

This report summarizes results of a System Pharmacology Analysis evaluating effects of Cardio Miracle on biological processes involved in the development and progression of Diabetes and shows that Cardio Miracle possesses a combination of functionalities that are ideally suited for intercepting development and progression of diabetes and associated comorbidities.

CARDIO MIRACLE FOR DIABETES

Emergent System Analytics
prepared by Anton Fliri

Introduction

CM, marketed by Evolution Nutraceuticals,¹ contains a mixture of arginine,² citrulline,³ cholecalciferol vitamin D, various vitamins, quercetin, minerals and over 700 natural products that can be isolated from herbal and vegetable product constituents (see supplemental section).⁴ Previous studies have shown that antioxidants added to a combination of arginine, citrulline and vitamin D synergistically increases NO and peroxynitrite ratios that are critical for preventing endothelial cells dysfunction (ED) and development of cardiovascular, metabolic and inflammatory diseases.⁵ Furthermore, it has been shown that interactions between CM ingredients upregulate caveola mediated endocytosis (CME), down regulate TGF beta activity, increase the production of calcitriol, increase the bioavailability of cholecalciferol vitamin D,⁶ and activate autophagy.^{7,8,9}

Background

Over 8% of the world population have type 2 diabetes (T2D).¹⁰ Five percent of these people have type 1 diabetes (T1D) and the rest has type 2 (T2D). However, this grouping of highly heterogeneous disorders (see supplemental section) is insufficient for disease stratification and outcome prediction.¹¹ Among key risk factors precipitating T2D is Obesity associated chronic inflammation and cardiovascular disease.¹² Thus, causes of diabetes involve overproduction of proinflammatory cytokines triggering inflammatory condition which damage insulin secreting pancreatic islet β -cells and precipitates decreased responsiveness of β -cells to glucagonlike peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP) which results in hyperglycemia.¹³ Hyperglycemia, in turn, causes endothelial dysfunction which makes diabetes not only a metabolic disease but also a cardiovascular disease.¹⁴ In fact, ischemic stroke, accounts for most of the morbidity, hospitalizations, and death in patients with diabetes. Comorbidities associated with T2D and shown in the supplemental section include coronary artery diseases,¹⁵ hypertension,¹⁶ dyslipidemia, high LDL cholesterol.¹⁷ neuropathy, retinopathy, nephropathy, and cognitive declines.

During the very early stages of diabetes, there is a striking loss of glucose-induced first-phase insulin release which predicts development of hyperglycemia.¹⁸ These early states called prediabetes, are also associated with a pseudo-insulin resistance which is a stage associated with reduced recycling of insulin receptors via clathrin and caveola mediated endocytosis. Impairment of insulin receptor recycling results in altered insulin responses and insulin clearance rather than a genuine insensitivity of INSR signaling.¹⁹ More advanced stages of disease progression, involve development of Insulin resistance, which is a condition where normal or even elevated levels of insulin produce an impaired glucose disposal responses.²⁰ At this stage, pancreatic β cells, pushed to secrete more insulin, become exhausted but are still being replenished through renewed β cells growth; however, once this β cell renewal capacity is exhausted, there is no backup to meet insulin demands which accelerates development of full blown diabetes and associated comorbidities. Accelerating this stage of disease progression are Increases in TGF beta 1 activity and impairment of autophagy, which plays a key regulatory role in the organization and function of pancreatic islet β -cells.^{21,22,23}

Gap Analysis: Retrospective analysis of T2D treatment outcomes suggests that current hypoglycemic agents (OHA) frequently produce insufficient hyper glycemetic control and islet cell protection. Current treatments, by targeting single mechanisms of actions do not integrate mechanisms that support integrity of insulin receptor signaling, insulin secretion, healthy islet cell functions, and beta cell renewal. Moreover, current strategies for treatment

and prevention of diabetes do not adequately protect against microvascular complications precipitating diabetes associated comorbidities.²⁴

Nitric Oxide: A Key Cellular Mechanisms linking Onset of Cardiovascular Disease, Obesity, and Diabetes

NO production in our body is controlled by three different nitric oxide synthase enzymes (NOS) catalyzing the NADPH- and O₂-dependent oxidation of L-arginine to L-citrulline. The neuronal form of nitric oxide synthase NOS1 or n NOS is expressed in neurons, skeletal muscle, and epithelial cells. The inducible NOS enzyme, NOS2 or iNOS, has the highest capacity to generate NO and is expressed by most cell types in response to inflammatory stimuli.²⁵ The endothelial form of NOS enzymes, NOS3 or eNOS is expressed in the vascular endothelium, neurons, epithelial cells, cardiomyocytes, adipocytes, and hepatocytes.

A common premise linking obesity, onset of cardiovascular disease and insulin resistance is an imbalanced nitric oxide (NO) production. Thus, the bioavailability of NO is decreased in cardiovascular disease, obesity and development of insulin resistance.^{26,27,28}

The decline of NO levels in Obesity, is associated with decreases of endothelial NOS3 activity caused by a decreased phosphorylation of NOS3 at serine 1177 which reduces its activation and capacity to produce NO.²⁹ This lower NO production is further stymied in that obesity also leads to increases in the caveola scaffolding protein caveolin 1 which is a potent NOS3 inhibitor.³⁰ Of relevance to treatment /prevention of diabetes is the observation that Increasing NOS3 mediated NO production restores Insulin sensitivity.³¹

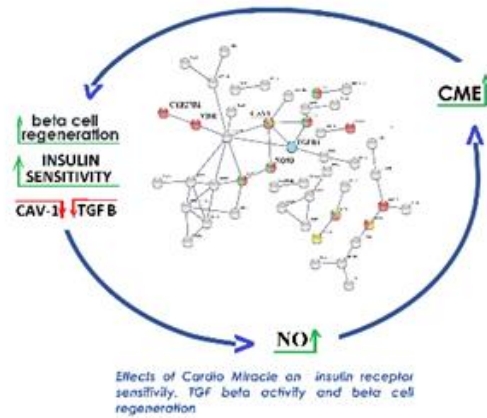
In contrast, the activation of the inducible nitric oxide synthase i NOS, or NOS2, in combination with actions facilitated by the proinflammatory cytokine IL1 beta causes the destruction of insulin producing pancreatic islet cells.^{32,33} In view of these detrimental effects, the role of NO in treatment of diabetes has been subject to controversy.³⁴ However, NO's negative effect of on insulin sensitivity can be blocked by inhibiting i NOS mediated NO production and by supporting eNOS activity.^{35, 36}

The Cardio Miracle Effect

CM, supports NOS3 mediated NO generation through the combination of Arginine, citrulline and cholecalciferol Vitamin D and inhibits i NOS mediated NO generation through the action of the CM ingredient quercetin which is an iNOS inhibitor.³⁷ Furthermore, NO derived from endothelial NOS3 activates caveola mediated endocytosis which (1) increases insulin receptor sensitivity;³⁸ (2) prevents pancreatic islet β -cells dysfunctions,³⁹ (3) reverses impairment of glucose and arginine stimulated insulin secretion, (4) decreases islet inflammation, decreases excessive transforming growth factor- β receptors signaling forming a pathogenic positive feedback loop.^{40,41,42} The combination of these functionalities allow CM to support pancreatic beta cell regeneration and assists treatment of diabetes and associated comorbidities.^{43,44} Lastly by activating CME and autophagy, CM decreases excessive Caveolin1 levels which are elevated in obesity, cardiovascular disease and diabetes and reduce e NOS mediated NO production. In doing so, CM attacks the root causes of cardiovascular and metabolic disease.

Cardio Miracle Functionalities

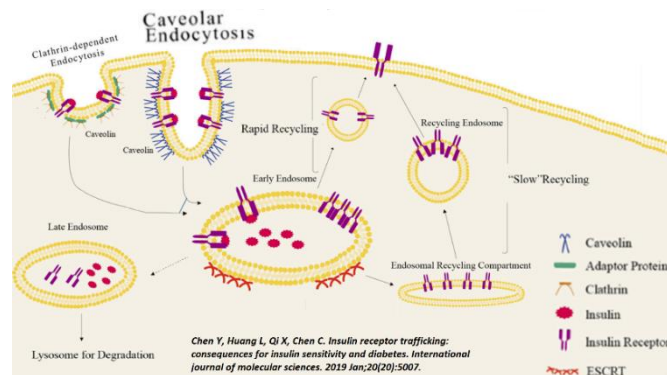
CM, by decreasing elevated levels of caveolin 1, CM supports functioning of a positive feedback loop that protects pancreatic beta cells, supports beta cell regenerations, increases insulin sensitivity, supports insulin secretion. Thus, decreasing Caveolin 1 levels with *Olenlandia diffusa* have been shown to decrease blood glucose levels and pancreatic tissue damage.⁴⁵ Thus, CM's capacity to increase bioavailable levels of NOS 3 derived NO supports the activation of caveola mediated endocytosis (CME).⁴⁶ The activation of CME, in turn, assists in the internalization and recycling of insulin receptor which increases insulin sensitivity in early stages of diabetes.⁴⁷ Likewise, the activation of CME causes the down regulation of excessive TGF beta 1 activity,⁴⁸ which forms a pathogenic feedback in diabetes.⁴⁹ CM, by down regulating TGF beta activity and by activating autophagy, supports the regeneration of exhausted pancreatic beta cell.⁵⁰



The combination of CM functionalities are ideal aligned for slowing development of diabetes and supporting current modalities for treatment of diabetes and its comorbidities.

The Cardio Miracle Difference (1) : CM supports insulin receptor (INSR) activities:

Impairment of INSR activities leads to insulin resistance, which is a key factor in development of type 2 diabetes mellitus (T2DM). INSR activities are regulated in part by INSR internalization and recycling. Among the many regulatory mechanisms Controlling INSR activities is the insulin activated internalization of INSR via caveola mediated (CME) or clathrin dependent endocytosis and subsequent trafficking to early endosome (EE), where INSR is dephosphorylated, sorted and either moved into lysosome for degradation or recycled back to the plasma membrane. The importance of CME mediated regulation of insulin receptor activity has been made apparent in experiments using the CME inhibitor Genistein which substantially decreased the number of high affinity insulin receptors in livers that have been treated and untreated with insulin.⁵¹ Moreover it has been shown that decreased INSR activities are early markers signaling onset of insulin resistance and development of T2DM.⁵² Cardio Miracle, by activating CME supports the recycling of insulin receptor and hence is anticipated to prevent/ slow development of insulin resistance and diabetes.



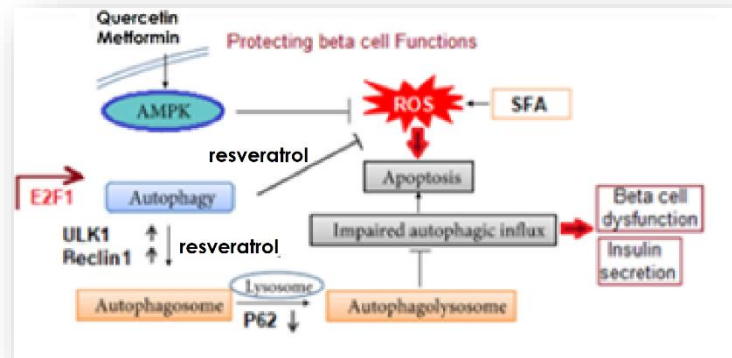
The Cardio Miracle difference (2): Supporting pancreatic beta cell functions.

