chaveri JP. Utility of Curcumin for the treatment of type2 diabetes mellitus: evidence from pre Clinical and Clinical studies. *J Nutr Intermediary Metab*. 2018;14:29–41.

91. Na LX, Li Y, Pan HZ, et al. Curcuminoids exert glucose lowering effect in type2 Diabetes by decreasing serum free fatty acids: a a randomized, double blind, placebo controlled trial . *MolNutr Food Res*. 2013;57(9):1565–7.

92. Rahimi HR, Mohammadpour AH, Dastani M, et al. The Effects of nanocurcumin on HbA1c , fasting blood glucose and lipid profiles in diabetic subjects:a randomized Clinical trial. *Avicenna J Phytomed*. 2016;6(5):567–77.

93. Cione E, LaTorre C, Cannataro R, et al. Quercetin epigallocatechin gallate, Curcumin and Resveratrol from Dietary source to human microRNA modulation. *Molecules*. 2019;25(1):1–26.

94. Sanchez M, Gonzalez – Burgos E, Iglessias I, et al. The Pharmacological activity of (Camellia sinensis (L)Kuntze)on metabolic and endocrine disorders:a systematic review. *Biomolecules*. 2020;10(4):1–27.

95. Mahmoudi F, Al–OzairiE, Haines D, et al. Effects of Diabetea Tea™ consumption on inflammatory cytokines and metabolic markers in type2 Diabetesmellitus patients. *J Ethnopharmacol*. 2016;194:1069–1077.

96. Toolseo NA, Aruoma OJ, Gunness TK, x et al. Effectiveness of Green tea in a randomized, human cohort relevance to diabetes and its complications. *Biomed Res In*t. 2013;2013:412379.

97. Rafieian Kopaei M, Motamedi P, Vakili I, et al. Green tea and type2. *J Neuropharmacol.* 2014;3(1):21–3.

98. Guasch –Ferre M, Merino J, Sun Q, et al. Dietary Polyphenols , Mediterranean diet , pre diabetes and type2 diabetes:a narrative reviewof the evidence. *OxidMed CellLongev*. 2017;2017:6723931.

99. Hadi S, Alipour M, Aghamohammadi V, et al. Improvement in fasting blood sugar, Anthropometric measurement andhs–CRP after consumption of epigallocatechin–3– gallate(EGCG)in patients with type2 diabetes mellitus. *Nutr Food Sci*. 2019;50(2):348–59.

100. Hussein H, GreenIR, Abbas G, et al. Protein tyrosine phosphatase 1B((PTP1B) inhibitors as potential anti diabetes agents: patent review. *Expert Opin Ther Patents.* 2019;29(9):1–14.

101. ZhengW H, Kar S, Quinton R . Insulin like growth factor–1 induced phosphorylation of transcriptional factorFKHRL1.1 is mediated by phosphatidyl inositide 3 –kinase/ AKT kinase and role of this pathway in Insulin like growth factor–1 induced survival of cultured hippocampal , neurons. *Mol Pharmacol*. 2002;62(2):225–233.

102. Jiang CS, Liang LF, Gu, YW.(). Natural products possessing Protein tyrosine phosphatase 1B–(PTP1B) inhibitory activity found in the last decades. *Acta* Pharmacol *Sin.* 2012;*33:*1217–45.

103. Gonzalez– Rodriquez A, Santamaria B, Mas–Gutierrez JA, et al. Resveratrol treatment restores peripheral insulin sensitivity in diabetic mice in a sirt 1 independent ma n ner. *Mol Nutr Food*. 2015;59(8):1431–42.

104. Rodgers JT, LerinC, Haas W, et al. Nutrient control of glucose homeostasis through a complex of PGC–1 alpha and SIRT1. *Nature*. 2005;434(7029):113–118.

105. LiX, Lee YJ, Jin F, et al. Sirt 1 negatively regulates FcepsilonR1 mediated mast cell activation through AMPK and PTPIB dependent processes. *Sci Rep*. 2017;7(1):6444.

106. Chuang CC, Martinez K, Xie G, et al. Quercetin is equally or more effective than Resveratrol in attenuating Tumor necrosis factor alpha–mediated inflammation and insulin resistance in primary human adipocytes. *Am JClin Nutr*. 2010;92(6):1511–1521.

