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TYPE 2 DIABETES MELLITUS AND MULTI-TARGET TREATMENT OPTIONS

Piyush Chahal* and Garima Gupta

*Research scholar, School of Pharmacy, Monad University, N.H. 9, Delhi Hapur Road, Village & Post Kastla, Kasmabad, Pilkhuwa - 245304, Hapur (U.P), India

Abstract: Diabetes mellitus is a collection of physiological dysfunctions defined by hyperglycemia caused by insulin resistance, insufficient insulin production, or excessive glucagon secretion. Type 2 diabetes, which is far more frequent, is largely an issue of gradually poor glucose regulation caused by a combination of dysfunctional pancreatic beta cells and insulin resistance. The goal of this article is to review the basic science of type 2 diabetes and its complications, as well as to discuss the most recent treatment options.

Index Terms **- Diabetes, Type 2 diabetes, recent treatment options**

1 DIABETES

Diabetes is a chronic condition managed to bring on by either insufficient insulin production by the pancreas or inefficient insulin utilization by the body. A hormone called insulin controls blood sugar. Uncontrolled diabetes frequently results in hyperglycemia, or elevated blood sugar, which over time causes substantial harm to many different bodily systems, including the neurons and blood vessels. 8.5% of persons who were 18 years of age and older had diabetes in 2014. A total of 1.5 million deaths were directly related to diabetes in 2019, and 48% of these deaths occurred in those under the age of 70.

1.1 TYPE 2 DIABETES

It is a chronic medical condition known as type 2 diabetes that causes blood sugar, or glucose levels, to rise. Normally, the hormone insulin aids in the transfer of glucose from the blood to the cells, where it is used as fuel. However, type 2 diabetes impairs the body's cells' ability to respond to insulin as well as it should. Later stages of the ailment may also result in inadequate insulin production by the body. Chronically high blood glucose levels brought on by uncontrolled type 2 diabetes may produce several symptoms as well as potentially life-threatening consequences.

1.2 SYMPTOMS OF TYPE 2 DIABETES

At first, the symptoms may be slight and simple to ignore. Early warning signs could include a lack of energy, exhaustion, increased thirst, frequent urination, impaired vision, numbness, tingling, or discomfort in feet or hands. The issues that can occur if your blood glucose levels have been elevated for a long time include eye issues (diabetic retinopathy), feelings of neuropathy, or numbness in extremities, renal disease (nephropathy), gum disease, cardiac arrest, or stroke.

Diabetes-related premature mortality rates occurring before the age of 70 rose by 5% between 2000 and 2016. From 2000 to 2010, the premature death rate in high-income countries fell, but from 2010 to 2016, it rose. Both times, the premature mortality rate from diabetes increased in lower-middle-income countries. In contrast, between 2000 and 2016, there was an 18% global decline in the likelihood of dying between the ages of 30 and 70 from any of the four major non-communicable diseases (cancer, chronic respiratory diseases, diabetes, or cardiovascular disorders).

1.3 PATHOPHYSIOLOGY

Type 2 diabetes is distinguished by insulin insensitivity caused by insulin resistance, decreased insulin production, and eventual pancreatic beta-cell failure. This reduces glucose transit into the liver, muscle cells, and fat cells. Hyperglycemia causes an increase in fat breakdown. The impaired alpha-cell function has recently been linked to the development of type 2 diabetes. As a result of this failure, fasting-induced increases in glucagon and hepatic glucose are not controlled by a meal. Hyperglycemia occurs as a result of insufficient insulin levels and increasing insulin resistance. Incretins are key mediators of insulin release and, in the case of GLP-1, glucagon suppression in the stomach. Although GIP activity is reduced in people with type 2 diabetes, GLP-1 insulinotropic effects are maintained, making GLP-1 a potentially helpful therapeutic approach. GLP-1, like GIP, is rapidly inactivated in vivo by DPP-IV. GLP-1 analogs with increased half-lives and DPP-IV inhibitors, which block the breakdown of endogenous GLP-1 and GIP, have been developed as treatments for this condition. Both kinds of drugs have shown promise in terms of not only normalizing fasting and postprandial glucose levels but also improving beta-cell activity and mass. The role of mitochondrial dysfunction in the development of insulin resistance and the pathogenesis of type 2 diabetes is being studied. Adipose tissue is also very significant, as the endocrine organ hypothesis suggests (secretion of various adipocytokines, i.e., leptin, TNF-alpha, resistin, and adiponectin implicated in insulin resistance and possibly beta-cell dysfunction). The majority of those suffering from type 2 diabetes are obese, with central visceral adiposity. As a result, adipose tissue is critical in the genesis of type 2 diabetes. Although the portal/visceral hypothesis plays a crucial role in high non-esterified fatty acid concentrations, two additional

developing ideas are the ectopic fat storage syndrome and (the deposition of triglycerides in muscle, liver, and pancreatic cells). These two theories form the foundation for future research into the relationship between insulin resistance and beta-cell dysfunction in type 2 diabetes, as well as the relationship between our obesogenic environment and DM risk (Fujioka K., 2007).