Insufficient pancreatic β -cell mass or insulin-producing β -cells are implicated in development of insulin resistance and all forms of diabetes. In this respect, clinical studies suggest that saturated fatty acid induced mitochondrial dysfunction plays a key role in beta cell dysfunction. Thus, levels of circulating saturated fatty acids (SFA) are elevated in subjects with obesity, insulin resistance, dyslipidemia, diabetes, and diabetic nephropathy.^{53, 54} Investigations on how SFA contribute to the generation of diabetes and associated pathologies suggest that SFA trigger chronic low level inflammation which, in turn, triggers stress responses and impairment of autophagy flux and impairment of mitochondrial and pancreatic beta cell functions.^{55, 56, 57} Suggesting a causal relationship between mitochondrial impairment and beta cell dysfunction is the observations that the number of mitochondria are decreased in insulin-resistant skeletal muscle cells. This observation prompted the suggestion that impairment of mitochondrial function in β cells contributes to insulin-resistance and diabetic nephropathy and that the protection of mitochondrial functions offers opportunity for improving treatments of T2D.^{58,59}

A mechanism proposed for protecting mitochondria and β cell functions is the activation of mitochondrial autophagy (termed mitophagy), which is a process that selectively degrades damaged mitochondria and reverses mitochondrial dysfunction.^{60, 61}

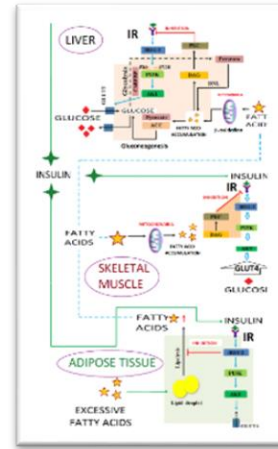
Supporting mitophagy with Cardio Miracle ingredients

as a strategy for treatment of diabetes is the observations that the transcription factor E2F1, which is key regulator in the expression of autophagy associated genes, plays a key role in the maintenance of β -cell identity and insulin secretion. Thus, loss of E2F1 functions triggers glucose intolerance associated with defective insulin secretion, altered α -to- β -cell ratios and a downregulation of many β -cell genes.⁶² Maintenance of α -to- β -cell ratios relies on the fine tuning of E2F1 activities by histone deacetylases HDAC6 and HDAC1 which serve as mitochondrial nutrient sensors and play a role in maintaining in β -cell health. Elevated levels of the cholesterol metabolite 27-hydroxycholesterol associated with insulin resistance,⁶³ by affecting the cytoplasmic localization of HDAC1 negatively affects mitophagy,⁶⁴ and beta cell health. This effect is reversed by HDAC1 inhibitor resveratrol found in CM;s grape seed extract.⁶⁵



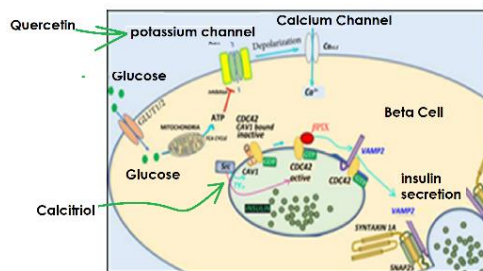
Effects of CM's quercetin and grape seed extract combination.

CM's projected anti-diabetic effect spectrum includes improvement of insulin-mediated suppression of hepatic glucose production and enhancement of insulin-stimulated glucose disposal in skeletal muscle. Molecular mechanisms involved affect AMPK signaling, increases in insulin receptor (INSR) tyrosine kinase activity, enhancement of glycogen synthesis, activation glucose GLUT4 transporters, increasing antioxidant activities and regulating autophagy via the PI3K/AKT/mTOR pathways.⁶⁶ Less clarity exists concerning CM's ability to modify lipid metabolism.⁶⁷ For pinpointing mechanisms involved we used SystaMedic's Systems Pharmacology platform which identified that CM not only modulates PI3K/AKT/mTOR pathways and ATP/ADP ratios but also links Vitamin D receptor, retinoic acid receptor, and fatty acid receptor signaling pathways.⁶⁸ The relevance of this MOA for assessing CM effects on diabetes comes from observations that Pancreatic islets express high levels of G-protein coupled receptors GPRC5C, GPR40 and GPR142 which, are involved in regulating functional β -cell mass.^{69,70} The antidiabetic drug Metformin, increases endothelial NO production,⁷¹ which, in turn, affects the expression of these receptors and triggers the relocation and degradation of the PML-RAR α fusion protein which regulates the expression of the leptin-receptor (OB-R) long isoform.^{72, 73} This particular leptin receptor isoform modulates interleukin-6 signaling and activates via JAK-STAT signaling leptin actions. Thus, the anti-diabetic effects of CM extend beyond effects on AMPK signaling and include the regulation of leptin signaling. The recognition of CM's capacity to regulate both glucose homeostasis and body fat could be used to identify anti-obesity ingredient combinations.^{74, 75} Thus, by regulating the expression of leptin-receptor (OB-R) long isoform, CM modulates the sensitivity of the "adipo-insular axis" which, in turn finetunes insulin synthesis, secretion in pancreatic β -cells and lipid metabolism.



The Cardio Miracle Difference (3): Increasing insulin secretion:

High glucose level precipitated increases in ATP/ADP ratio cause the closure of the ATP-sensitive K⁺ channel Kv2.1, which in turn prompts the opening of the voltage-dependent Ca²⁺ channel Cav1.2.



Insulin secretion is initiated by the dissociation of Caveolin 1 from a GDP_CDC42 complex. This dissociation step is supported by CM ingredient ViD which by activating SRC kinase causing the phosphorylation of CAV1 at Tyr14 and its dissociation from the CDC42 complex. Upon dissociation, cdc42-GDP binds to G protein β PIX which interacts with protein VAMP2-bound to insulin secretory granules. These vesicles are then targeted to fusion with the plasma membrane resulting in insulin secretion. The transient receptor potential melastatin 2 (TRPM2) channel plays a key role in regulating glucose-induced and incretin-potentiated insulin secretion.⁷⁶ In that, glucose metabolism and glucagon-like peptide 1 (GLP-1) receptor stimulation increase the activity of TRPM2 channels via cAMP signaling. Glucagon-like peptide-1 (GLP-1), the most potent incretins stimulate glucose-induced insulin secretion and inhibits glucagon secretion which leads to a decrease in hepatic glucose production and

lowering of blood glucose levels. GLP-1 also improves beta-cell proliferation and prevents beta-cell destruction by cytotoxic agents. Both of these antidiabetic mechanisms involve caveola. mediated endocytosis.⁷⁷ Accordingly, CM by supporting these mechanisms supports insulin release and treatments for diabetes

Supplemental Section

Diabetes associated Comorbidities affected by CM

DIABETES COMORBIDITIES			
OBESITY	FALL	NEPHROPATHY	ALBUMINURIA
HYPERTENSION	ANXIETY	BULIMIA NERVOSA	CARDIOMYOPATHY
DIABETES MELLITUS	HEPATIC STEATOSIS	THROMBOEMBOLISM	PANCREATITIS
WEIGHT GAIN	NEOPLASM	CACHEXIA	HIRSUTISM
INFLAMMATION	HYPERINSULINISM	CHRONIC OBSTRUCTIVE PULMONARY DISEASE	BACK PAIN
NERVOUS	ANOREXIA	HYPOGLYCEMIA	METASTASIS
DEATH	ARTHRITIS	SNORING	CUSHING'S SYNDROME
NECROSIS	PROSTATE CANCER	ACANTHOSIS	HYPOXEMIA
FATTY LIVER	THROMBOSIS	ISCHEMIA	FATIGUE
SLEEP APNEA	BLEEDING	HYPERACTIVITY	ERECTILE DYSFUNCTION
INFECTION	RENAL DISEASE	HYPERURICEMIA	DAYTIME SLEEPINESS
ATHEROSCLEROSIS	GASTROESOPHAGEAL REFLUX	URINARY INCONTINENCE	HEADACHES
HYPERGLYCEMIA	ALANINE AMINOTRANSFERASE	INFLUENZA	FEAR
DEPRESSION	FRACTURE	COLON CANCER	ALCOHOL PROBLEM
BREAST CANCER	MENOPAUSE	ADDICTION	DYSPNEA
STROKE	ENDOMETRIAL CANCER	RELAXATION	TENSION
WOUND	OSTEOPOROSIS	PSORIASIS	ATROPHY
ASTHMA	INFERTILITY	HEPATITIS B	CONGESTIVE HEART FAILURE
HYPOVENTILATION	ABUSE	STARVATION	METABOLIC DISORDER
HYPERLIPIDEMIA	TRAUMA	ATRIAL FIBRILLATION	ENDOCRINE DISORDER
HYPERTROPHY	HYPOXIA	HYPOTHYROIDISM	VENOUS THROMBOSIS
HYPERTRIGLYCERIDEMIA	HERNIA	NEUROPATHY	SHOCK
HYPERCHOLESTEROLEMIA	SCHIZOPHRENIA	RETINOPATHY	OVARIAN CANCER
CORONARY ARTERY DISEASE	RENAL FAILURE	PULMONARY EMBOLISM	RESPIRATORY FAILURE
MYOCARDIAL INFARCT	ANEMIA	MALABSORPTION	IMMUNODEFICIENCY
HYPERPHAGIA	NECK STIFFNESS	DEMENCIA	SEPSIS
CARDIAC FAILURE	PROTEINURIA	ADENOMA	PNEUMONIA
CARCINOMA	ESSENTIAL HYPERTENSION	EMESIS	HYPOPNEA
STRAIN	ISCHEMIC HEART DISEASE	OCCLUSION	NAUSEA
HEPATITIS	HYPERSOMNIA	GALLSTONES	GOUT

MAPK9, MAPT, MB, MC3R, MC4R, MFN1, MFN2, MGAM, MGEA5, MGLL, MGP, MIF, MLXIPL, MLYCD, MME, MMP1, MMP2, MMP9, MPO, MRC1, MSTN, MT-CO1, MTHFR, MTNR1B, MTOR, MTP, MYC, MYD88, MYH6, MYOD1, MYOG, NAMPT, NCF1, NCF2, NCOR1, NEUROD1, NEUROG3, NFE2L2, NFKBIA, NGF, NIT1, NKX2-2, NKX6-1, NKX6-2, NOD2, NOS1, NOS2, NOS3, NOTCH1, NOX1, NOX4, NPC1L1, NPHS1, NPHS2, NPPB, NPY, NQO1, NR0B2, NR1D1, NR1H3, NR1H4, NR1I2, NR3C1, NR3C2, NRF1, NRIP1, OGT, OLR1, OMA1, OXT, P2RY12, P4HB, PARP1, PAX4, PAX6, PC, PCK1, PCSK1, PCSK2, PCSK9, PDE3B, PDE5A, PDK4, PDX1, PECAM1, PER2, PGF, PI3, PIK3C2A, PINK1, PLA2G1B, PLA2G7, PLAT, PLEK, PLG, PLIN1, PLIN2, PLTP, PNLIP, PNPLA2, PNPLA3, POMC, PON1, PPARA, PPARG, PPARGC1A, PPARGC1B, PPIA, PPIG, PPY, PRKAB1, PRKCA, PRKCB, PRKCD, PRKCE, PRL, PTEN, PTGS2, PTPN1, PTPN11, PTPN2, PTPN22, PTPRC, PTPRN, PTPRN2, PTS, PTX3, PYY, RAPGEF3, RAPGEF4, RARRES2, RBP4, REL, RELA, REN, RETN, RHEB, RHOA, RICTOR, RPS6KB1, RPTOR, RUNX2, SAA1, SAG, SCARB1, SCARB2, SCD, SELE, SELL, SELP, SEPP1, SERPINA1, SERPINA2, SERPINC1, SERPINE1, SFTA3, SGK1, SH2B1, SHBG, SHC1, SI, SIRT1, SIRT2, SIRT4, SIRT5, SIRT6, SIRT7, SLC22A1, SLC27A1, SLC27A2, SLC27A4, SLC27A5, SLC2A1, SLC2A12, SLC2A14, SLC2A2, SLC2A3, SLC2A4, SLC30A10, SLC30A8, SLC47A1, SLC5A1, SLC5A11, SLC5A2, SLC5A4, SMAD2, SMAD3, SNCA, SOCS1, SOCS3, SOD1, SOD2, SOD3, SORT1, SOST, SP6, SPP1, SQSTM1, SRC, SREBF1, SREBF2, SST, STAP2, STAT1, STAT3, STAT5B, STAT6, STK11, TAC1, TAS1R2, TAS1R3, TBC1D1, TBC1D4, TBL1X, TCF7L2, TEK, TFAM, TFRC, TG, TGFB1, TGM2, TH, THBS1, THY1, TIMP1, TLR2, TLR3, TLR4, TLR5, TLR9, TM6SF2, TNF, TNFRSF10A, TNFRSF1A, TNFRSF1B, TNFRSF25, TNFSF11, TNNT2, TOR1A, TP53, TPO, TRAF6, TRH, TRIM63, TSC2, TSPAN8, TTR, TXN, TXNIP, UCP1, UCP2, UCP3, ULK1, VAMP2, VCAM1, VDAC1, VDR, VEGFA, VR1, VWF, XBP1,

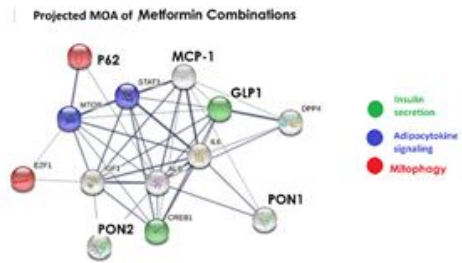
Evaluation of network overlap of the protein interaction network shown in table 1 with the previously identified CM interactome consisting of 1320 proteins identified 226 proteins shared by both networks. (See Table 2)

