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Review Article

A Short Review on Anti-Diabetic Agent

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ABSTRACT

Different type of natural and synthetic agents for the treatment of Type 2 diabetes mellitus improve the metabolic profile but do not reestablished normality. They also reduce chronic diabetic complications, but they do not remove completely them. Thus, for the treatment of type2 diabetes mellitus new agents with novel actions are required to complement and extend the capabilities of existing treatments. Insulin resistance and beta-cell failure, which are main cause in the pathogenesis of Type 2 diabetes, in this review we discussed about some natural and synthetic molecule and their targets and some old oral ant diabetic drug and their mode of action.

Keywords: diabetes mellitus, DM type 1 & DM type 2, anti-diabetes drugs, anti-diabetes molecule

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by increase glucose level in blood and changes in lipid and protein metabolism [1]. Because the body cannot release or use insulin normally. Insulin is a hormone which is released by pancreas which maintaining sugar level in blood [2]. Diabetes mellitus are of two type one is insulin dependent [3] and another is non-insulin dependent. Insulin dependent diabetes called type 1(IDDM), also known as "juvenile diabetes" because it occurs in the young children and adolescents. it is an autoimmune disorder where antibodies are produced against the β cells which release insulin, are destroyed[3].

Non-insulin dependent called type 2 diabetes mellitus (NIDDM) or "adult-onset diabetes "because occurs in adult. Serious prolong complications include some serious disease like heart disease, stroke, kidney failure, foot ulcers and damage to the eyes[1] DM can be found worldwide and the population is increasing. According to WHO projections, about 300 million or more people will be affected by diabetes by the year 2025.[4] The estimated number of diabetic patients in 2030 will be more than double that in 2005.[4] according toIDF in 2009 India has the largest number of people — 50.8 million suffering from diabetes in the world, followed by China (43.2 million) and the United States (26.8 million). India continues to be the "diabetes capital" of the world, and by 2030, nearly 9 per cent of the country's population is likely to be affected from the disease, warns the fourth edition of the World Diabetes Atlas launched by the IDF at the 20th World Diabetes Congress in Montreal, Canada. Worldwide, as of 2013, an estimated 382 million people have diabetes, with type 2 diabetes making about 90% of the cases.[5,6] This

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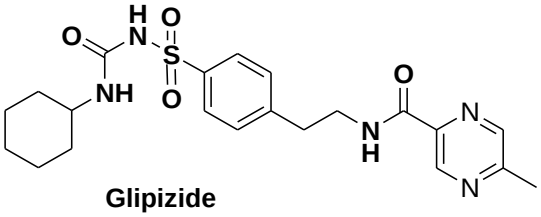
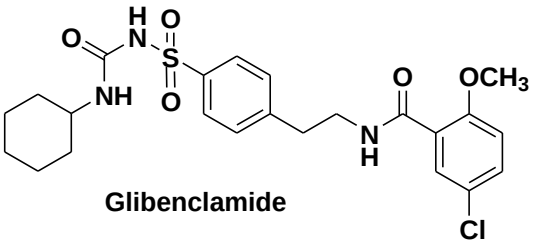
is equal about 8.3% of the adults population,[6] equal rates in both women and men.[7] Worldwide in 2012 and 2013 diabetes resulted in 1.5 to 5.1 million deaths per year, making it the 8th leading cause of death.[8,9] Diabetes overall at least doubles the risk of death. The number of people with diabetes is estimated up to rise to 592million by 2035.[10]The economic costs of diabetes globally was estimated in 2013 at $548 billion[9]and in the United States in 2012 $245 billion.[11]

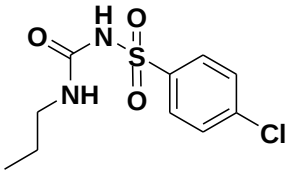
Some Oral anti-diabetic drugs-
Type of anti-diabetic drugs-
- Sulfonylureas/insulin tropics
- Biguanides
- a-Glycosidase inhibitors
- Thiazolidinedione
- DPP-4 inhibitors (Glistens)

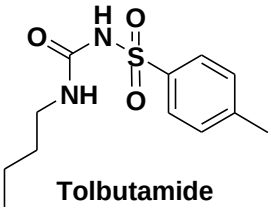
Sulfonylureas/insulin tropics-mechanism and targets-
Sulfonylureas reduce the blood glucose level by stimulating the release of insulin from the pancreatic β-cell and sensitivity of peripheral tissue to insulin, number of insulin receptor and suppressing gluconeogenesis in the liver.
It bind to receptors on the pancreatic β-cell, and block the k+ on these receptor. It reduce potassium conductance and increased insulin secretion**.**

Side effects-Hypoglycemia, weight gain
Example and their structure-

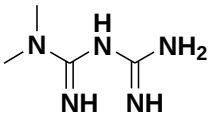


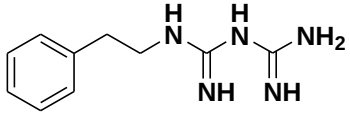






Biguanides-mechanism and action is not clear,suppressing hepatic gluconeogenesis
Side effect-Gastrointestinal disturbances, lactic acidosis