1.4 COMPLICATIONS

1.4.1 Stroke and Heart Disease: Cardiovascular disease accounts for up to 65% of all deaths among diabetics. Ischemic heart disease and stroke account for the biggest share of diabetic morbidity. Furthermore, as previously noted, diabetes patients have a 2 to 4 times higher risk of dying from cardiac disease than non-diabetics. Diabetes patients are also two to four times more likely to have a stroke than non-diabetics. More than 70% of persons with diabetes have high blood pressure or are using hypertension drugs. The relevance of hyperglycemia in diabetes-related cardiovascular problems remains unclear (Stamler J. et al., 1993).

1.4.2 Peripheral Vascular Disease: The narrowing of blood vessels that supply blood to the arms, legs, stomach, and kidneys causes peripheral arterial disease, also known as peripheral vascular disease. Diabetes increases the risk of peripheral vascular disease by age, duration of diabetes, and the existence of neuropathy. Additional cardiovascular disease risks variables, such as C-reactive protein and homocysteine levels, are also linked to an increased risk of peripheral vascular disease (King KD. et al., 2005).

1.4.3 Retinopathy: Diabetic retinopathy is the most common microvascular complication among people with diabetes and results in more than 10,000 new cases of blindness per year. In addition, retinopathy is associated with prolonged hyperglycemia, it is slow to develop (Harris R., and Leininger L., 1993).

1.4.4 Nephropathy: The cause of diabetic nephropathy is unknown. There are several risk factors involved, some of which are changeable and others that are not. One of the primary modifiable risk factors for the development of diabetic nephropathy is metabolic control. Strict metabolic management reduces the chance of developing microalbuminuria and the risk of development to persistent proteinuria in persons with type 1 or type 2 diabetes (Deshpande AD. et al.,2008).

1.5 Management of type 2 diabetes

Rather than dietary and lifestyle changes. There was a significant reduction in the incidence of type 2 diabetes with a combination of maintaining a body mass index of 25 kg/m2, eating high fiber and unsaturated fat and a diet low in saturated and trans-fats and glycemic index, regular exercise, avoiding smoking and drinking moderately. It is suggested that lifestyle changes can avoid the majority of type 2 diabetes. Individuals with type 2 diabetes should have a medical nutrition examination, and lifestyle recommendations should be individualized based on physical and functional abilities.

1.6 AGENTS FOR TYPE 2 DIABETES

1.6.1 Oral hypoglycemic agents: Oral hypoglycemic agents are a group of drugs used to help reduce the amount of sugar present in the blood. They are not insulin, but they stimulate the pancreas to produce insulin. Oral hypoglycemic agents are usually used in the treatment of adult-onset diabetes (also known as Type 2 or non-insulin-dependent diabetes mellitus).

1.6.1.1 Biguanides: Metformin, the most commonly used biguanide in overweight and obese patients, inhibits hepatic glucose synthesis, increases insulin sensitivity, accelerates glucose uptake by phosphorylating GLUT-enhancer factor, promotes fatty acid oxidation, and decreases gastrointestinal glucose absorption.

1.6.1.2 Sulfonylureas: Sulphonylureas are a group of oral drugs that lower blood sugar levels in people with type 2 diabetes by stimulating the pancreas to produce more insulin and improving the body's ability to utilize that insulin by blocking ATP-sensitive potassium channels at the pancreatic beta-cell membrane, sulfonylureas increase insulin production without dependence on glucose (Pearson et al., 2000). They can be administered alone or in conjunction with other diabetic medications. They are typically taken once or twice a day, with or right before a meal.

1.6.1.3 Meglitinides: Meglitinides are short-acting secretagogues like sulfonylureas, although not structurally related. Their mode of action differs from sulfonylureas in that they cause the pancreas to secrete insulin. The meglitinides bind to an ATP-dependent K+ channel on beta-cell membranes (similar but not identical to that occupied by sulphonylurea); the resulting depolarization of pancreatic beta cells causes Ca++ influx and increased insulin secretion (Holstein & Egberts, 2013).