Table 2
Network overlap of CM network with diabetes network
ACNA1C , CACNA1D , CACNA1F , CACNA1S , KCNA5 , PPP3CA , PPP3CB , CAMK2D , CD38 , FKBP1B , PSMD9 , RAPGEF4 , RYR2 , SRI , BLK , DOC2B , EFNA5 , EPHA5 , LRRC8A , MCU , SLC25A22 , SLC8B1 , SYT9 , TFAP2B , HNF4A , LRP5 , SFRP1 , TM7SF3 , ABCC8 , ADCY1 , ADCY2 , ADCY3 , ADCY4 , ADCY5 , ADCY6 , ADCY7 , ADCY8 , ADCY9 , BAD , CFTR , GNAS , ITPR3 , JAK2 , KCNB1 , KCNJ11 , PFKFB2 , PRKACA , PRKACB , PRKACG , PRKCE , PFKL , SERP1 , SNAP25 , STX1A , STX4 , STXB4 , SYT7 , VAMP2 , AACCS , ALOX5 , BMP8A , CELA2A , GPLD1 , MIDN , OXCT1 , PIM3 , CAV1 , FOXO1 , G6PC2 , GCK , HLA-DRB1 , INS , IRS1 , IRS2 , MYRIP , NEUROD1 , PDX1 , PTPN11 , RBP4 , RFX6 , SLC2A1 , SLC2A2 , SLC30A8 , SREBF1 , UCP2 , ADRA2A , CASR , CCKAR , CHRM3 , CNR1 , FFAR1 , GNA11 , GNAQ , GPER1 , MTNR1B , PFKM , PLA2G6 , PLCB1 , PLCB2 , PLCB3 , PLCB4 , ATP1A1 , ATP1A2 , ATP1A3 , ATP1A4 , ATP1B1 , ATP1B2 , ATP1B3 , ATP1B4 , FAM3D , FXD2 , HMG3 , ANO1 , GPR27 , JAGN1 , KCNMA1 , KCNMB1 , KCNMB2 , KCNMB3 , KCNMB4 , KCNN1 , KCNN2 , KCNN3 , KCNN4 , KCNU1 , MPC2 , NLGN2 , NOV , RFX3 , TSSC1 , ADCYAP1 , ADCYAP1R1 , CHGA , GCG , GIP , GIPR , GLP1R , GPR119 , NKX6-1 , TCF7L2 , UCN3 , CCL5 , IFNG , IL1B , IL6 , NOS2 , NR0B2 , TNF , VDR , ARNTL , CLOCK , GPR68 , KLF7 , NR1D1 , PER2 , SIRT6 , SLC16A1 , ATF2 , ATF4 , ATF6B , CAMK2A , CAMK2B , CAMK2G , CREB1 , CREB3 , CREB3L1 , CREB3L2 , CREB3L3 , CREB3L4 , CREB5 , HIF1A , NR1H4 , REST , CARTPT , CCK , DRD2 , ENSA , GHRL , GHSR , ISL1 , LEP , SSTR5 , TRH , TRPM4 ,

ICA1 , PARK2 , PICK1 , PRKCA , PRKCB , PRKCG , ACSL4 , C2CD2L , CAPN10 , CDK16 , CPT1A , FOXA2 , TRPM2 , VSNL1 , ABCA12 , BAIAP3 , BRSK2 , FAM132A , NNAT , OSBP , PCLO , RAB3A , RIMS2 , RPH3AL , SLC9B2 , SYTL4 , TCIRG1 , ABAT , ACVR1C , GLUD1 , GLUL , HADH , INHBB , LRP5L , NDUFAF2 , PCK2 , PPARC , SIRT2 , SIRT4 , SOX4 , UQCCL2 , TGFB1,TGFB1

Functional analysis of network proteins shown in table 2 using k means clustering identified

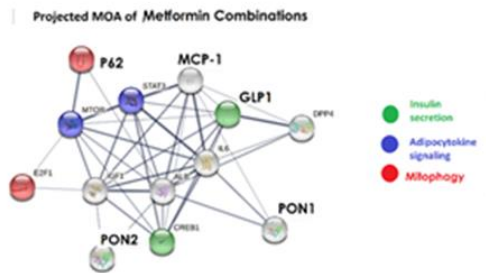
Projected Sores of CM /drug/natural product Interaction



Substance	Interaction Score	Substance	Interaction Score
Metformin	683	Dutogliptin	2
Sitagliptin	278	Eucalyptus globulus	2
Glucagon	233	Hydralazine	2
Vildagliptin	113	Morus	2
Liraglutide	75	Morus alba	2
Linagliptin	65	Pramlintide	2
Alogliptin	56	prolyl-hydroxyproline	2
Exenatide	43	Psoralen	2
Saxagliptin	40	Sotagliflozin	2
Empagliflozin	31	Teduglutide	2
Canagliflozin	21	Trelagliptin	2
Dapagliflozin	20	Abelmoschus	1
Fenretinide	14	Abelmoschus esculentus	1
Teneligliptin	12	Alpha-Aminoisobutyric Acid	1
Valsartan	11	Carmegliptin	1
Glibenclamide	10	cumini	1
Rimonabant	10	Eucalyptus	1
Lixisenatide	9	EUCALYPTUS CALOPHYLLA	1
Anagliptin	8	Gymnema sylvestre	1
Gemigliptin	8	Lupinus	1
Glimepiride	7	Miglitol	1
Albiglutide	6	Phosphatidylglycerol	1

Evogliptin	5	Polysorbate 20	1
Mannose 6-phosphate	5	Psidium	1
Semaglutide	5	Taspoglutide	1
Glipizide	4	Terminalia	1
Gliclazide	3	terminalia arjuna	1
Pipistrellus abramus	3	Trandolapril	1
Coptis chinensis	2	Voglibose	1

CM secondary combination partners ranked using interaction scores for target MOA



Substances 2-3	Synergy Score
collagen	972
Hernandezine	384
Zinc	299
Aicar	143
myoinositol	142
Guanosine	110
Rosiglitazone	64
Fisetin	36
Retinol	29
Rotenone	26
Crocin	25
Amylase	22

Medline References (2017-2020) for Mechanism of Action Protein Interaction Network targeted by CardioMiracle.

Pub Med Reference	Publication year	Reference title	Protein Targets	Statistical significance of reference
PMID:32082483	2020	Role of Caveolin-1 in Diabetes and Its Complications.	STAT3,IGF1,DPP4,MTOR,IL6,GCG, CREB1	4.48E-09
PMID:32095994	2020	Post-Transplantation Diabetes Mellitus.	DPP4,MTOR,GCG,CREB1	3.62E-06

PMID:32110076	2020	Comparative Effectiveness of Long-Acting GLP-1 Receptor Agonists in Type 2 Diabetes: A Short Review on the Emerging Data.	ALB,DPP4,GCG	5.13E-06
PMID:32429334	2020	Evaluation of Viburnum opulus L. Fruit Phenolics Cytoprotective Potential on Insulinoma MIN6 Cells Relevant for Diabetes Mellitus and Obesity.	ALB,DPP4,GCG	5.13E-06
PMID:32020552	2020	Efficacy of Vildagliptin Added to Continuous Subcutaneous Insulin Infusion (CSII) in Hospitalized Patients with Type 2 Diabetes.	ALB,DPP4,GCG	6.91E-06
PMID:32337293	2020	Effect of Combination Therapy of Canagliflozin Added to Tenelegliptin Monotherapy in Japanese Subjects with Type 2 Diabetes Mellitus: A Retrospective Study.	ALB,DPP4,GCG	6.91E-06
PMID:31677134	2020	Rationale, Design, and Methods of the Study of Comparison of Canagliflozin vs. Tenelegliptin Against Basic Metabolic Risks in Patients with Type 2 Diabetes Mellitus (CANTABLE study: Protocol for a Randomized, Parallel-Group Comparison Trial).	ALB,DPP4,GCG	8.49E-06
PMID:32140368	2020	Evaluation of the Safety and Efficacy of Tenelegliptin at a Higher Dose in Indian Type 2 Diabetes Patients: A Retrospective Analysis.	ALB,DPP4,GCG	8.49E-06
PMID:31992158	2020	Sodium-Glucose Cotransporter 2 Inhibition for the Prevention of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis.	ALB,DPP4,GCG	1.03E-05
PMID:32168854	2020	Effect of Dipeptidyl-Peptidase 4 Inhibitors on Circulating Oxidative Stress Biomarkers in Patients with Type 2 Diabetes Mellitus.	ALB,DPP4,GCG	1.03E-05
PMID:31958307	2020	Glucose time in range and peripheral neuropathy in type 2 diabetes mellitus and chronic kidney disease.	ALB,DPP4,GCG	1.24E-05
PMID:32115517	2020	Beneficial Effects of Ipragliflozin on the Renal Function and Serum Uric Acid Levels in Japanese Patients with Type 2 Diabetes: A Randomized, 12-week, Open-label, Active-controlled Trial.	ALB,DPP4,GCG	1.24E-05
PMID:32211075	2020	Omarigliptin decreases inflammation and insulin resistance in a pleiotropic manner in patients with type 2 diabetes.	ALB,DPP4,GCG	1.24E-05
PMID:31692374	2020	12th Roche Diabetes Care Network Meeting: April 11-13, 2019, Copenhagen, Denmark.	ALB,DPP4,GCG	1.47E-05
PMID:31863344	2020	A Multinational Real-World Study on the Clinical Characteristics of Patients with Type 2 Diabetes Initiating Dapagliflozin in Southern Europe.	ALB,DPP4,GCG	1.47E-05
PMID:31915054	2020	Systematic review and meta-analysis protocol for efficacy and safety of Momordica charantia L.	ALB,DPP4,GCG	1.71E-05

		on animal models of type 2 diabetes mellitus.		
PMID:32210695	2020	Diabetes as a risk factor for Alzheimer's disease in the Middle East and its shared pathological mediators.	IGF1,DPP4,IL6,GCG	1.79E-05
PMID:32003832	2020	Role of sodium-glucose cotransporter 2 inhibition to mitigate diabetic kidney disease risk in type 1 diabetes.	ALB,DPP4,GCG	1.96E-05
PMID:32139602	2020	Glucagon receptor antagonist upregulates circulating GLP-1 level by promoting intestinal L-cell proliferation and GLP-1 production in type 2 diabetes.	ALB,DPP4,GCG	2.21E-05
PMID:32190049	2020	SGLT2 Inhibitors, GLP-1 Agonists, and DPP-4 Inhibitors in Diabetes and Microvascular Complications: A Review.	ALB,DPP4,GCG	2.21E-05
PMID:32238798	2020	Identification of Potential Therapeutic Targets and Pathways of Liraglutide Against Type 2 Diabetes Mellitus (T2DM)	DPP4,MTOR,GCG	2.21E-05
PMID:32158490	2020	Management of type 2 diabetes: consensus of diabetes organizations.	ALB,DPP4,GCG	3.13E-05
PMID:32150819	2020	Insulin: The Friend and the Foe in the Development of Type 2 Diabetes Mellitus.	IGF1,MTOR,GCG	6.44E-05
PMID:32265637	2020	Brain Metabolism Alterations in Type 2 Diabetes: What Did We Learn From Diet-Induced Diabetes Models?	IGF1,IL6,GCG	0.00015
PMID:31571983	2019	The relationship between pancreatic cancer and type 2 diabetes: cause and consequence.	STAT3,ALB,IGF1,DPP4,MTOR,IL6,GCG	2.14E-10
PMID:30687888	2019	Novel Treatment Opportunities Against Cognitive Impairment in Parkinson's Disease with an Emphasis on Diabetes-Related Pathways.	IGF1,DPP4,MTOR,GCG,CREB1	2.92E-07
PMID:30928925	2019	Rationale, design and study protocol of the randomised controlled trial: Diabetes Interventional Assessment of Slimming or Training to Lessen Inconspicuous Cardiovascular Dysfunction (the DIASTOLIC study)	ALB,DPP4,IL6,GCG	3.26E-07
PMID:31902143	2019	Diabetes and Cancer: Cancer Should Be Screened in Routine Diabetes Assessment.	IGF1,DPP4,MTOR,GCG	3.26E-07
PMID:31372166	2019	The Influence of Psychological Stress on the Initiation and Progression of Diabetes and Cancer.	STAT3,MTOR,IL6,GCG,CREB1	4.40E-07
PMID:31338868	2019	Liraglutide treatment reduced interleukin-6 in adults with type 1 diabetes but did not improve established autonomic or polyneuropathy.	ALB,DPP4,IL6,GCG	5.79E-07
PMID:30863490	2019	A novel therapeutic approach to colorectal cancer in diabetes: role of metformin and rapamycin.	STAT3,ALB,MTOR,IL6	6.65E-07