107. Kostrzewa T, Przychodzen P, Gorska–Ponikowska M, et al..(). Curcumin and cinnamaldehyde as PTPIB inhibitors with Antidiabetic and Anti Cancer Potential. *Anticancer Res. 2019;39*(2);745–749..

108. Li JM, Li YC, Kong LD, et al. Curcumin inhibits hepatic protein tyrosine phosphatase 1B and prevents hepatic hypertriglyceridemia andhepatic steatosis in fructose fed rats. *Hepatol(BaltimoreMd).* 2010;51(5):1555–1566.

109. Ding XO, Gu TT, Wang W, et al. Curcumin protects against fructose –induced podocyte insulin signaling impairment, through upregulation of miR206. *Mol Nutr Food Res*. 2015;59(12):2355–2370.

110. BustanjiY, TahaMO, Al Maseri M, et al. Docking stimulation and in vitro assay unveils potent inhibitory action of Papaverine against protein tyrosine phosphatase 1B. *Bol Pharm Bull.* 2009;32(4):640–645.

111. XuF, Wang F, WangZ, et al. uptakeacti vities of bis(2, 3) dibromo–4, 5–dihydroxyl)ether, a novel marine natural product from red alga odothaliacorymbifera with protein tyrosine phosphatase 1B inhibition, in vitro and in vivo. *PLoSONE*. 2016;11(1):e0147748–e.

112. Kim DH, Paudel P, Yu T, et al. Characteristization of the inhibitory activity of natural tanshinones from Salvia miltiorrhiza Bunze rootson protein tyrosine phosphatase 1B. *Chemico–biol Interact*. 2017;278:65–73.

113. Lee SH, Kim YS, Lee SJ, et al. The protective effective of Salvia miltiorrhiza in ananimal model of experimentally induced Diabetic Nephropathy. *J Ethnopharmacol*. 2011;137(3):1409–1414.

114. Yue KK, Lee KW, Can KK, et al. Danshen prevents the occurrence of Oxidative stressin the eye and aorta of Diabeticrats without affecting the hyperglycaemic state. *J Ethnopharmacol*. 2006;106(1):136–141.

115. Brasnyo P, Molnar GA, Mohas M, et al. Resveratrol improves insulin sensitivity, reduces Oxidative stress and acti vates the Akt pathway in type2 diabetic patients. *Br JNutr* .2011;106(3):383–9.

116. BhattJK, Thomas S, Nanjan M. Resveratrol supplementation improves glycaemic control in type2 diabetes mellitus. *Nutr Res*. 2012;32(7):537–541.

117. Yoshi no J, ConteC, Fontana J, Mittendorfer B, ImaiS, SchechtmanKR, et al. Resveratrol supplementation does not improve Metabolicfunction in nonobese women with normal glucose tolerance. *Cell Metab*. 2012;16(5):658–664.

118. Chachay VS, McDonald GA, Martin JH, et al. Resveratrol does not benefit patients with non alcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2014;12(12):2092–20103.

119. Poulsen MM, Vesteraard PF, Clasen BF, et al. High dose Resveratrol supplementation in obese men:an investigator initiated randomized, placebo controlled Clinical trial of substrate metabolism , insulin sensitivity, and body Composition. *Diabetes*. 2013;62(4):186–195.

120. Zamora–Ros R, Urpi –Sarda M, Lamuela–Raventos RM, et al. Highurinary levels of Resveratrol metabolites are associated with a reduction in the Prevalence of cardiovascular risk factors in high risk patients. *Pharmacol Res*. 2012;65(6):615–620.

121. Ramirez– Garza, SL, Laveriano– SantosEP, Marhuenda– Munoz M, et al. Health effects of Resveratrol results from human intervention trials. *Nutrients*. 2018;10(12):1–18.

122. Mauvais– JarvisF. Is estradiol a biomarker of type2 Diabetes risk in postmenopausal women ? *Diabetes*. 2017;66(3):568–570.

123. Muka T, Nano J, Jaspers I, et al. Association of steroid sex hormone and sex hormone binding globulin with the risk of type2 Diabetes in women:a population based cohort study and meta–analysis . *Diabetes*. 2017;66(3):577–586.