α-Glucosidase inhibitors-it reduce the glucose absorption from upper intestines and do not causes hypoglycemia

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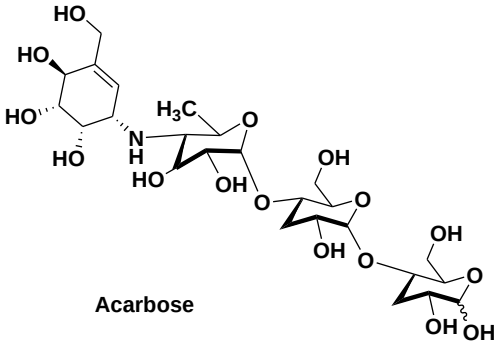
Eide effect-Gastrointestinal disturbance

Example and their structure-

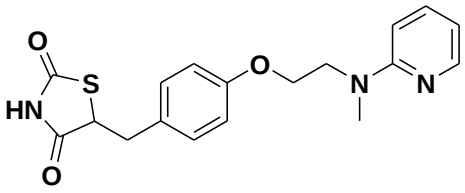


Acarbose

Thiazolidinediones- they are agonist at the PPARϒ receptor. It increase insulin mediated glucose transport in to muscle and fat tissue and reduce hepatic gluconeogenesis and lower incidence of hypoglycemia

Side effect-cause severe hepatotoxicity and weight and anemia

Example and their structure-

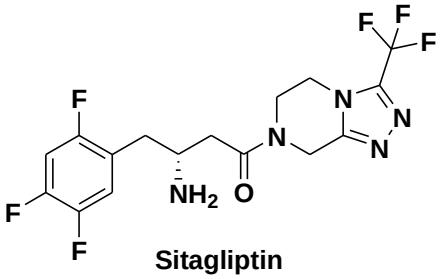


Rosiglitazone

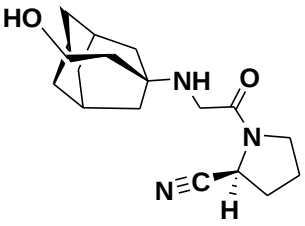
DPP-4 inhibitors (Gliptins)- Reduce glucagon and blood glucose levels by inhibiting DPP-4

Side effect-Nasopharyngitis, Headache, Nausea, Hypersensitivity, Skin reactions

Example and their structure-



Sitagliptin



Vildagliptin

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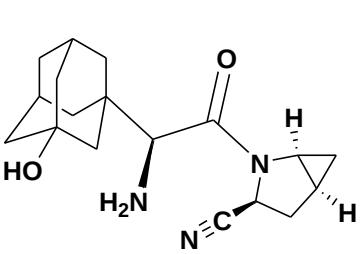
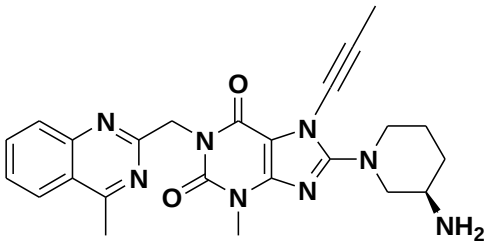
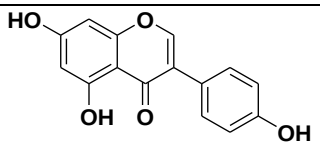
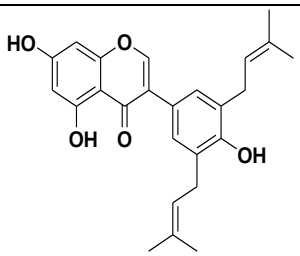
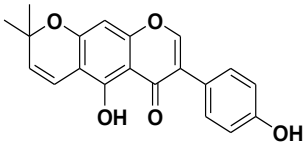
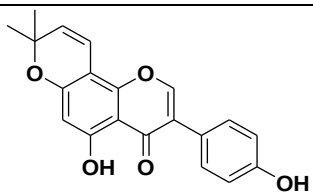