PMID:31496802	2019	Incident cancer risk in dipeptidyl peptidase-4 inhibitor-treated patients with type 2 diabetes mellitus.	IGF1,DPP4,MTOR,GCG	6.65E-07
PMID:30302966	2019	Soluble Dipeptidyl Peptidase-4 Levels Are Associated with Decreased Renal Function in Patients with Type 2 Diabetes Mellitus.	ALB,DPP4,IL6,GCG	7.75E-07
PMID:30710452	2019	Leucine-glycine and carnosine dipeptides prevent diabetes induced by multiple low-doses of streptozotocin in an experimental model of adult mice.	ALB,DPP4,MTOR,GCG	7.75E-07
PMID:31572499	2019	Consensus recommendations for management of patients with type 2 diabetes mellitus and cardiovascular diseases.	ALB,DPP4,IL6,GCG	1.69E-06
PMID:31780586	2019	Design of a randomised controlled trial of the effects of empagliflozin on myocardial perfusion, function and metabolism in type 2 diabetes patients at high cardiovascular risk (the SIMPLE trial)	ALB,DPP4,IL6,GCG	2.22E-06
PMID:30312631	2019	Polychlorinated biphenyl exposures differentially regulate hepatic metabolism and pancreatic function: Implications for nonalcoholic steatohepatitis and diabetes.	STAT3,IGF1,IL6,GCG	2.60E-06
PMID:31523379	2019	Bone health in diabetes and prediabetes.	IGF1,DPP4,IL6,GCG	2.79E-06
PMID:30338340	2019	The transcription factor STAT6 plays a critical role in promoting beta cell viability and is depleted in islets of individuals with type 1 diabetes.	STAT3,ALB,IL6,GCG	3.07E-06
PMID:31470636	2019	From Pre-Diabetes to Diabetes: Diagnosis, Treatments and Translational Research.	ALB,DPP4,IL6,GCG	3.35E-06
PMID:30744071	2019	Mechanism and Potential of Egg Consumption and Egg Bioactive Components on Type-2 Diabetes.	ALB,DPP4,IL6,GCG	3.62E-06
PMID:30788808	2019	Population Pharmacokinetics of Semaglutide for Type 2 Diabetes.	ALB,DPP4,GCG	3.62E-06
PMID:31576500	2019	Diabetic kidney disease: new clinical and therapeutic issues. Joint position statement of the Italian Diabetes Society and the Italian Society of Nephrology on 'The natural history of diabetic kidney disease and treatment of hyperglycemia in ...	ALB,DPP4,IL6,GCG	4.58E-06
PMID:31847392	2019	Non-Coding RNAs in IGF-1R Signaling Regulation: The Underlying Pathophysiological Link between Diabetes and Cancer.	STAT3,IGF1,IL6,GCG	4.98E-06
PMID:30863012	2019	Profile of semaglutide in the management of type 2 diabetes: design, development, and place in therapy.	ALB,DPP4,GCG	5.13E-06
PMID:30912340	2019	Retrospective Analysis of the Efficacy of Dapagliflozin in Patients with Type 2 Diabetes in a Primary Clinic in Korea.	ALB,DPP4,GCG	5.13E-06

PMID:30992008	2019	Visit-to-visit fasting plasma glucose variability is an important risk factor for long-term changes in left cardiac structure and function in patients with type 2 diabetes.	ALB,DPP4,GCG	5.13E-06
PMID:31218007	2019	Autophagy-induced degradation of Notch1, achieved through intermittent fasting, may promote beta cell neogenesis: implications for reversal of type 2 diabetes.	STAT3,IGF1,DPP4,CREB1	5.90E-06
PMID:31133864	2019	Is the Brain a Key Player in Glucose Regulation and Development of Type 2 Diabetes?	STAT3,IGF1,IL6,GCG	6.91E-06
PMID:31781663	2019	Incipient Diabetes Treated with Long-Term Classical Prescription.	ALB,DPP4,GCG	6.91E-06
PMID:30099845	2019	Glucagon-like peptide-1 receptor agonists for type 2 diabetes: A rational drug development.	ALB,DPP4,GCG	8.49E-06
PMID:30819188	2019	Evidence-based and tailored medication in type 2 diabetes: a pathway learned from clinical trials.	ALB,DPP4,GCG	8.49E-06
PMID:31074209	2019	Hyperglycemia in non-obese patients with type 2 diabetes is associated with low muscle mass: The Multicenter Study for Clarifying Evidence for Sarcopenia in Patients with Diabetes Mellitus.	ALB,DPP4,GCG	8.49E-06
PMID:31087027	2019	Management of Preexisting Diabetes in Pregnancy: A Review.	ALB,DPP4,GCG	8.49E-06
PMID:31183384	2019	A Randomized Study to Compare the Effects of Once-Weekly Dulaglutide Injection and Once-Daily Glimepiride on Glucose Fluctuation of Type 2 Diabetes Mellitus Patients: A 26-Week Follow-Up.	DPP4,IL6,GCG	8.49E-06
PMID:31236280	2019	Characteristics of Adults With Type 2 Diabetes Mellitus by Category of Chronic Kidney Disease and Presence of Cardiovascular Disease in Alberta Canada: A Cross-Sectional Study.	ALB,DPP4,GCG	8.49E-06
PMID:31494602	2019	Analysis of English general practice level data linking medication levels, service activity and demography to levels of glycaemic control being achieved in type 2 diabetes to improve clinical practice and patient outcomes.	ALB,DPP4,GCG	8.49E-06
PMID:31496913	2019	Evaluation of Paraoxonase, Arylesterase, and Homocysteine Thiolactonase Activities in Patients with Diabetes and Incipient Diabetes Nephropathy.	PON1,PON2,ALB	1.03E-05
PMID:30246473	2019	Cardiovascular disease prevalence and risk factor prevalence in Type 2 diabetes: a contemporary analysis.	ALB,DPP4,GCG	1.03E-05
PMID:31390159	2019	Long-term outcome of islet transplantation on insulin-dependent diabetes mellitus: An observational cohort study.	MTOR,IL6,GCG	1.03E-05
PMID:31583645	2019	Thyroid Dysfunction and Type 2 Diabetes Mellitus: Screening	ALB,IGF1,GCG	1.03E-05

		Strategies and Implications for Management.		
PMID:31212911	2019	Can Epigenetics of Endothelial Dysfunction Represent the Key to Precision Medicine in Type 2 Diabetes Mellitus?	DPP4,IL6,GCG,CREB1	1.07E-05
PMID:31275881	2019	The effects of high intensity interval training on appetite management in individuals with type 2 diabetes: influenced by participants weight.	DPP4,IL6,GCG	1.24E-05
PMID:31317516	2019	Glucagon-Like Peptide-1 Receptor Analogues in Type 2 Diabetes: Their Use and Differential Features.	ALB,DPP4,GCG	1.24E-05
PMID:31615494	2019	Increment of plasma glucose by exogenous glucagon is associated with present and future renal function in type 2 diabetes:a retrospective study from glucagon stimulation test.	ALB,DPP4,GCG	1.24E-05
PMID:30156056	2019	Effects of metformin and alogliptin on body composition in people with type 2 diabetes.	ALB,DPP4,GCG	1.47E-05
PMID:30506340	2019	A Review of Practical Issues on the Use of Glucagon-Like Peptide-1 Receptor Agonists for the Management of Type 2 Diabetes.	ALB,DPP4,GCG	1.47E-05
PMID:30771017	2019	Diabetes Management in Older Adults With Chronic Kidney Disease.	ALB,DPP4,GCG	1.47E-05
PMID:30773997	2019	Bioactive compounds in plant materials for the prevention of diabetesand obesity.	DPP4,MTOR,GCG	1.47E-05
PMID:30830898	2019	Calycosin Ameliorates Diabetes-Induced Renal Inflammation via the NF-KB Pathway In Vitro and In Vivo.	DPP4,IL6,GCG	1.47E-05
PMID:31033218	2019	Long-term safety and efficacy of the sodium-glucose cotransporter 2 inhibitor, tofogliflozin, added on glucagon-like peptide-1 receptor agonist in Japanese patients with type 2 diabetes mellitus: A 52-week open-label, multicenter, ...	ALB,DPP4,GCG	1.47E-05
PMID:31215299	2019	Efficacy of Long-Term Remote Ischemic Conditioning on Vascular and Neuronal Function in Type 2 Diabetes Patients With Peripheral Arterial Disease.	ALB,DPP4,GCG	1.47E-05
PMID:31269877	2019	Changes in the Prescription of Glucose-Lowering Medications in Patients With Type 2 Diabetes Mellitus After a Cardiovascular Event: A Call to Action From the DATAFILE Study.	ALB,DPP4,GCG	1.47E-05
PMID:31950036	2019	The Effects of Once-Weekly Dulaglutide and Insulin Glargine on Glucose Fluctuation in Poorly Oral-Antidiabetic Controlled Patients with Type 2 Diabetes Mellitus.	DPP4,IL6,GCG	1.47E-05
PMID:29802679	2019	Soluble CD163 correlates with lipid metabolic adaptations in type 1 diabetes patients during ketoacidosis.	ALB,IL6,GCG	1.71E-05
PMID:30026043	2019	Copeptin and Estimated Insulin Sensitivity in Adults With and	ALB,IGF1,GCG	1.71E-05

		Without Type 1 Diabetes: The CACTI Study.		
PMID:30788048	2019	SGLT-2 inhibitors in non-alcoholic fatty liver disease patients with type 2 diabetes mellitus: A systematic review.	ALB,DPP4,GCG	1.71E-05
PMID:30912033	2019	Safety and Efficacy of Empagliflozin as Add-On Therapy to GLP-1 Receptor Agonist (Liraglutide in Japanese Patients with Type 2 Diabetes Mellitus: A Randomised, Double-Blind, Parallel-Group Phase 4 Study.	ALB,DPP4,GCG	1.71E-05
PMID:31227028	2019	PRODIG (Prevention of new onset diabetes after transplantation by a short term treatment of Vildagliptin in the early renal post-transplant period study: study protocol for a randomized controlled study.	DPP4,MTOR,GCG	1.71E-05
PMID:31308448	2019	Effect of Saxagliptin on Endothelial Function in Patients with Type 2 Diabetes: A Prospective Multicenter Study.	ALB,DPP4,GCG	1.71E-05
PMID:31551068	2019	Comparative risk evaluation for cardiovascular events associated with dapagliflozin vs. empagliflozin in real-world type 2 diabetes patients: a multi-institutional cohort study.	ALB,DPP4,GCG	1.71E-05
PMID:31646466	2019	Combining GLP-1 Receptor Agonists and Basal Insulin in Older Adults with Type 2 Diabetes: Focus on Lixisenatide and Insulin Glargine.	ALB,DPP4,GCG	1.71E-05
PMID:30341767	2019	Liraglutide, Sitagliptin, and Insulin Glargine Added to Metformin: The Effect on Body Weight and Intrahepatic Lipid in Patients With Type 2 Diabetes Mellitus and Nonalcoholic Fatty Liver Disease.	DPP4,IL6,GCG	1.96E-05
PMID:31003482	2019	Clinical Management of Intermittent Fasting in Patients with Diabetes Mellitus.	IGF1,DPP4,GCG	1.96E-05
PMID:31026084	2019	Pharmacokinetic and pharmacodynamic modelling for renal function dependent urinary glucose excretion effect of ipragliflozin, a selective sodium-glucose cotransporter 2 inhibitor, both in healthy subjects and patients with type 2 diabetes ...	ALB,DPP4,GCG	1.96E-05
PMID:31139316	2019	Novel pharmacological therapy in type 2 diabetes mellitus with established cardiovascular disease: Current evidence.	ALB,DPP4,GCG	1.96E-05
PMID:31191067	2019	Cystic Fibrosis-Related Diabetes: Pathophysiology and Therapeutic Challenges.	DPP4,IL6,GCG	1.96E-05
PMID:31208420	2019	Effect of dipeptidyl-peptidase-4 inhibitors on C-reactive protein in patients with type 2 diabetes: a systematic review and meta-analysis.	DPP4,IL6,GCG	1.96E-05
PMID:31518492	2019	Efficacy and safety of once-weekly exenatide after switching	ALB,DPP4,GCG	1.96E-05