1.6.1.4 Thiazolidinediones: Thiazolidinediones are agents that raise insulin sensitivity in vital parts by acting on intracellular metabolic pathways to improve insulin action. Additionally, thiazolidinediones raise levels of adiponectin, lower hepatic gluconeogenesis, and boost insulin-dependent glucose absorption in both muscle and fat.

1.6.1.5 Dipeptidyl peptidase 4 (DPP-4) inhibitors: DPP-4 inhibitors lower blood sugar by helping the body increase the level of the hormone insulin after meals (fda.gov).

1.6.1.7 Glucagon-like peptide-1 agonists: These slow digestion and improve blood glucose levels.

1.6.1.8 Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors: These help your kidneys remove sugar in your body through urine.

1.6.1.9 Bromocriptine was developed (Quick-release) for the treatment of type 2 diabetes. Unfortunately, the mechanism of action is unclear. According to studies, they reduce mean HbA1c levels by 0.0% to 0.2% after 24 weeks of treatments (Mikhail N., 2011).

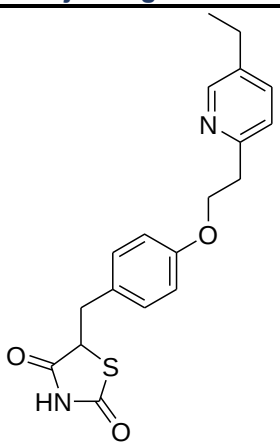
1.7 PHYTOCONSTITUENTS AS ANTIDIABETIC AGENTS

Certain herbs may lower blood glucose; however, their test results are subject to several factors. Firstly, each herb contains thousands of components, only a few of which may be therapeutically effective. Secondly, different parts of an herb have different ingredient profiles. Moreover, different extraction methods may yield different active ingredients. Thirdly, herbal formulae containing multiple herbs may have synergistic effects. Phytoconstituents from plants and herbs showed good results in the management of Type 2 diabetes see table no. 2.

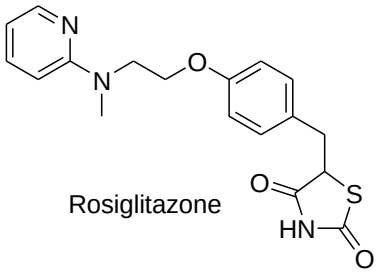
Table 1 Agents used to treat/manage type 2 diabetes

Drugs	Dose	No. of Dose/Day	Reference
Sulfonylureas			
Glimepiride	1-8 mg	1	drugs.com
Glibenclamide	5-15 mg	2	medicalguidelines.msf.org
Gliclazide	40-320 mg	1	healthnavigator.org
Acetohexamide	250-1500 mg	1-2	medindia.net
Chlorpropamide	100-250 mg	1	drugbank.com
Tolbutamide	1-2 g	1	drugbank.com
Meglitinides			
Repaglinide	0.5-2 mg 16 mg	with each meal Per day	drugbank.com
Nateglinide	60-120 mg	3-4	drugbank.com
Mitiglinide	5-20 mg	3	Phillippe HM and Wargo KA 2010
Thiazolidinediones			
Pioglitazone	15-30 mg	3	medscape.com
Rosiglitazone	4-8 mg	1	drugs.com
Troglitazone	Removed from the us market 3/21/00		rxlist.com
Ciglitazone	It is considered the prototypical compound for the thiazolidinedione class. Ciglitazone was never used as a medication, but it sparked interest in the effects of		drugbank.com
Dipeptidyl peptidase 4 (DPP-4) inhibitors			
Sitagliptin	100 mg	3	medscape.com
Vildagliptin	100 mg	2	ema.europa.eu
Saxagliptin	2.5-5 mg	3	medscape.com
Linagliptin	5 mg	1	drugs.com
Alogliptin	25 mg	1	drugs.com
Biguanides			
Buformin	It was withdrawn from the market in most countries due to a high risk of causing lactic acidosis.		drugs.com
Phenformin	it is generally considered to be associated with an unacceptably high incidence of lactic acidosis, often fatal, it is still available in some countries.		drugs.com
Metformin	**Immediate-release** 500 mg 850 mg **Extended-release** 500 to 1000 mg 500 mg increments weekly as tolerated Maximum dose: 2000 mg	 2 1 1 1	drugs.com
Glycosidase inhibitors			
Acarbose	25mg 50mg, 100mg	1 1	drugs.com
SGLT2 inhibitors			
Canagliflozin	100-300 mg	1	drugs.com
Dapagliflozin	5-10 mg	1	drugs.com
Empagliflozin	10-25 mg	1	drugs.com
Ertugliflozin	5-15 mg	1	drugs.com
GLP-1 receptor agonists			
Dulaglutide	0.75-4.5 mg	Subcutaneously once a week	drugs.com
Exenatide	5-10 mcg	Twice a day within the 60-minute period before the morning and evening meals	drugs.com