Saxagliptin



Linagliptin

Some anti-diabetic agent -

S.N.	Name and source	Activity & Mechanism	Structure of compound
1	Genistein [12] branches of Tetracera scandens (Dilleniaceae	Glucose-uptake activity in basal and insulin-stimulated L6 myotubes (0–25 mM), acting by AMPK activation and GLUT4 and GLUT1 (IC_{50}range= 20–37 µM)	 5,7-dihydroxy-3-(4-hydroxyphenyl)-4*H*-chromen-4-one
2	3',5'-diprenylgenistein branches of Tetracera scandens (Dilleniaceae)	Glucose-uptake activity in basal and insulin-stimulated L6 myotubes (0–25 mM), acting by AMPK activation and GLUT4 and GLUT1 (IC_{50}range= 20–37 µM)	 5,7-dihydroxy-3-(4-hydroxy-3,5-bis(3-methylbut-2-enyl)phenyl)-4*H*-chromen-4-one
3	Alpinumisoflavone branches of Tetracera scandens (Dilleniaceae)	Glucose-uptake activity in basal and insulin-stimulated L6 myotubes (0–25 mM), acting by AMPK activation and GLUT4 and GLUT1 (IC_{50}range= 20–37 µM)	 **5-hydroxy-7-(p-hydroxyphenyl)-2,2-dimethyl-2H-6H-benzodipyran-6-one**
4	Derrone branches of Tetracera scandens (Dilleniaceae	Glucose-uptake activity in basal and insulin-stimulated L6 myotubes (0–25 mM), acting by AMPK activation and GLUT4 and (IC_{50}range= 20–37 µM)	 5-Hydroxy-3-(4-hydroxyphenyl)-8,8-dimethyl-4H,8H-benzo[1,2-b:3,4-b']dipyran-4-one;3-(4-Hydroxyphenyl)-5-hydroxy-8,8-dimethyl-4H,8H-benzo[1,2-b:3,4-b']dipyran-4-one

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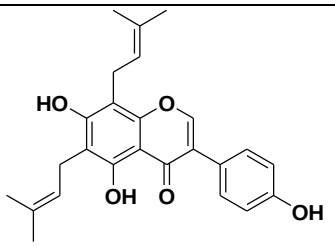
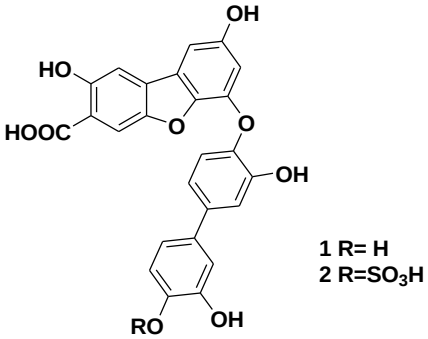
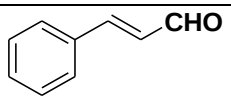
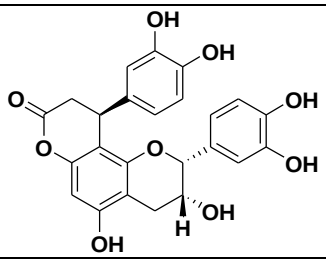
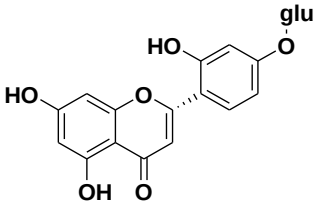
5	6,8-diprenylgenistein branches of Tetracera scandens (Dilleniaceae	Glucose-uptake activity in basal and insulin stimulated L6 myotubes (0–25 mM), acting by AMPK activation and GLUT4 and GLUT1 over-expressio (IC_{50}range= 20–37 µM)	 5,7-dihydroxy-3-(4-hydroxyphenyl)-6,8-bis(3-methylbut-2-enyl)-4*H*-chromen-4-one
6	Vanilic acid & sulphate Derivatives[13] Green algae Cladophora socialis	Inhibition of protein tyrosine phosphatase 1B (PTP1B),an important enzyme in regulating the insulin receptor, with IC50 values of 3.7µM	 1 R= H 2 R=SO_3H
7	Cinamaldehyde Cinanamonum zeylanicum Biume	Inhibition of protein tyrosine phosphatase 1B (PTP1B),an important enzyme in regulating the insulin receptor, with IC50 values of 1.7 µM	 cinnamaldehyde
8	Cinchonain Ib Eriobotrya japonica[14]LINDL (Rosaceae) leaves	Enhanced insulin secretion from INS-1 cells (rat insulinoma cell), as well as reduced plasma insulin level in ratsafter 108 mg /kgoral administration	
9	Steppogenin-4'-O-β-D-glucoside[15] root bark of Morus alba L. (Moraceae)	Showed a hypoglycemic effect at 50 mg kg_1 (p.o.) in alloxan-induced diabetic mice	 Steppogenin-4'-O-β-D-glucoside