		from twice-daily exenatide in patients with type 2 diabetes.		
PMID:30791439	2019	Essential Roles for the Non-Canonical IKB Kinases in Linking Inflammation to Cancer, Obesity, and Diabetes.	STAT3,MTOR,IL6,GCG	2.18E-05
PMID:31080438	2019	From the Incretin Concept and the Discovery of GLP-1 to Today's Diabetes Therapy.	ALB,DPP4,GCG	2.21E-05
PMID:31417608	2019	Therapeutic Silencing of Centromere Protein X Ameliorates Hyperglycemia in Zebrafish and Mouse Models of Type 2 Diabetes Mellitus.	IGF1,MTOR,GCG	2.21E-05
PMID:31396083	2019	Rhizoma coptidis as a Potential Treatment Agent for Type 2 Diabetes Mellitus and the Underlying Mechanisms: A Review.	IGF1,DPP4,GCG,CREB1	2.51E-05
PMID:31183921	2019	Effectiveness of Eriomin(R in managing hyperglycemia and reversal of prediabetes condition: A double-blind, randomized, controlled study.	DPP4,IL6,GCG	2.51E-05
PMID:31440988	2019	Cardiorenal Protection: Potential of SGLT2 Inhibitors and GLP-1 Receptor Agonists in the Treatment of Type 2 Diabetes.	ALB,DPP4,GCG	2.51E-05
PMID:31536546	2019	Clinical factors associated with bacterial translocation in Japanese patients with type 2 diabetes: A retrospective study.	DPP4,IL6,GCG	2.51E-05
PMID:30806837	2019	Triglycerides: Emerging Targets in Diabetes Care? Review of Moderate Hypertriglyceridemia in Diabetes.	ALB,DPP4,GCG	2.81E-05
PMID:31291713	2019	Diabetes Mellitus is Associated with Inferior Prognosis in Patients with Chronic Lymphocytic Leukemia: a Propensity Score-Matched Analysis.	ALB,IGF1,IL6	2.81E-05
PMID:31749761	2019	Ketosis-Prone Type 2 Diabetes: A Case Series.	ALB,DPP4,GCG	2.81E-05
PMID:31172455	2019	Rationale, Design for the ASSET Study: A Prospective Randomized Study Comparing Empagliflozin's Effect to Sitagliptin on Cardiac Fat AccumulationFunction in Patients with Type 2 Diabetes.	ALB,DPP4,GCG	3.13E-05
PMID:30670722	2019	Using a Targeted Proteomics Chip to Explore Pathophysiological Pathways for Incident Diabetes-The Malmoe Preventive Project.	PON1,DPP4,GCG	3.13E-05
PMID:30738003	2019	Case of fulminant type 1 diabetes induced by the anti-programmed death-ligand 1 antibody, avelumab.	ALB,IGF1,GCG	3.13E-05
PMID:30759730	2019	IL-10 Could Play a Role in the Interrelation between Diabetes Mellitus and Osteoarthritis.	STAT3,IGF1,IL6	3.13E-05
PMID:31583009	2019	Network Pharmacology Analysis of Traditional Chinese Medicine Formula Xiao Ke Yin Shui Treating Type 2 Diabetes Mellitus.	MTOR,IL6,GCG	3.13E-05

PMID:31654243	2019	Benefit-Risk Assessment of Alogliptin for the Treatment of Type 2 Diabetes Mellitus.	ALB,DPP4,GCG	3.13E-05
PMID:30628962	2019	Herbal medicine in the treatment of patients with type 2 diabetes mellitus.	DPP4,IL6,GCG	3.46E-05
PMID:31214280	2019	Circulating Oxidative Stress Biomarkers in Clinical Studies on Type 2 Diabetes and Its Complications.	PON1,ALB,DPP4	3.46E-05
PMID:31243198	2019	A Patient with Nivolumab-related Fulminant Type 1 Diabetes Mellitus whose Serum C-peptide Level Was Preserved at the Initial Detection of Hyperglycemia.	ALB,IGF1,GCG	3.46E-05
PMID:31686269	2019	Major Advances and Discoveries in Diabetes - 2019 in Review.	IGF1,IL6,GCG	3.46E-05
PMID:30293774	2019	Preserving Insulin Secretion in Diabetes by Inhibiting VDAC1 Overexpression and Surface Translocation in Beta Cells.	ALB,DPP4,GCG	4.20E-05
PMID:31191043	2019	Current perspective on the role of insulin and glucagon in the pathogenesis and treatment of type 2 diabetes mellitus.	DPP4,IL6,GCG	4.20E-05
PMID:31344857	2019	SOCS1-Derived Peptide Administered by Eye Drops Prevents Retinal Neuroinflammation and Vascular Leakage in Experimental Diabetes.	STAT3,ALB,IL6	4.20E-05
PMID:31695460	2019	IL6R inhibits viability and apoptosis of pancreatic beta-cells in type 2 diabetes mellitus via regulation by miR-22 of the JAKSTAT signaling pathway.	STAT3,IL6,GCG	4.20E-05
PMID:30850634	2019	Cross-disease analysis of Alzheimer's disease and type-2 Diabetes highlights the role of autophagy in the pathophysiology of two highly comorbid diseases.	IGF1,PIK3CG,ATG5,SQSTM1	4.37E-05
PMID:31555430	2019	The perceptions of natural compounds against dipeptidyl peptidase 4 in diabetes: from in silico to in vivo.	DPP4,IL6,GCG	5.00E-05
PMID:31514368	2019	Influence of Vitamin D on Islet Autoimmunity and Beta-Cell Function in Type 1 Diabetes.	DPP4,IL6,GCG	5.91E-05
PMID:31637222	2019	Changes in Host Response to Mycobacterium tuberculosis Infection Associated With Type 2 Diabetes: Beyond Hyperglycemia.	DPP4,IL6,GCG	6.44E-05
PMID:31779058	2019	Regulation of Diabetes: a Therapeutic Strategy for Alzheimer's Disease?	IGF1,IL6,GCG	6.44E-05
PMID:31902144	2019	Adult Stem Cells: Beyond Regenerative Tool, More as a Bio-Marker in Obesity and Diabetes.	IGF1,DPP4,IL6	6.44E-05
PMID:30786741	2019	Diabetes Mellitus and Cardiovascular Disease.	DPP4,IL6,GCG	7.00E-05
PMID:31212945	2019	The New Era for Renal-Cardiovascular Treatment in Type 2 Diabetes.	ALB,DPP4,GCG	7.00E-05

PMID:31294084	2019	Relationship between dietexercise and pharmacotherapy to enhance the GLP-1 levels in type 2 diabetes.	DPP4,IL6,GCG	7.00E-05
PMID:31524257	2019	Identification of core genes and pathways in type 2 diabetes mellitus by bioinformatics analysis.	STAT3,ALB,DPP4	7.58E-05
PMID:30691224	2019	Epigallocatechin Gallate Modulates Muscle Homeostasis in Type 2 Diabetes and Obesity by Targeting Energetic and Redox Pathways: A Narrative Review.	STAT3,ALB,IL6	0.00011
PMID:30250166	2019	Prevention of atherothrombotic events in patients with diabetes mellitus: from antithrombotic therapies to new-generation glucose-lowering drugs.	DPP4,IL6,GCG	0.00013
PMID:30478982	2019	PCNA and JNK1-Stat3 pathways respectively promotes and inhibits diabetes-associated centrosome amplification by targeting at the ROCK114-3-3Sigma complex in human colon cancer HCT116 cells.	STAT3,ALB,IL6	0.00013
PMID:31428057	2019	Anabolic and Pro-metabolic Functions of CREB-CRTC in Skeletal Muscle: Advantages and Obstacles for Type 2 Diabetes and Cancer Cachexia.	IGF1,IL6,CREB1	0.00013
PMID:31210034	2019	Understanding Bile Acid Signaling in Diabetes: From Pathophysiology to Therapeutic Targets.	DPP4,MTOR,GCG	0.00014
PMID:31240819	2019	Lipotoxicity plays a key role in the development of both insulin resistance and muscle atrophy in patients with type 2 diabetes.	IGF1,MTOR,IL6	0.00015
PMID:30538427	2018	Mechanism involved in insulin resistance via accumulation of Beta-amyloid and neurofibrillary tangles: link between type 2 diabetes and Alzheimer's disease.	STAT3,IGF1,PIK3CG,MTOR,IL6,GCG,CREB1	3.77E-09
PMID:30100874	2018	The Pathogenesis of Diabetes Mellitus by Oxidative Stress and Inflammation: Its Inhibition by Berberine.	PON1,STAT3,ALB,DPP4,IL6,GCG	5.14E-08
PMID:30567377	2018	Using Mouse and Drosophila Models to Investigate the Mechanistic Links between Diet, Obesity, Type II Diabetes, and Cancer.	STAT3,IGF1,MTOR,IL6,GCG	5.40E-08
PMID:30097599	2018	Autophagy upregulation as a possible mechanism of arsenic induced diabetes.	IGF1,PIK3CG,MTOR,ATG5,SQSTM1,GCG	6.94E-08
PMID:30525054	2018	Molecular Modulation of Osteoblasts and Osteoclasts in Type 2 Diabetes.	IGF1,DPP4,MTOR,IL6,GCG,CREB1	8.62E-08
PMID:30233674	2018	Cellular signaling pathways regulating Beta-cell proliferation as a promising therapeutic target in the treatment of diabetes.	STAT3,ALB,IGF1,MTOR,IL6,GCG	1.16E-07
PMID:29669555	2018	The role of dipeptidylpeptidase-4 inhibitors in management of cardiovascular disease in diabetes; focus on linagliptin.	DPP4,MTOR,IL6,GCG,CREB1	2.58E-07
PMID:29636045	2018	Sarcopenic obesity assessed using dual energy X-ray absorptiometry	ALB,DPP4,IL6,GCG	5.79E-07

		(DXA can predict cardiovascular disease in patients with type 2 diabetes: a retrospective observational study.		
PMID:30046616	2018	Addressing Stem Cell Therapeutic Approaches in Pathobiology of Diabetes and Its Complications.	STAT3,ALB,IGF1,IL6,GCG	6.65E-07
PMID:29289692	2018	Activation of Nrf2 signaling by natural products-can it alleviate diabetes?	STAT3,DPP4,MTOR,SQSTM1,IL6	1.36E-06
PMID:30371206	2018	Liraglutide Treatment Reduces Endothelial Endoplasmic Reticulum Stress and Insulin Resistance in Patients With Diabetes Mellitus.	ALB,DPP4,IL6,GCG	1.69E-06
PMID:30619349	2018	Linagliptin Attenuates the Cardiac Dysfunction Associated With Experimental Sepsis in Mice With Pre-existing Type 2 Diabetes by Inhibiting NF-KB.	ALB,DPP4,IL6,GCG	1.69E-06
PMID:28891325	2018	Epigenetics and Immunometabolism in Diabetes and Aging.	STAT3,IGF1,MTOR,IL6,CREB1	2.26E-06
PMID:30542324	2018	Role of Endocrine-Disrupting Engineered Nanomaterials in the Pathogenesis of Type 2 Diabetes Mellitus.	IGF1,MTOR,IL6,GCG	2.41E-06
PMID:30090738	2018	Nonalcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus.	ALB,DPP4,IL6,GCG	2.79E-06
PMID:30355995	2018	Type 2 Diabetes Mellitus and Alzheimer's Disease: Role of Insulin Signalling and Therapeutic Implications.	IGF1,DPP4,IL6,GCG	3.07E-06
PMID:30108523	2018	Molecular Mechanisms of Metformin for Diabetes and Cancer Treatment.	STAT3,MTOR,GCG,CREB1	3.35E-06
PMID:29702529	2018	The Interface of Pancreatic Cancer With Diabetes, Obesity, and Inflammation: Research Gaps and Opportunities: Summary of a National Institute of Diabetes and Digestive and Kidney Diseases Workshop.	IGF1,DPP4,MTOR,IL6	3.35E-06
PMID:29377010	2018	Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums.	IGF1,MTOR,GCG,CREB1	3.86E-06
PMID:29864201	2018	Impact of an integrated diabetes service involving specialist outreach and primary health care on risk factors for micro- and macrovascular diabetes complications in remote Indigenous communities in Australia.	ALB,DPP4,GCG	5.13E-06
PMID:30371301	2018	Effect of Once-Weekly Exenatide on Clinical Outcomes According to Baseline Risk in Patients With Type 2 Diabetes Mellitus: Insights From the EXSCEL Trial.	ALB,DPP4,GCG	5.13E-06
PMID:29545773	2018	Impact of Normoglycemia in Reducing Microvascular Complications in Patients with Type 2 Diabetes: A Follow-Up Study.	ALB,IGF1,DPP4	6.91E-06
PMID:30255388	2018	The Effects of Novel Antidiabetic Drugs on Albuminuria in Type 2	ALB,DPP4,GCG	6.91E-06