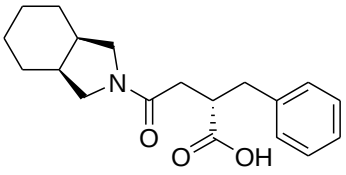
Figure 1 chemical structure of agents used to treat/manage type 2 diabetes

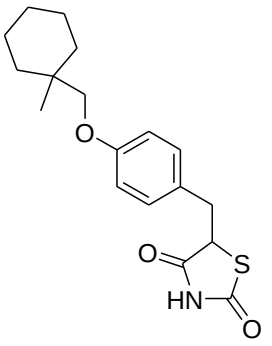


Pioglitazone

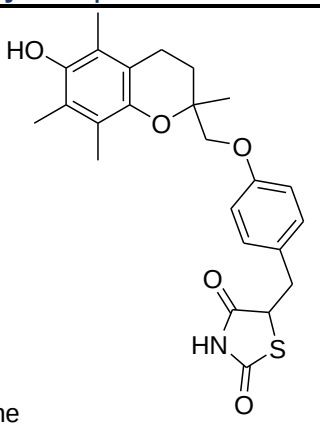


Rosiglitazone

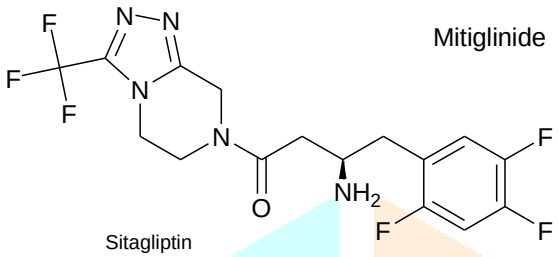




Ciglitazone

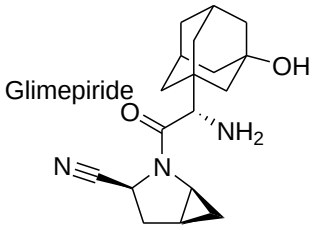


Troglitazone



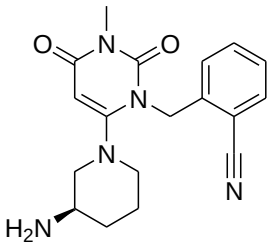
Sitagliptin

Mitiglinide

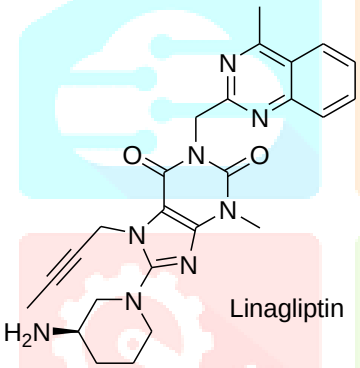


saxagliptin

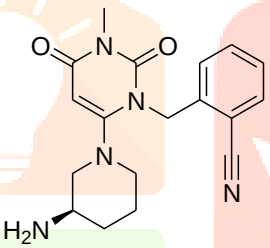
Glimepiride



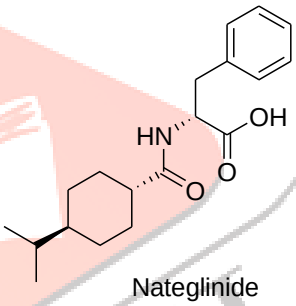
alogliptin



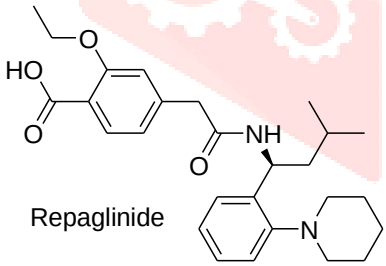
Linagliptin



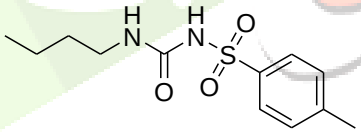
Alogliptin



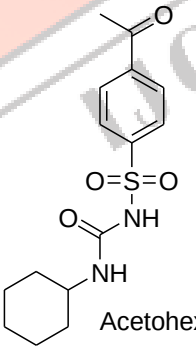