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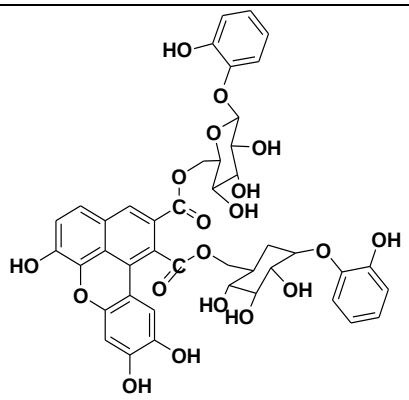
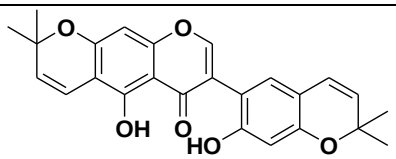
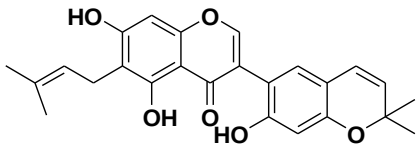
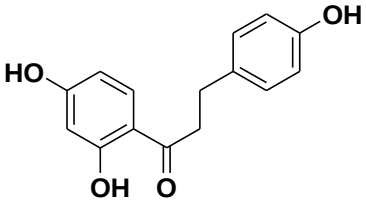
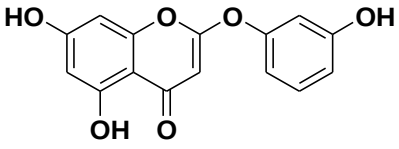
10	Two bis(catechol glycoside) esters[16] leaves of Dodecadenia grandiflora (Lauraceaes	Compounds (100 mg kg_1 bw, p.o.) showed significantantihyperglycemic activity in STZ-induced diabetic rats	 1-(5-(2-hydroxyphenoxy)-2,3,4-trihydroxycyclohexyl)methyl 2-(6-(2-hydroxyphenoxy)-tetrahydro-3,4,5-trihydroxy-2*H*-pyran-2-yl)methyl 6,9,10-trihydroxybenzo[*kl*]xanthene-1,2-dicarboxylate
11	kraussianone-1 & kraussianone-2[17] Roots of Eriosema kraussianum N. E. Br. (Fabaceae)	Compounds 1and 12 (20–80 mg/ kgp.o.) resulted in dose-dependent hypoglycaemia in rats, with glibenclamide (10 mg/ kgbw, p.o.) as the positive control	 **kraussianone-1**  **kraussianone-2**
12	Davidigenin[18] Artemisia dracunculus L. (Asteraceae),	This extract inhibited aldose reductase (ALR2) activity by 58% to 77% at 3.75 mg/ mL	 1-(2,4-dihydroxyphenyl)-3-(4-hydroxyphenyl)propan-1-one
13	6,demethoxycapillarisn Artemisia dracunculus L. (Asteraceae),	Inhibited phosphoenol pyruvate carboxykinase (PEPCK) mRNA levels related to the gluconeogenesis pathway, with IC50 values of 43µM,it also activated the PI3K pathway, similarly to insulin,	 **2-(3-hydroxyphenoxy)-5,7-dihydroxy-4*H*-chromen-4-one**

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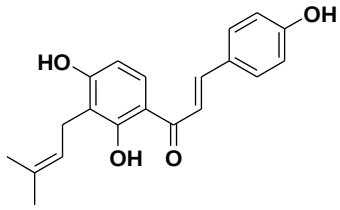
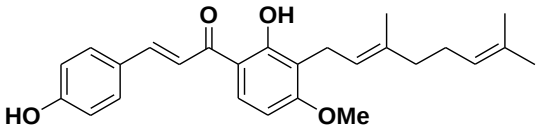
14	4-hydroxyderricin[19] ethanol extract of Angelica keiskei Koidzumi (Apiaceae/Umbelliferae)	Preventedprogression of diabetes in genetically impaired KK-Ay mice, which develop diabetes and show hyperglycemia with aging because of insulin resistance (positive control: 0.05% diet of pioglitazone).30showed acute blood glucose lowering effects (50 mg kg_1 bw) in ALX-induced diabetic rats and promoted glucose-induced insulin secretion after oral treatment in hyperglycemic rats.	 (*E*)-1-(2,4-dihydroxy-3-(3-methylbut-2-enyl)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one
15	Xanthoangelol[19] ethanol extract of Angelica keiskei Koidzumi (Apiaceae/Umbelliferae)	.Preventedprogression of diabetes in genetically impaired KK-Ay mice, which develop diabetes and show hyperglycemia with aging because of insulin resistance (positive control: 0.05% diet of pioglitazone).30showed acute blood glucose lowering effects (50 mg kg_1 bw) in ALX-induced diabetic rats and promoted glucose-induced insulin secretion after oral treatment in hyperglycemic rats.	 (2*E*)-1-(2-hydroxy-4-methoxy-3-((*E*)-3,7-dimethylocta-2,6-dienyl)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one