		Diabetes Mellitus: A Systematic Review and Meta-analysis of Randomized Controlled Trials.		
PMID:29416527	2018	The Impact of Type 2 Diabetes on Bone Fracture Healing.	ALB,IGF1,DPP4,IL6	8.49E-06
PMID:29637459	2018	Safety and Efficacy of Tenepliptin in Patients with Type 2 Diabetes Mellitus and Impaired Renal Function: Interim Report from Post-marketing Surveillance.	ALB,DPP4,GCG	8.49E-06
PMID:30206903	2018	Comprehensive Evaluation of Combination Therapy with Basal Insulin and Either Lixisenatide or Vildagliptin in Japanese Patients with Type 2 Diabetes: A Randomized, Open-Label, Parallel-Group, Multicenter Study.	ALB,DPP4,GCG	8.49E-06
PMID:30627161	2018	A Dipeptidyl Peptidase-4 Inhibitor Suppresses Macrophage Foam Cell Formation in Diabetic dbdb Mice and Type 2 Diabetes Patients.	DPP4,IL6,GCG	8.49E-06
PMID:28671753	2018	Glycaemic outcomes of an Individualized treatment approach for older vulnerable patients: A randomized, controlled study in type 2 diabetes Mellitus (IMPERIUM).	ALB,DPP4,GCG	1.03E-05
PMID:29427024	2018	Comparison of the effects of linagliptin and voglibose on endothelial function in patients with type 2 diabetes and coronary artery disease: a prospective, randomized, pilot study (EFFORT).	ALB,DPP4,GCG	1.03E-05
PMID:29491712	2018	Dietary black-grained wheat intake improves glycemic control and inflammatory profile in patients with type 2 diabetes: a randomized controlled trial.	ALB,IL6,GCG	1.03E-05
PMID:29707088	2018	Impact of Dapagliflozin Therapy on Renal Protection and Kidney Morphology in Patients With Uncontrolled Type 2 Diabetes Mellitus.	ALB,DPP4,GCG	1.03E-05
PMID:29915538	2018	Efficacy and Safety of Once-Weekly Semaglutide for the Treatment of Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.	ALB,DPP4,GCG	1.03E-05
PMID:30158516	2018	Very high-protein and low-carbohydrate enteral nutrition formula and plasma glucose control in adults with type 2 diabetes mellitus: a randomized crossover trial.	DPP4,MTOR,GCG	1.03E-05
PMID:30487974	2018	Mealtime dosing of a rapid-acting insulin analog reduces glucose variability and suppresses daytime cardiac sympathetic activity: a randomized controlled study in hospitalized patients with type 2 diabetes.	ALB,DPP4,GCG	1.03E-05
PMID:28686352	2018	Ratio of visceral-to-subcutaneous fat area predicts cardiovascular events in patients with type 2 diabetes.	ALB,DPP4,GCG	1.24E-05

PMID:29557063	2018	Renal Hyperfiltration in Adolescents with Type 2 Diabetes: Physiology, Sex Differences, and Implications for Diabetic Kidney Disease.	ALB,DPP4,GCG	1.24E-05
PMID:30121725	2018	Up-Titration Strategy After DPP-4 Inhibitor-Based Oral Therapy for Type 2 Diabetes: A Randomized Controlled Trial Shifting to a Single-Dose GLP-1 Enhancer Versus Adding a Variable Basal Insulin Algorithm.	ALB,DPP4,GCG	1.24E-05
PMID:30287671	2018	Glimepiride monotherapy versus combination of glimepiride and linagliptin therapy in patients with HNF1A-diabetes: a protocol for a randomised, double-blinded, placebo-controlled trial.	ALB,DPP4,GCG	1.24E-05
PMID:30705633	2018	Therapeutic Options Targeting Oxidative Stress, Mitochondrial Dysfunction and Inflammation to Hinder the Progression of Vascular Complications of Diabetes.	STAT3,DPP4,IL6,GCG	1.28E-05
PMID:30210604	2018	Meta-analysis of the benefit of sitagliptin treatment in patients with type 2 diabetes complicated with incipient nephropathy.	ALB,DPP4,GCG	1.47E-05
PMID:30145651	2018	Rationale and Design of the STOP-OB Study for Evaluating the Effects of Tofogliflozin and Glimepiride on Fat Deposition in Type 2 Diabetes Patients Treated with MetforminDPP-4 Inhibitor Dual Therapy.	ALB,DPP4,GCG	1.47E-05
PMID:29310647	2018	Have dipeptidyl peptidase-4 inhibitors ameliorated the vascular complications of type 2 diabetes in large-scale trials? The potential confounding effect of stem-cell chemokines.	ALB,DPP4,GCG	1.47E-05
PMID:29322486	2018	Dapagliflozin and Empagliflozin Ameliorate Hepatic Dysfunction Among Chinese Subjects with Diabetes in Part Through Glycemic Improvement: A Single-Center, Retrospective, Observational Study.	ALB,DPP4,IL6	1.47E-05
PMID:29507611	2018	Dapagliflozin improves treatment satisfaction in overweight patients with type 2 diabetes mellitus: a patient reported outcome study (PRO study)	ALB,DPP4,GCG	1.47E-05
PMID:29550776	2018	Impact of a multifactorial treatment programme on clinical outcomes and cardiovascular risk estimates: a retrospective cohort study from a specialised diabetes centre in Denmark.	ALB,DPP4,GCG	1.47E-05
PMID:29664069	2018	Liraglutide Enhances Autophagy and Promotes Pancreatic Beta Cell Proliferation to Ameliorate Type 2 Diabetes in High-Fat-Fed and Streptozotocin-Treated Mice.	DPP4,ATG5,GCG	1.47E-05
PMID:29721333	2018	Diabetes mellitus and bone health: epidemiology, etiology and	IGF1,DPP4,GCG	1.47E-05

		implications for fracture risk stratification.		
PMID:29931506	2018	There is a Close Association Between the Recovery of Liver Injury and Glycemic Control after SGLT2 Inhibitor Treatment in Japanese Subjects with Type 2 Diabetes: A Retrospective Clinical Study.	ALB,DPP4,GCG	1.47E-05
PMID:30473097	2018	LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept.	ALB,DPP4,GCG	1.47E-05
PMID:28178395	2018	Characteristics of sleep-wake cycle and sleep duration in Japanese type 2 diabetes patients with visceral fat accumulation.	ALB,DPP4,GCG	1.71E-05
PMID:29508275	2018	EADSG Guidelines: Insulin Therapy in Diabetes.	ALB,DPP4,GCG	1.71E-05
PMID:30116437	2018	Long-Term Effects of Ipragliflozin on Diabetic Nephropathy and Blood Pressure in Patients With Type 2 Diabetes: 104-Week Follow-up of an Open-Label Study.	ALB,DPP4,GCG	1.71E-05
PMID:30567565	2018	Pancreatic cancer associated with obesity and diabetes: an alternative approach for its targeting.	STAT3,IGF1,IL6,GCG	1.96E-05
PMID:29402270	2018	Effect of sitagliptin on tissue characteristics of the carotid wall in patients with type 2 diabetes: a post hoc sub-analysis of the sitagliptin preventive study of intima-media thickness evaluation (SPIKE)	DPP4,IL6,GCG	1.96E-05
PMID:29435980	2018	The diabetes drug liraglutide reverses cognitive impairment in mice and attenuates insulin receptor and synaptic pathology in a non-human primate model of Alzheimer's disease.	ALB,GCG,CREB1	1.96E-05
PMID:29600504	2018	Clinical Trajectories, Healthcare Resource Use, and Costs of Diabetic Nephropathy Among Patients with Type 2 Diabetes: A Latent Class Analysis.	ALB,DPP4,GCG	1.96E-05
PMID:29623219	2018	Management Strategies for Posttransplant Diabetes Mellitus after Heart Transplantation: A Review.	DPP4,MTOR,GCG	1.96E-05
PMID:29954090	2018	Systematic Review of Efficacy and Safety of Newer Antidiabetic Drugs Approved from 2013 to 2017 in Controlling HbA1c in Diabetes Patients.	ALB,DPP4,GCG	1.96E-05
PMID:30479647	2018	Intermittent administration of a fasting-mimicking diet intervenes in diabetes progression, restores Beta cells and reconstructs gut microbiota in mice.	IGF1,GCG,CREB1	1.96E-05
PMID:30513818	2018	Thromboxane-Dependent Platelet Activation in Obese Subjects with Prediabetes or Early Type 2 Diabetes: Effects of Liraglutide- or	IGF1,IL6,GCG	1.96E-05

		Lifestyle Changes-Induced Weight Loss.		
PMID:29263194	2018	Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a Diabetes Care Editors' Expert Forum.	ALB,DPP4,GCG	2.21E-05
PMID:29382975	2018	Standards of Medical Care in Diabetes-2018 Abridged for Primary Care Providers.	ALB,DPP4,GCG	2.21E-05
PMID:29535952	2018	Consensus Recommendations on Sulfonylurea and Sulfonylurea Combinations in the Management of Type 2 Diabetes Mellitus - International Task Force.	ALB,DPP4,GCG	2.21E-05
PMID:29599686	2018	Alignments of endocrine, anthropometric, and metabolic parameters in type 2 diabetes after intervention with an Okinawa-based Nordic diet.	ALB,DPP4,GCG	2.21E-05
PMID:29773079	2018	Effects of linagliptin on endothelial function and postprandial lipids in coronary artery disease patients with early diabetes: a randomized, placebo-controlled, double-blind trial.	ALB,DPP4,GCG	2.21E-05
PMID:30545359	2018	GLP-1RAs in type 2 diabetes: mechanisms that underlie cardiovascular effects and overview of cardiovascular outcome data.	ALB,DPP4,GCG	2.21E-05
PMID:29570955	2018	Human pancreatic Alfa- to Beta-cell area ratio increases after type 2 diabetes onset.	DPP4,IL6,GCG	2.51E-05
PMID:29589385	2018	Evolution of Diabetes Care in Hong Kong: From the Hong Kong Diabetes Register to JADE-PEARL Program to RAMP and PEP Program.	ALB,IGF1,DPP4	2.51E-05
PMID:29950475	2018	Protocol for Meal-time Administration of Exenatide for Glycaemic Control in Type 1 Diabetes Cases (The MAG1C trial: a randomised, double-blinded, placebo-controlled trial).	ALB,IL6,GCG	2.51E-05
PMID:30197969	2018	Renal Outcomes of Antidiabetic Treatment Options for Type 2 Diabetes-A Proposed MARE Definition.	ALB,DPP4,GCG	2.51E-05
PMID:30352589	2018	Lower extremity arterial disease in patients with diabetes: a contemporary narrative review.	ALB,DPP4,GCG	2.51E-05
PMID:30510163	2018	Engineering of a GLP-1 analogue peptideanti-PCSK9 antibody fusion for type 2 diabetes treatment.	ALB,DPP4,GCG	2.51E-05
PMID:30347717	2018	The Proposal of Molecular Mechanisms of Weak Organic Acids Intake-Induced Improvement of Insulin Resistance in Diabetes Mellitus via Elevation of Interstitial Fluid pH.	ALB,DPP4,GCG	2.81E-05
PMID:30533942	2018	Obesity, Diabetes and Gastrointestinal Malignancy: The	IGF1,MTOR,IL6	3.13E-05

		role of Metformin and other Anti-diabetic Therapy.		
PMID:29915558	2018	Diabetes Mellitus Secondary to Cushing's Disease.	IGF1,DPP4,GCG	3.13E-05
PMID:28799229	2018	Sitagliptin-mediated preservation of endothelial progenitor cell function via augmenting autophagy enhances ischaemic angiogenesis in diabetes.	ALB,DPP4,GCG	3.46E-05
PMID:29230944	2018	Long term (4 years improved insulin sensitivity following islet cell transplant in type 1 diabetes.)	ALB,IGF1,GCG	3.46E-05
PMID:30470170	2018	The role of advanced glycation end-products in the development of coronary artery disease in patients with and without diabetes mellitus: a review.	ALB,DPP4,IL6	3.46E-05
PMID:30539027	2018	Th1Th2 Dichotomy in Obese Women with Gestational Diabetes and Their Macrosomic Babies.	ALB,IGF1,IL6	3.46E-05
PMID:29934664	2018	Histones and heart failure in diabetes.	STAT3,DPP4,IL6,GCG	3.82E-05
PMID:28501906	2018	Medication use for the treatment of diabetes in obese individuals.	ALB,DPP4,GCG	3.82E-05
PMID:29988851	2018	Coagonist of glucagon-like peptide-1 and glucagon receptors ameliorates kidney injury in murine models of obesity and diabetes mellitus.	ALB,IL6,GCG	3.82E-05
PMID:30157689	2018	Association between angiopoietin-like protein 2 and lectin-like oxidized low-density lipoprotein receptor 1 ligand containing apolipoprotein B in patients with type 2 diabetes.	ALB,DPP4,IL6	3.82E-05
PMID:30231777	2018	Impact of bariatric surgery on cardiovascular and renal complications of diabetes: a focus on clinical outcomes and putative mechanisms.	ALB,IL6,GCG	3.82E-05
PMID:30513800	2018	Fatty Acid-Binding Protein 4-An 'Inauspicious' Adipokine-In Serum and Urine of Post-Partum Women with Excessive Gestational Weight Gain and Gestational Diabetes Mellitus.	ALB,IGF1,IL6	3.82E-05
PMID:29992107	2018	An update on natural compounds in the remedy of diabetes mellitus: A systematic review.	ALB,DPP4,GCG	4.20E-05
PMID:30567315	2018	PI3Kinases in Diabetes Mellitus and Its Related Complications.	IGF1,PIK3CG,MTOR	4.20E-05
PMID:32232085	2018	Review of the role of the nervous system in glucose homoeostasis and future perspectives towards the management of diabetes.	STAT3,IL6,GCG	4.20E-05
PMID:29411291	2018	Post-Liver Transplantation Diabetes Mellitus: A Review of Relevance and Approach to Treatment.	DPP4,MTOR,GCG	4.59E-05
PMID:29866130	2018	Influence of high density lipoprotein cholesterol levels on circulating monocytic angiogenic cells functions in individuals with type 2 diabetes mellitus.	PON1,ALB,IGF1	5.00E-05