124. HillbornE, Stal O, Jansson A. Estrogen and androgens converting enzyme 17 β—hydroxysteroid dehyrogenase and their involvement in Cancer with a special focus on 17 β—hydroxysteroid dehyrogenase type1, 2 and Breast Cancer. *Oncotarget*. 2017;8(18):30552–62.

125. Stupana I, Stretch G, Hayball P. Olive oil phenols inhibit human hepatic microsomal activity. *J Nutr*. 2000;130(9):2367–70.

126. YuPL, PuHF, Chen SY, et al. Catechin, epicatechin and epigallocatechin on testosterone production in in rat leydig cells. J CellBiochem. 2010;110(2):333–342.

127. Bannerjee B, Nandi P, Chakraborty S, et al. Protective effects of Resveratrol on benzo(a)pyre ne i nduced testicular dysfunction of steroidogenesis and steroidogenic acute regulatory gene expression in leydig cells. *Front Endocrinol*. 2019;10:272.

Citation: Kaur KK, Allahbadia G, Singh M. Therapeutic potential and epigenetic alterations of plant phytochemicals (as epi-drugs) for the treatment of type 2 diabetes mellitus: a systematic review. *Adv Obes Weight Manag Control.* 2021;11(6):195–206. DOI: 10.15406/aowmc.2021.11.00355

128. Sharma P, Aslam Khan, Singh R. Curcumin and Quercetin ameliorated cypermethrin and deltamethrin induced reproductive system impairment in male wistar rats by upregulating the activity of pituitary–gonadal hormones and steroidogenic enzymes. Int J Fertil Steril 2018;12(1):72–80.

129. Rajan RK, SS M, Balaji B. Soy isoflavones exert beneficial effects on letrozole induced rat Polycystic ovary syndrome(PCOS) model through anti androgens mechanisms. *Pharm Biol*. 2017;55(1):242–51.

130. HuGX, Zhao BH, ChuCH, et al. Effects of Genistein and equol on human and rat testicular 3 β—hydroxysteroid dehyrogenase and 17 β–hydroxysteroid dehyrogenase 3 activities. *AsianJ Androl*. 2010;12(4):519–26.

131. De Bock M, Derraik JG, Brenn CM, et al. Olive (OIea EuropeaeL.) leaf polyphenols improve insulin sensitivity in middle aged over weight men:a randomized, placebo– controlled , crossover trial. *PLoSONE*. 2013;8(3):e57622. e laji

132. Wainstein J, Ganz T, Boaz M, et al. Olive oil leaf extract as a hypoglycemia agent in both human diabetic subjects and in rats. *JMed Food*. 2012;15(7):605–610.

133. Silva S, Bronze MR, Figueira ME, et al. Impact of a 6 week Olive oil supplementation in healthy adults on urinary proteomic biomarkers of coronary artery disease , Chronic Kidney Disease, and Diabetes(types 1 and 2):a randomized, parallel controlled , double blind study. *AmJClinNutr*. 2010;92(6):1511–1521.

134. Santengelo C, Filesi C, Vari R, et al. Consumption of extra virgin olive oil rich in phenolic compounds improves metabolic control in patients wi th type2 Diabetes mellitus.:possible involvement of reduced levels of Circulating visfatin. *J Endocrinol Investig*. 2016;39(11):1295–1301.

135. Salas– Salvado J, Bullo M, Estruch R, et al. Prevention of Diabetes with Mediterranean Diets:a subgroup analysis of a randomized trial. trial. *Ann Internal Med*. 2014;160(1):1–10.

136. Lasa A, MirandaJ, Bullo M, Casas R, Salas– Salvado J, Larretxi I, et al. Comparative effect of two Mediterranean Diets versus a low fat diet on glycemic control in individuals with type2 Diabetes. *Eur J ClinNutr*. 2014;68(7):767–772.

137. Konstantinidou V, Khymenets O, Covas MI, et al. Time course of changes in the expression of insulin sensitivity related genes after , an acute load of virgin olive oil .*Omics*. 2009 ;13(5):431–8.

138. Nakaishi Y, Bando M, Shimizu H, et al. Structure analysis of Human Glutamine –fructose–6 phosphate aminotransferase:a key regulator of type2 Diabetes. *FEBS Lett.* 2009;583(1):163–7.

139. Lindsay JE, Rutter J. Nutrient sensing and metabolic decisions. *Comp Biochem Physiol Part B Biochem Mol Biol*. 2004;139(4):543–59.