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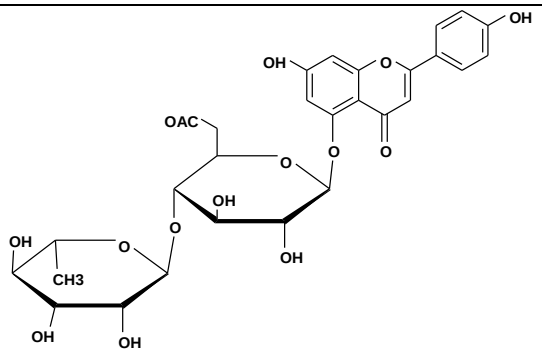
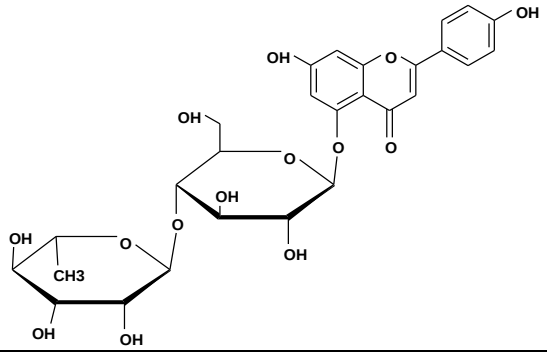
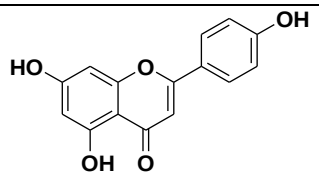
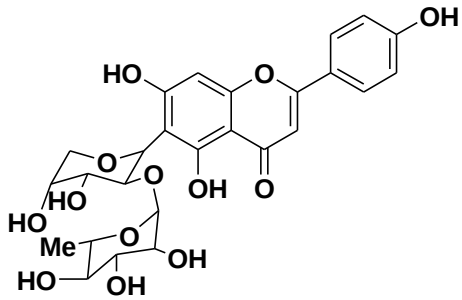
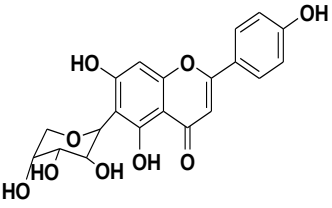
16	Apigenin-5-O-[α-L-rhamnopyranosyl-(1-4)-6-O-β-Dacetylglucopyranoside][20] leaves of Cephalotaxus sinensis	Anti-hyperglycemic	
17	Apigenin-5-O-[a-L-rhamnopyranosyl-(1-4)-6-O-β-D-glucopyranoside[20] leaves of Cephalotaxus sinensis	Anti-hyperglycemic	
18	Apigenin[21] leaves of Cephalotaxus sinensis	Increased level of glucose transporterGLUT-4 was also seen from mice adipocytes treated with 14 (0.1mg, 2 mg/ml.	 5,7-dihydroxy-2-(4-hydroxyphenyl)-4*H*-chromen-4-one
19	Apigenin-O-{20-O-α-L-rhamnopyranosyl) -β-L-fucopyranoside[21] Averrhoa carambola L.	Acute blood glucose lowering effects (50 mg/ kg bw) in ALX-induced diabetic rats and promoted glucose-induced insulin secretion after oral treatment in hyperglycemic rats	
20	Apigenin-6-C-β-L-fucopyranoside [21] Averrhoa carambola L	(50 mg/kgbw, p.o.) Lowered blood glucose in hyperglycemic rats, promoted glucose-induced insulin secretion, and stimulated glycogen synthesis	 6-(tetrahydro-3,4,5-trihydroxy-2*H*-pyran-2-yl)-5,7-dihydroxy-2-(4-hydroxyphenyl)-4*H*-chromen-4-one

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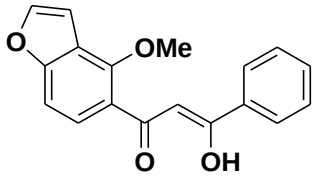
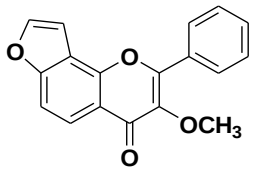
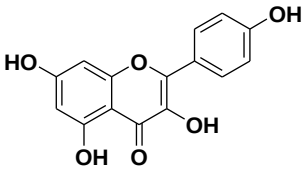
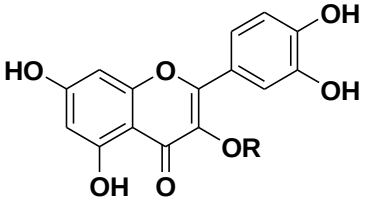
21	Pongamol[22] fruit of Pongamia pinnata (L.) Pierre (Fabaceae)	Exhibited anti-hyperglycemic activity. In streptozotocin (STZ)-induced diabetic rats, the blood glucose lowering effects of pongamol were 22% ,	 (*Z*)-3-hydroxy-1-(4-methoxybenzofuran-5-yl)-3-phenylprop-2-en-1-one
22	Karanjin[22] fruit of Pongamia pinnata (L.) Pierre (Fabaceae)	exhibited anti hyperglycemic activity. In streptozotocin (STZ)-induced diabetic rats, the blood glucose lowering effects of karanjin 20%	 3-methoxy-2-phenyl-4*H*-furo[2,3-*h*]chromen-4-one
23	Kaempferol[23] Euonymus alatus (Celastraceae)	compound 1 (5–50 mM) significantly improved insulin-stimulated glucose uptake in mature 3T3-L1 adipocytes, and they also served as weak partial agonists in a PPAR-g reporter gene assay without inducing differentiation of 3T3-L1 preadipocytes, an effect shown by traditional PPAR-g agonists	 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4*H*-chromen-4-one
24	Quercetin[23] Euonymus alatus (Celastraceae	(5–50 mM) Significantly improved insulin-stimulated glucose uptake in mature 3T3-L1 adipocytes, and they also served as weak partial agonists in a PPAR-g reporter gene assay without inducing differentiation of 3T3-L1 preadipocytes, an	 1-R = H,Quercetin 2-Quercetin-3-O-Glucoside, R= Glucose 3-Quercetin-O-Galectoside, R= Galectoside