PMID:29325553	2018	Sitagliptin improved glucose assimilation in detriment of fatty-acid utilization in experimental type-II diabetes: role of GLP-1 isoforms in Glut4 receptor trafficking.	ALB,DPP4,GCG	5.43E-05
PMID:29724198	2018	The synergistic effects of saxagliptin and metformin on CD34+ endothelial progenitor cells in early type 2 diabetes patients: a randomized clinical trial.	IGF1,DPP4,IL6	7.00E-05
PMID:30400566	2018	Maternal Beta-Cell Adaptations in Pregnancy and Placental Signalling: Implications for Gestational Diabetes.	MTOR,IL6,GCG	7.00E-05
PMID:29710777	2018	Egg and Soy-Derived Peptides and Hydrolysates: A Review of Their Physiological Actions against Diabetes and Obesity.	DPP4,IL6,GCG	7.58E-05
PMID:30373146	2018	The Pathophysiology of Gestational Diabetes Mellitus.	STAT3,IGF1,IL6	8.16E-05
PMID:30183752	2018	Generation and selection of pluripotent stem cells for robust differentiation to insulin-secreting cells capable of reversing diabetes in rodents.	ALB,IGF1,GCG	9.49E-05
PMID:30692925	2018	Potential Nexus of Non-alcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus: Insulin Resistance Between Hepatic and Peripheral Tissues.	MTOR,IL6,GCG	9.49E-05
PMID:29454372	2018	A novel combination of bortezomib, lenalidomide, and clarithromycin produced stringent complete response in refractory multiple myeloma complicated with diabetes mellitus - clinical significance and possible mechanisms: a case report.	ALB,IGF1,IL6	0.00012
PMID:29527102	2018	RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2017.	ALB,DPP4,GCG	0.00012
PMID:29765322	2018	Therapeutic Potential of Ginsenosides as an Adjuvant Treatment for Diabetes.	STAT3,IL6,GCG	0.00013
PMID:29282247	2018	Highlighting Diabetes Mellitus: The Epidemic Continues.	ALB,DPP4,GCG	0.00016
PMID:29845781	2018	Type 1 Diabetes Mellitus: Cellular and Molecular Pathophysiology at A Glance.	PON1,ALB,IL6	0.00016
PMID:28325798	2017	Management of Inpatient Hyperglycemia and Diabetes in Older Adults.	ALB,DPP4,IL6,GCG	2.58E-07
PMID:28978007	2017	Differences in risk factors of malignancy between men and women with type 2 diabetes: A retrospective case-control study.	IGF1,DPP4,MTOR,GCG	3.26E-07
PMID:28489581	2017	High glucose induces formation of tau hyperphosphorylation via Cav-1-mTOR pathway: A potential molecular mechanism for diabetes-induced cognitive dysfunction.	ALB,DPP4,MTOR,GCG	6.65E-07

PMID:28149833	2017	Assessment of the link between in utero exposure to 2-aminoanthracene (2AA and type-1 diabetes (T1D)	STAT3,ATG5,IL6,GCG	7.75E-07
PMID:28376855	2017	Effects of the SGLT2 inhibitor dapagliflozin on HDL cholesterol, particle size, and cholesterol efflux capacity in patients with type 2 diabetes: a randomized placebo-controlled trial.	PON1,ALB,IL6,GCG	1.02E-06
PMID:28515792	2017	Mesenchymal stem cell therapy in type 2 diabetes mellitus.	IGF1,DPP4,IL6,GCG	1.85E-06
PMID:28280846	2017	Obesity, Type 2 Diabetes and Bone in Adults.	IGF1,DPP4,IL6,GCG	2.22E-06
PMID:27832452	2017	Clinical Pharmacokinetics and Pharmacodynamics of Antihyperglycemic Medications in Children and Adolescents with Type 2 Diabetes Mellitus.	ALB,IGF1,DPP4,GCG	2.41E-06
PMID:28443255	2017	Glucagon-like peptide-1 and glucagon-like peptide-1 receptor agonists in the treatment of type 2 diabetes.	ALB,DPP4,IL6,GCG	2.41E-06
PMID:28352640	2017	A Different Perspective for Management of Diabetes Mellitus: Controlling Viral Liver Diseases.	IGF1,DPP4,IL6,GCG	2.79E-06
PMID:28824543	2017	Is There a Role for Bioactive Lipids in the Pathobiology of Diabetes Mellitus?	IGF1,DPP4,IL6,GCG,CREB1	2.92E-06
PMID:28434032	2017	Diabetes, bone and glucose-lowering agents: basic biology.	DPP4,MTOR,IL6,GCG	3.62E-06
PMID:28179965	2017	Primary Care-Based Investigation of the Effect of Sitagliptin on Blood Pressure in Hypertensive Patients With Type 2 Diabetes.	ALB,DPP4,GCG	5.13E-06
PMID:28096223	2017	Combination Therapy With Exenatide Plus Pioglitazone Versus BasalBolus Insulin in Patients With Poorly Controlled Type 2 Diabetes on Sulfonylurea Plus Metformin: The Qatar Study.	ALB,DPP4,GCG	5.13E-06
PMID:28179966	2017	Efficacy and Safety of Vildagliptin as an Add-On Therapy in Inadequately Controlled Type 2 Diabetes Patients Treated With Basal Insulin.	ALB,DPP4,GCG	5.13E-06
PMID:28761645	2017	Is glycemia control in Canadians with diabetes individualized? A cross-sectional observational study.	ALB,DPP4,GCG	5.13E-06
PMID:28252104	2017	Altered gene expression and repressed markers of autophagy in skeletal muscle of insulin resistant patients with type 2 diabetes.	ALB,MTOR,ATG5,SQSTM1	5.37E-06
PMID:28164134	2017	Diabetes-Induced Reactive Oxygen Species: Mechanism of Their Generation and Role in Renal Injury.	ALB,MTOR,ATG5,IL6,CREB1	6.76E-06
PMID:28921919	2017	Oral glucose lowering with linagliptin and metformin compared with linagliptin alone as initial treatment in Asian patients with newly diagnosed type 2 diabetes and marked	ALB,DPP4,GCG	6.91E-06

		hyperglycemia: Subgroup analysis of a randomized clinical trial.		
PMID:28122172	2017	Association of type 2 diabetes and an inflammatory marker with incident bone fracture among a Japanese cohort.	ALB,IGF1,IL6	6.91E-06
PMID:28526920	2017	Effects of semaglutide on beta cell function and glycaemic control in participants with type 2 diabetes: a randomised, double-blind, placebo-controlled trial.	ALB,DPP4,GCG	6.91E-06
PMID:28744255	2017	Glycemic and Metabolic Effects of Two Long Bouts of Moderate-Intensity Exercise in Men with Normal Glucose Tolerance or Type 2 Diabetes.	DPP4,IL6,GCG	6.91E-06
PMID:29209633	2017	Protein Intake, Especially Vegetable Protein Intake, Is Associated with Higher Skeletal Muscle Mass in Elderly Patients with Type 2 Diabetes.	ALB,MTOR,IL6	6.91E-06
PMID:28465145	2017	Energy sensing pathways: Bridging type 2 diabetes and colorectal cancer?	IGF1,MTOR,ATG5,SQSTM1	7.83E-06
PMID:28683283	2017	Inhibition of IKKEpsilon and TBK1 Improves Glucose Control in a Subset of Patients with Type 2 Diabetes.	STAT3,DPP4,IL6,GCG	8.46E-06
PMID:28982699	2017	Sitagliptin 100 mg vs glimepiride 1-3 mg as an add-on to insulin and metformin in type 2 diabetes (SWIM	ALB,DPP4,GCG	8.49E-06
PMID:28416496	2017	Long-term cost reduction of routine medications following a residential programme combining physical activity and nutrition in the treatment of type 2 diabetes: a prospective cohort study.	DPP4,IL6,GCG	8.49E-06
PMID:28662684	2017	Atypical blood glucose response to continuous and interval exercise in a person with type 1 diabetes: a case report.	ALB,IGF1,GCG	8.49E-06
PMID:28721686	2017	Rationale for, Initiation and Titration of the Basal InsulinGLP-1RA Fixed-Ratio Combination Products, IDegLira and IGlarLixi, for the Management of Type 2 Diabetes.	ALB,DPP4,GCG	8.49E-06
PMID:28728559	2017	Effect of insulin therapy and dietary adjustments on safety and performance during simulated soccer tests in people with type 1 diabetes: study protocol for a randomized controlled trial.	ALB,DPP4,GCG	8.49E-06
PMID:28205322	2017	Efficacy and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: The DURATION-NEO-2 randomized clinical study.	ALB,DPP4,GCG	1.03E-05
PMID:27762088	2017	Preventive effect of ipragliflozin on nocturnal hypoglycemia in patients with type 2 diabetes treated with basal-bolus insulin therapy: An open-label, single-center, parallel, randomized control study.	ALB,DPP4,GCG	1.03E-05

PMID:27790855	2017	Determinants of hemoglobin A1c level in patients with type 2 diabetes after in-hospital diabetes education: A study based on continuous glucose monitoring.	ALB,DPP4,GCG	1.03E-05
PMID:28242866	2017	Cross-Over Study Comparing Postprandial Glycemic Increase After Addition of a Fixed-Dose Mitiglinide/Voglibose Combination or a Dipeptidyl Peptidase-4 Inhibitor to Basal Insulin Therapy in Patients with Type 2 Diabetes Mellitus.	ALB,DPP4,GCG	1.03E-05
PMID:28589103	2017	Effect of symbiotic supplementation on glycemic control, lipid profiles and microalbuminuria in patients with non-obese type 2 diabetes: a randomized, double-blind, clinical trial.	ALB,IL6,GCG	1.03E-05
PMID:28596970	2017	Type 2 Diabetes in Young Females Results in Increased Serum Amyloid A and Changes to Features of High Density Lipoproteins in Both HDL2 and HDL3.	PON1,DPP4,GCG	1.03E-05
PMID:28868829	2017	Factors Associated with Improved Glycemic Control by Direct-Acting Antiviral Agent Treatment in Egyptian Type 2 Diabetes Mellitus Patients with Chronic Hepatitis C Genotype 4.	ALB,DPP4,IL6	1.03E-05
PMID:28881791	2017	Dipeptidyl peptidase 4 inhibitor use is associated with a lower risk of incident acute kidney injury in patients with diabetes.	ALB,DPP4,GCG	1.03E-05
PMID:28921915	2017	Weekly glucagon-like peptide-1 receptor agonist albiglutide as monotherapy improves glycemic parameters in Japanese patients with type 2 diabetes mellitus: A randomized, double-blind, placebo-controlled study.	ALB,DPP4,GCG	1.03E-05
PMID:29113364	2017	Alpha-glucosidase inhibitors and risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis.	IGF1,DPP4,GCG	1.03E-05
PMID:27898589	2017	Growth in patients with type 1 diabetes.	ALB,IGF1,IL6	1.24E-05
PMID:28515791	2017	Vildagliptin has the same safety profile as a sulfonylurea on bone metabolism and bone mineral density in post-menopausal women with type 2 diabetes: a randomized controlled trial.	IGF1,DPP4,GCG	1.24E-05
PMID:28779212	2017	Topical administration of DPP-IV inhibitors prevents retinal neurodegeneration in experimental diabetes.	ALB,DPP4,GCG	1.24E-05
PMID:28761062	2017	T2DiACoD: A Gene Atlas of Type 2 Diabetes Mellitus Associated Complex Disorders.	PON1,ALB,DPP4,IL6,CREB1	1.40E-05
PMID:27837465	2017	Empagliflozin: Role in Treatment Options for Patients with Type 2 Diabetes Mellitus.	ALB,DPP4,GCG	1.47E-05
PMID:28067320	2017	Relationship between frequency of hypoglycemic episodes and	DPP4,IL6,GCG	1.47E-05