140. Zhang H, JiaY, Cooper JJ, et al. Common variants in Glutamine –fructose–6 phosphate aminotransferase (GFPT2) gene are associated with type2 Diabetes, Diabetic nephropathy increased GFPT2 mRNA levels. *J Clin Endocrinol Metab.* 2004;89(2):748–755.

141. Hebert LF Jr, Daniels MC, Zhou J, et al. Over expression, of Glutamine –fructose–6 phosphate aminotransferase in transgenic mice leads to insulin resistance. *J Clin Investig*. 1996;98(4):930–936.

142. Shetty AK, Salimath PV. Renoprotective effects of fenugreek(Trigonella foenum –graecimL.)during experimental Diabetes. *Erur e Journal ClinNutr Metab.* 2009;4(3):e137–e42.

143. Pararakh P. Insilico antidiabetic activity of linalool isolated from Coriandrum sativum L, fruits . *Ann Int J Cancer Cell Biol Res.* 2018;2(1):2–6.

144. Neilakantan N, Narayanan M, deSouxa RF, et al. Effects of fenugreek(Trigonella foenum –graecimL.) intake on glycemia:a meta–analysis of Clinical trials. *Nutr J.* 2014;13:7.

145. Lu FR, Shen L, Qin Y, et al. Clinical observation on Trigonella foenum –graecimL total saponins in combination with sulfonyl ureas in the treatment of type2 Diabetes mellitus. *Chin J Integr Med*. 2008;14(1):56–60.

146. Kaur M, Singh N, Sharma G, et al. To study the efficacy and tolerability of fenugreek seed powder as add on therapy with metformin in patients of type2 Diabetes mellitus. *Int J Basic Clin Pharmacol*. 2016;5(2):378–383.

147. Sharma RD, Sarkar A, Hazara DK, et al. Use of fenugreek seed powder in the management of non insulin dependent Diabetes mellitus. *Nutr Res*. 1996;16(8):1331–1339.

148. Gong J, Fang K, Dong FI, et al. Effects of fenugreek on hyperglycemia and hyperlipidemia in Diabetes and prediabetes:a meta–analysis . *J Ethnopharmacol*. 2016;194(3):260–268.

149. Jiang H, Khan S, Wang Y, et al. SIRT 6 regulates TNF alpha secretion through hydrolysis of long chain fatty acyl lysine. *Nature*. 2013;496(7443):110–113.

150. Zhang X, Khan S, Jiang H, et al. Identifying the functional contribution of the defatty acetylase activity of SIRT 6. *Nat Chem Biol.* 2016;12(8):614–620.

151. Mostoslavvsky R, Chua RF, Lombard D B, et al. Genomic instability and aging like phenotype in the absence of mammalian SIRT 6. *Cell*. 2006;124(2):315–329.

152. Zhong I, D'Urso A, Toiber D, et al. The histone deacetylase Sirt6 regulates glucose homeostasis via Hif–1 alpha. *Cell*. 2010;140(2):280–293.

153. Dominy JEJr, Lee Y, Jedrychowski, MF, et al. The , deacetylase Sirt6 activates the acetyl transferase GCN5and suppresses hepatic gluconeogenesis . *Mol Cell*. 20182;48(6):900–913.

154. Le L. Computational study of antidiabetic activities of bioactive compounds in Zingiber officianale. *World J Pharm Pharm Sci.* 2014;3(6):1995–2011.

155. Rahmatullah M, Hasa n SK, AliZ, et al. Anti hyperglycemic and anti nociceptive, activities of methanolic extract of Euphorbia thymfolia L. whole plants. *IntegrnMed*. 2012;10(2):228–232.

156. Nguyen Vo TH, Tran N, Nguyen D, et al. An in Silico Study on Antidiabetic Activity of Bioactive Compounds in Euphorbia Thymifolia Linn. *SpringerPlus.* 2016;5(1):1359.

Citation: Kaur KK, Allahbadia G, Singh M. Therapeutic potential and epigenetic alterations of plant phytochemicals (as epi-drugs) for the treatment of type 2 diabetes mellitus: a systematic review. *Adv Obes Weight Manag Control.* 2021;11(6):195–206. DOI: 10.15406/aowmc.2021.11.00355