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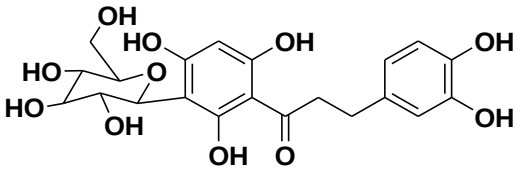
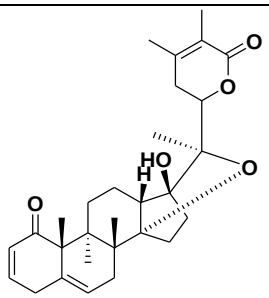
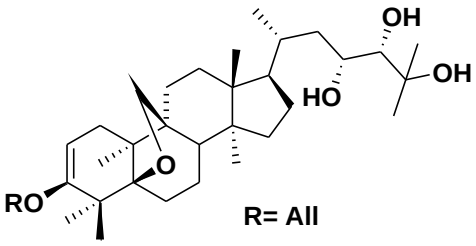
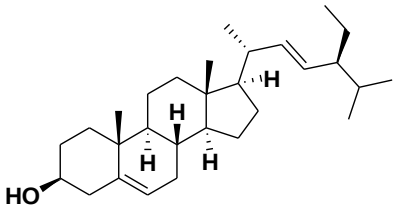
		effect shown by traditional PPAR-g agonists	
25	Aspalathin[24] (FabaceaeAspalathus linearis),	Increase glucose uptake by L6 myotubes at 1–100 mM concentrations in a dose-dependent manner, and to increase insulin secretion from cultured RIN-5F cells at 100 mM	 **2',3,4,4',6'-pentahydroxy-3-C-ß-D-glucopyranosyldihydrochalcone**
26	Coagulin C[25] aqueous extract of Withania coagulans Dunal (Solanaceae)	Inhibited post-diet glucose rise	 **(17a,20R,22R)-17-Hydroxy-14,20:22,26-diepoxyergosta-2,5,24-triene-1,26-dione**
27	Karaviloside[26]XI bitter melon (Momordica charantia)	Stimulated glucose transporter 4 (GLUT4) translocation to the cell membrane, which was associated with increased activity of AMPK	 **R= All**
28	Stigmasterol[27] bark of Butea monosperma (Lam.) Kuntze (Fabaceae)	Reduced serum triiodothyronine(T3),thyroxin (T4) and glucose concentrations were found as well as decreased activity of hepatic G-6-Pase and increased insulinlevels, indicating that it exhibits both thyroid-inhibiting and hypoglycemic properties	 (3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-17-((*E*,2*R*,5*S*)-5-isopropylhept-3-en-2-yl)-10,13-dimethyl-1*H*-cyclopenta[*a*]phenanthren-3-ol

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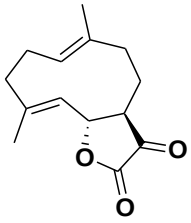
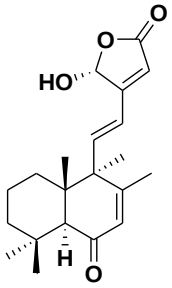
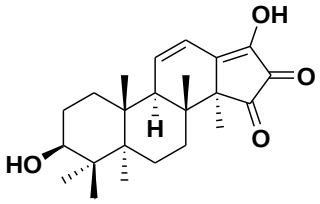
29	Costunolide[28] Roots of Costus Speciosus	Decreased glycosylated hemoglobin (HbA1c), serum total cholesterol, LDL cholesterol,and triglyceride levels were seen as well as increased plasma insulin, tissue glycogen, HDL cholesterol, and serum protein	 (3a*R*,6*E*,10*E*,11a*R*)-4,5,8,9-tetrahydro-6,10-dimethylcyclodeca[*b*]furan-2,3(3a*H*,11a*H*)-dione
30	Spicatanol[29] Hedychium spicatum Ham. Ex Smith (Zingiberaceae)	Intestinal a-glucosidase inhibitory activities IC50 of 34.1 µM.	 (*R*)-4-((1*E*)-2-((4a*S*,5*S*,8a*S*)-1,2,3,4,4a,5,8,8a-octahydro-1,1,4a,5,6-pentamethyl-8-oxonaphthalen-5-yl)vinyl)-5-hydroxyfuran-2(5*H*)-one
31	Palbinone[30] Paeonia suffruticosa Andrew (Paeoniaceae)	Exhibited the most potent activity by increasing the levels of phospho-AMPK, phospho-ACC, and phospho-GSK-3b in a dose-dependent manner, and triggering glucose uptake and glycogen synthesis in insulin-resistant human HepG2 cells	 (3*S*,5*R*,8*R*,9*R*,10*R*,14*S*)-1,3,4,5,6,7,8,10-octahydro-3,17-dihydroxy-4,4,5,8,10,14-hexamethyl-2*H*-cyclopenta[*a*]phenanthrene-15,16(9*H*,14*H*)-dione