		changes in carotid atherosclerosis in insulin-treated patients with type 2 diabetes mellitus.		
PMID:28225432	2017	The use of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes & chronic kidney disease.	ALB,DPP4,GCG	1.47E-05
PMID:28391776	2017	Mechanism of the blood pressure-lowering effect of sodium-glucose cotransporter 2 inhibitors in obese patients with type 2 diabetes.	ALB,DPP4,GCG	1.47E-05
PMID:28761661	2017	Association of diabetic retinopathy with both sarcopenia and muscle quality in patients with type 2 diabetes: a cross-sectional study.	ALB,DPP4,GCG	1.47E-05
PMID:29176623	2017	Microneedle-array patches loaded with dual mineralized proteinpeptide particles for type 2 diabetes therapy.	DPP4,IL6,GCG	1.47E-05
PMID:28144042	2017	Standards of Medical Care in Diabetes-2017 Abridged for Primary Care Providers.	ALB,DPP4,GCG	1.71E-05
PMID:28253918	2017	Luseogliflozin reduces epicardial fat accumulation in patients with type 2 diabetes: a pilot study.	ALB,DPP4,IL6	1.71E-05
PMID:28469250	2017	Development of a Novel Zebrafish Model for Type 2 Diabetes Mellitus.	STAT3,DPP4,IL6	1.71E-05
PMID:28630427	2017	Insulin use and Excess Fracture Risk in Patients with Type 2 Diabetes: A Propensity-Matched cohort analysis.	IGF1,DPP4,GCG	1.71E-05
PMID:28786125	2017	Recent Advances in GLP-1 Receptor Agonists for Use in Diabetes Mellitus.	ALB,DPP4,GCG	1.71E-05
PMID:29061170	2017	Translating recent results from the Cardiovascular Outcomes Trials into clinical practice: recommendations from the Central and Eastern European Diabetes Expert Group (CEEDEG)	ALB,DPP4,GCG	1.71E-05
PMID:29285456	2017	Gemigliptin: Newer Promising Gliptin for Type 2 Diabetes Mellitus.	ALB,DPP4,GCG	1.71E-05
PMID:28060743	2017	2017 update on the relationship between diabetes and colorectal cancer: epidemiology, potential molecular mechanisms and therapeutic implications.	STAT3,IGF1,IL6,GCG	1.96E-05
PMID:28231835	2017	Vildagliptin, but not glibenclamide, increases circulating endothelial progenitor cell number: a 12-month randomized controlled trial in patients with type 2 diabetes.	DPP4,IL6,GCG	1.96E-05
PMID:28508457	2017	Effects of canagliflozin on cardiovascular risk factors in patients with type 2 diabetes mellitus.	ALB,DPP4,GCG	1.96E-05
PMID:28553763	2017	Clinical characteristics of patients with diabetes mellitus and fatty liver diagnosed by liverspleen Hounsfield units on CT scan.	ALB,DPP4,GCG	1.96E-05
PMID:28725273	2017	A randomized controlled trial comparing the effects of	ALB,DPP4,GCG	1.96E-05

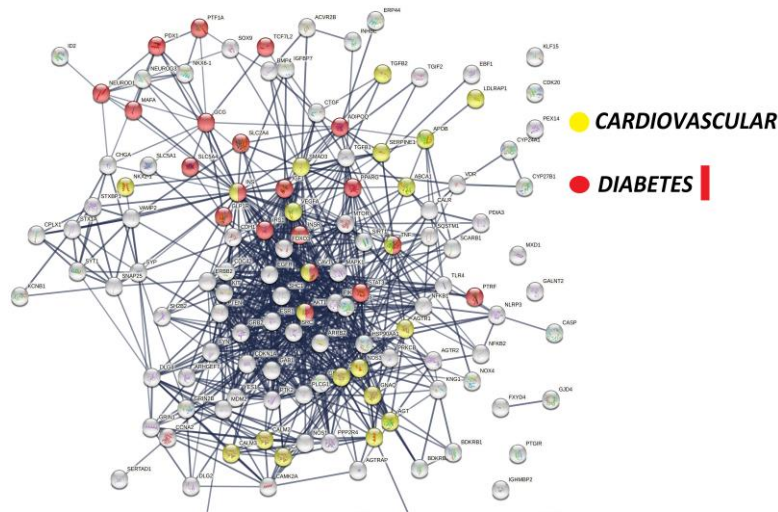
		dapagliflozin and DPP-4 inhibitors on glucose variability and metabolic parameters in patients with type 2 diabetes mellitus on insulin.		
PMID:28771387	2017	Minimizing Glycemic Fluctuations in Patients with Type 2 Diabetes: Approaches and Importance.	ALB,DPP4,GCG	1.96E-05
PMID:29187821	2017	Renoprotective Effect of Dipeptidyl Peptidase-4 Inhibitors in Patients with Type 2 Diabetes Mellitus.	ALB,DPP4,GCG	1.96E-05
PMID:27868359	2017	Linagliptin improves endothelial function in patients with type 2 diabetes: A randomized study of linagliptin effectiveness on endothelial function.	ALB,DPP4,GCG	2.21E-05
PMID:28636754	2017	Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial.	ALB,DPP4,GCG	2.21E-05
PMID:29075333	2017	The impact of type 2 diabetes on bone metabolism.	IGF1,DPP4,GCG	2.51E-05
PMID:29254185	2017	Hepatoprotective potential of isoquercitrin against type 2 diabetes-induced hepatic injury in rats.	ALB,DPP4,GCG	2.51E-05
PMID:29270319	2017	The Bidirectional Relationship between Tuberculosis and Diabetes.	DPP4,IL6,GCG	2.51E-05
PMID:27397060	2017	Effect of Glycemic Control on Chylomicron Metabolism and Correlation between Postprandial Metabolism of Plasma Glucose and Chylomicron in Patients with Type 2 Diabetes Treated with Basal-bolus Insulin Therapy with or without Vildagliptin.	ALB,DPP4,GCG	2.81E-05
PMID:27575011	2017	Vildagliptin reduces plasma stromal cell-derived factor-1Alfa in patients with type 2 diabetes compared with glimepiride.	ALB,DPP4,IL6	2.81E-05
PMID:27652617	2017	Cardiovascular safety of therapies for type 2 diabetes.	ALB,DPP4,GCG	2.81E-05
PMID:28706237	2017	Suppressed autophagic response underlies augmentation of renal ischemiareperfusion injury by type 2 diabetes.	ALB,MTOR,ATG5	2.81E-05
PMID:28769579	2017	Emerging use of combination therapies for the management of type 2 diabetes - focus on saxagliptin and dapagliflozin.	ALB,DPP4,GCG	2.81E-05
PMID:27980006	2017	Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis.	ALB,DPP4,GCG	3.13E-05
PMID:28356733	2017	A novel selective VPAC2 agonist peptide-conjugated chitosan modified selenium nanoparticles with enhanced anti-type 2 diabetes synergy effects.	ALB,DPP4,GCG	3.13E-05
PMID:28724428	2017	Mirroring the CANTOS revolution: is anti-inflammatory therapy for diabetes just around the corner?	DPP4,IL6,GCG	3.13E-05

PMID:29206832	2017	The effects of dipeptidyl peptidase-4 inhibitors on bone fracture among patients with type 2 diabetes mellitus: A network meta-analysis of randomized controlled trials.	IGF1,DPP4,GCG	3.13E-05
PMID:28217523	2017	Safe and pragmatic use of sodium-glucose co-transporter 2 inhibitors in type 2 diabetes mellitus: South Asian Federation of Endocrine Societies consensus statement.	ALB,DPP4,GCG	3.46E-05
PMID:28694926	2017	Diabetes-induced mechanophysiological changes in the small intestine and colon.	IGF1,DPP4,GCG	3.46E-05
PMID:29146657	2017	A randomised controlled trial of a duodenal-jejunal bypass sleeve device (EndoBarrier) compared with standard medical therapy for the management of obese subjects with type 2 diabetes mellitus.	ALB,IL6,GCG	3.46E-05
PMID:28659725	2017	System Level Meta-analysis of Microarray Datasets for Elucidation of Diabetes Mellitus Pathobiology.	STAT3,IGF1,IL6	4.20E-05
PMID:28270518	2017	Myricetin: a potent approach for the treatment of type 2 diabetes as a natural class B GPCR agonist.	ALB,DPP4,GCG	4.59E-05
PMID:28962617	2017	Oxidative stress and inflammation as central mediators of atrial fibrillation in obesity and diabetes.	DPP4,IL6,GCG	4.59E-05
PMID:29034006	2017	Canagliflozin reduces epicardial fat in patients with type 2 diabetes mellitus.	ALB,DPP4,IL6	4.59E-05
PMID:29066867	2017	Clinical and pharmacological hallmarks of rifapentine's use in diabetes patients with active and latent tuberculosis: do we know enough?	ALB,DPP4,GCG	4.59E-05
PMID:28235195	2017	Fasting-Mimicking Diet Promotes Ngn3-Driven Beta-Cell Regeneration to Reverse Diabetes.	ALB,IGF1,GCG	5.43E-05
PMID:29021829	2017	Review article: effects of type 2 diabetes therapies on bone metabolism.	IGF1,DPP4,GCG	5.43E-05
PMID:28767672	2017	Bi-stability in type 2 diabetes mellitus multi-organ signalling network.	IGF1,IL6,GCG	5.91E-05
PMID:28425473	2017	2D-DIGE as a strategy to identify serum biomarkers in Mexican patients with Type-2 diabetes with different body mass index.	ALB,DPP4,GCG	6.44E-05
PMID:28270856	2017	Resistance training to improve type 2 diabetes: working toward a prescription for the future.	MTOR,IL6,CREB1	7.00E-05
PMID:28340340	2017	Selective Chemical Inhibition of PGC-1 α Gluconeogenic Activity Ameliorates Type 2 Diabetes.	DPP4,GCG,CREB1	7.00E-05
PMID:28655134	2017	Multiple Mechanisms Linking Type 2 Diabetes and Alzheimer's Disease: Testosterone as a Modifier.	IGF1,IL6,GCG	8.16E-05
PMID:27306986	2017	Targeting orphan G protein-coupled receptors for the treatment of diabetes and its complications: C-peptide and GPR146.	ALB,DPP4,GCG	8.80E-05

PMID:28512448	2017	The Potential Role of Contraction-Induced Myokines in the Regulation of Metabolic Function for the Prevention and Treatment of Type 2 Diabetes.	STAT3,IGF1,IL6	8.80E-05
PMID:29213501	2017	Type 2 diabetes mellitus in the pathophysiology of Alzheimer's disease.	IGF1,IL6,GCG	8.80E-05
PMID:28507210	2017	Diabetes, Pancreatogenic Diabetes, and Pancreatic Cancer.	IGF1,DPP4,GCG	0.0001
PMID:27652986	2017	Adenosine monophosphate-activated protein kinase-based classification of diabetes pharmacotherapy.	DPP4,MTOR,GCG	0.00011
PMID:29098166	2017	Renoprotective Effects of the Dipeptidyl Peptidase-4 Inhibitor Sitagliptin: A Review in Type 2 Diabetes.	ALB,DPP4,GCG	0.00012
PMID:28376896	2017	Regulation of visceral and epicardial adipose tissue for preventing cardiovascular injuries associated to obesity and diabetes.	DPP4,IL6,GCG	0.00015
PMID:28230764	2017	Cinnamic Acid and Its Derivatives: Mechanisms for Prevention and Management of Diabetes and Its Complications.	ALB,DPP4,GCG	0.00016

Network Nodes used For Product Design and Scoring

CM EFFECTS ON DIABETES AND CARDIOVASCULAR DISEASE



¹ <https://www.cardiomiracle.com/>

² Cieri-Hutcherson, N.E., Jaenecke, A., Bahia, A., Lucas, D., Oluloro, A., Stimmel, L. and Hutcherson, T.C., 2021. Systematic review of L-arginine for the treatment of hypoactive sexual desire disorder and related conditions in women. *Pharmacy*, 9(2), p.71.

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