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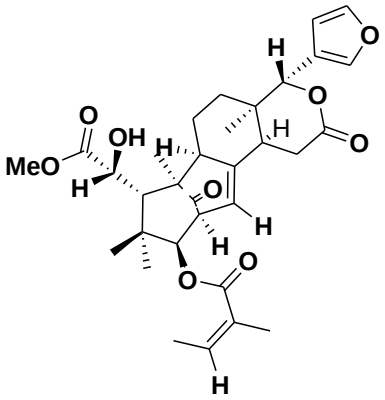
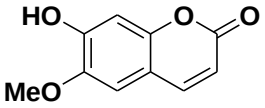
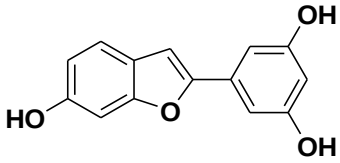
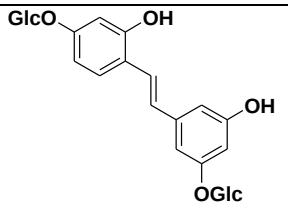
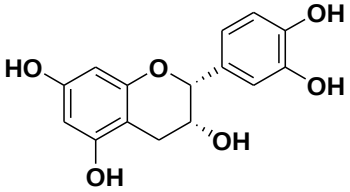
32	Swietenine[31] seeds of Swietenia macrophylla King. (Meliaceae)	Exhibited significant hypoglycemic activity comparable to that of human insulin in an in vitro glucose utilization assay	
33	Scopoletin (7-hydroxy-6-methoxycoumarin) [32] leaves of Aegle marmelos Linn. Corr (Rutaceae).	Inlevo-thyroxine-treated animals, decreased levels of serum thyroid hormones, glucose, and hepatic G-6-Pase were seen in the scopoletin-administrated group	 7-hydroxy-6-methoxy-2*H*-chromen-2-one
34	Moracin M[33] root bark of Morus alba L. (Moraceae),	Moracin M(100 mg /kg, p.o.) decreased the fasting blood glucose level	 5-(6-hydroxybenzofuran-2-yl)benzene-1,3-diol
35	Mullberroside A[33] root bark of Morus alba L. (Moraceae),	Hypoglycemic effects in alloxan-induced diabetic mice	 **(2S,3R,4S,5S,6R)-2-[3-hydroxy-4-[(E)-2-[3-hydroxy-5-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyphenyl]ethenyl]phenoxy]-6-(hydroxymethyl)oxane-3,4,5-triol**
36	Epicatechin[34] (Green tea)	Preventing T1D BY modulating immune function and thereby preserving islet mass	 (2*R*,3*R*)-3,4-dihydro-2-(3,4-dihydroxyphenyl)-2*H*-chromene-3,5,7-triol

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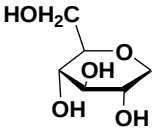
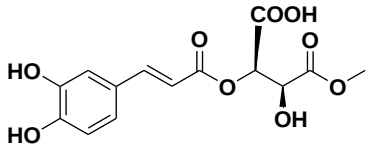
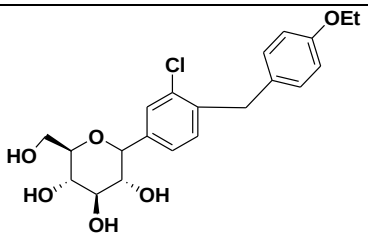
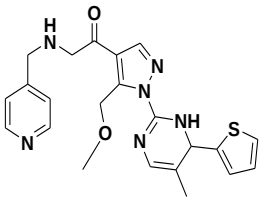
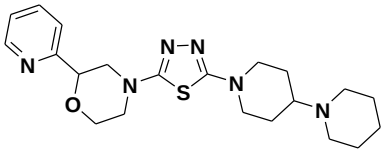
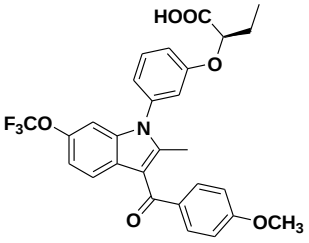
37	1,5 anhydro-D-glucitol[35] (nearly all food)	Potent and selective renal sodium-glucose cotransporter 2 (SGLT2) inhibitor with**anti-**hyperglycemic activity	 (3*S*,4*S*,5*R*)-tetrahydro-2-(hydroxymethyl)-2*H*-pyran-3,4,5-triol
38	Caftaric acid[36] (Corni Fructus)	Hypoglycemic and Beta-Cell Protective	 (2*R*,3*S*)-2-((*E*)-3-(3,4-dihydroxyphenyl)acryloyloxy)-3-(methoxycarbonyl)-3-hydroxypropanoic acid
39	Dapagliflozin[37]	Selective Renal Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitor for the Treatment of Type 2 Diabetes	 (3*R*,4*R*,5*S*,6*R*)-2-(4-(4-ethoxybenzyl)-3-chlorophenyl)-tetrahydro-6-(hydroxymethyl)-2*H*-pyran-3,4,5-triol
40	GPR-142[38]	EC50-1.5µM F=3.9% in cynomolgus monkey	 **2-((pyridin-4-yl)methylamino)-1-(1-(1,6-dihydro-5-methyl-6-(thiophen-2-yl)pyrimidin-2-yl)-5-(methoxymethyl)-1*H*-pyrazol-4-yl)ethanone**
41	4-(5-(4-(piperidin-1-yl)piperidin-1-yl)-1,3,4-thiadiazol-2-yl)-2-(pyridin-2-yl)morpholine[39]	Histamine H_3 receptor antagonist	 **4-(5-(4-(piperidin-1-yl)piperidin-1-yl)-1,3,4-thiadiazol-2-yl)-2-(pyridin-2-yl)morpholine**
42	(2*R*)-2-(3-{3 [(4Methoxyphenyl)carbonyl]-2-methyl-6(trifluoromethoxy)-1*H*-indol-1-yl}phenoxy)butanoic Acid[40]	Peroxisome Proliferator-Activated Receptor γ Modulator for the Treatment of Type 2 Diabetes Mellitus with a Reduced Potential to Increase Plasma and Extracellular Fluid Volume	 **(2R)-2-(3-{3 [(4Methoxyphenyl)carbonyl]-2-methyl-6(trifluoromethoxy)-1H-indol-1-yl}phenoxy)butanoic Acid**

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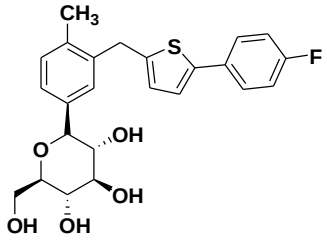
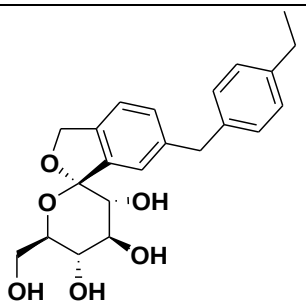
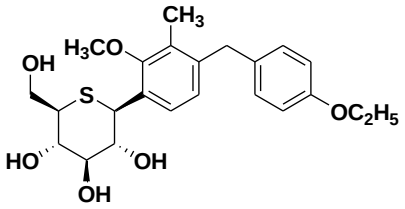
43	Canagliflozin[41]	Highly potent and selective SGLT2 inhibitor and showed pronounced anti-hyperglycemic effects in high-fat diet fed KK (HF-KK) mice	 (2*R*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-tetrahydro-6-(hydroxymethyl)-2*H*-pyran-3,4,5-triol
44	Tofogliflozin[42]	Highly Selective Sodium Glucose Cotransporter 2 (SGLT2) Inhibitor for the Treatment of Type 2 Diabetes IC_{50}(hSGLT2):2.9 nM IC_{50}(hSGLT1): 8,444 nM Selectivity : (hSGLT1)/ (hSGLT2)=2,912 fold F(%)(mice)=75% (monkey) 85%	 (1S,3'R,4'S,5'S,6'R)-6-(4-Ethylbenzyl)-6'-(hydroxymethyl)-3',4',5',6'-tetrahydro-3H-spiro[2-benzofuran-1,2'-pyran]-3',4',5'-triol hydrate (1:1)
45	(2S,3R,4R,5S,6R)-2-(4-(4-ethoxybenzyl)-2-methoxy-3-methylphenyl)-tetrahydro-6-(hydroxymethyl)-2H-thiopyran-3,4,5-triol[43]	Potent, Selective Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitor for Type2 Diabetes Treatment IC50:2.26Nm (hSGLT2) IC50:3990Nm(hSGLT1)	 (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-(4-ethoxybenzyl)-2-methoxy-3-methylphenyl)-tetrahydro-6-(hydroxymethyl)-2*H*-thiopyran-3,4,5-triol

CONCLUSION

In this review we discussed about some recent discoveries of pure anti-diabetes compound and their structure and biological activities.in this review we discussed some natural and synthetic compound which differ from anti-diabetes drug in structure and mechanism of action. Which may be helpful in designing and synthesis of new drugs.

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