Nateglinide



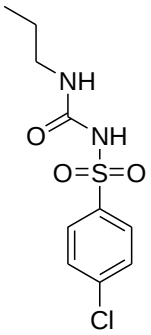
Repaglinide



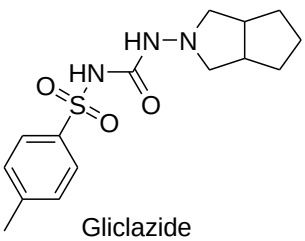
Tolbutamide



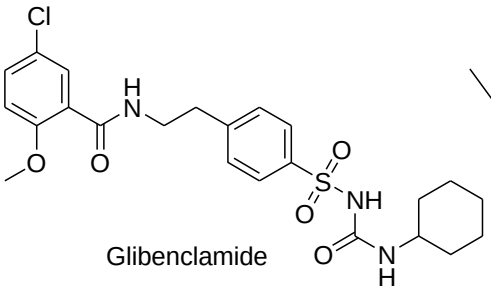
Acetohexamide



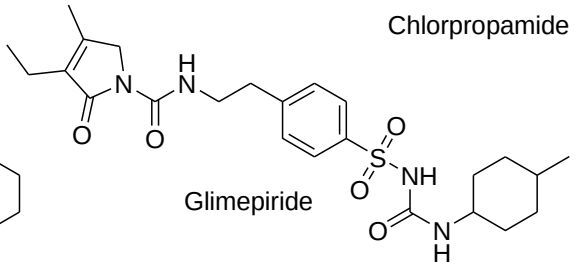
Chlorpropamide



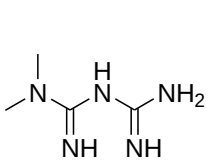
Gliclazide

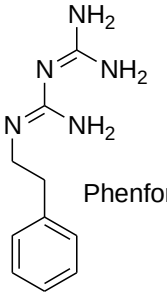


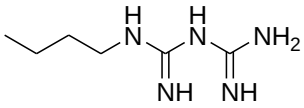
Glibenclamide

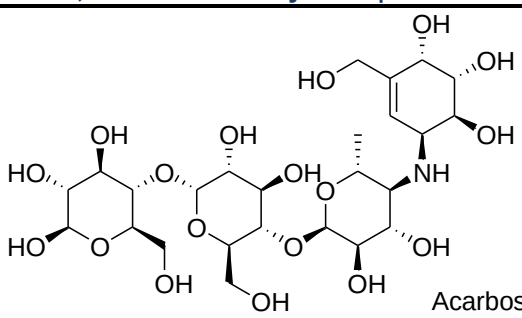


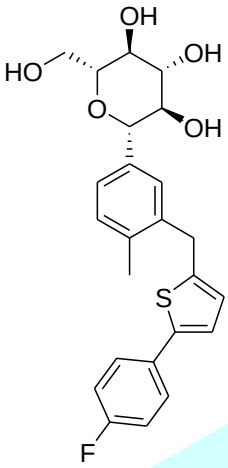
Glimepiride

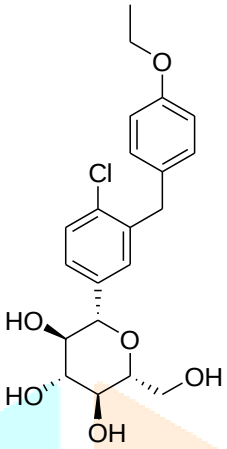

Metformin

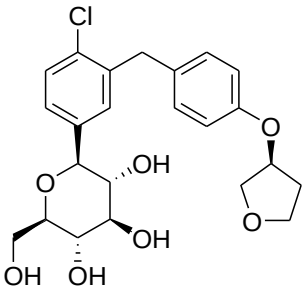

Phenformin


Buformin


Acarbose


Canagliflozin


Dapagliflozin


Empagliflozin

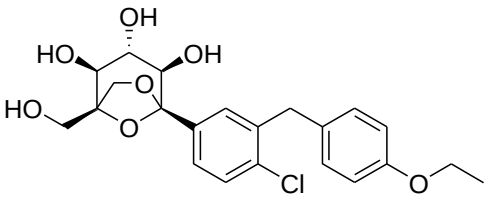

Ertugliflozin

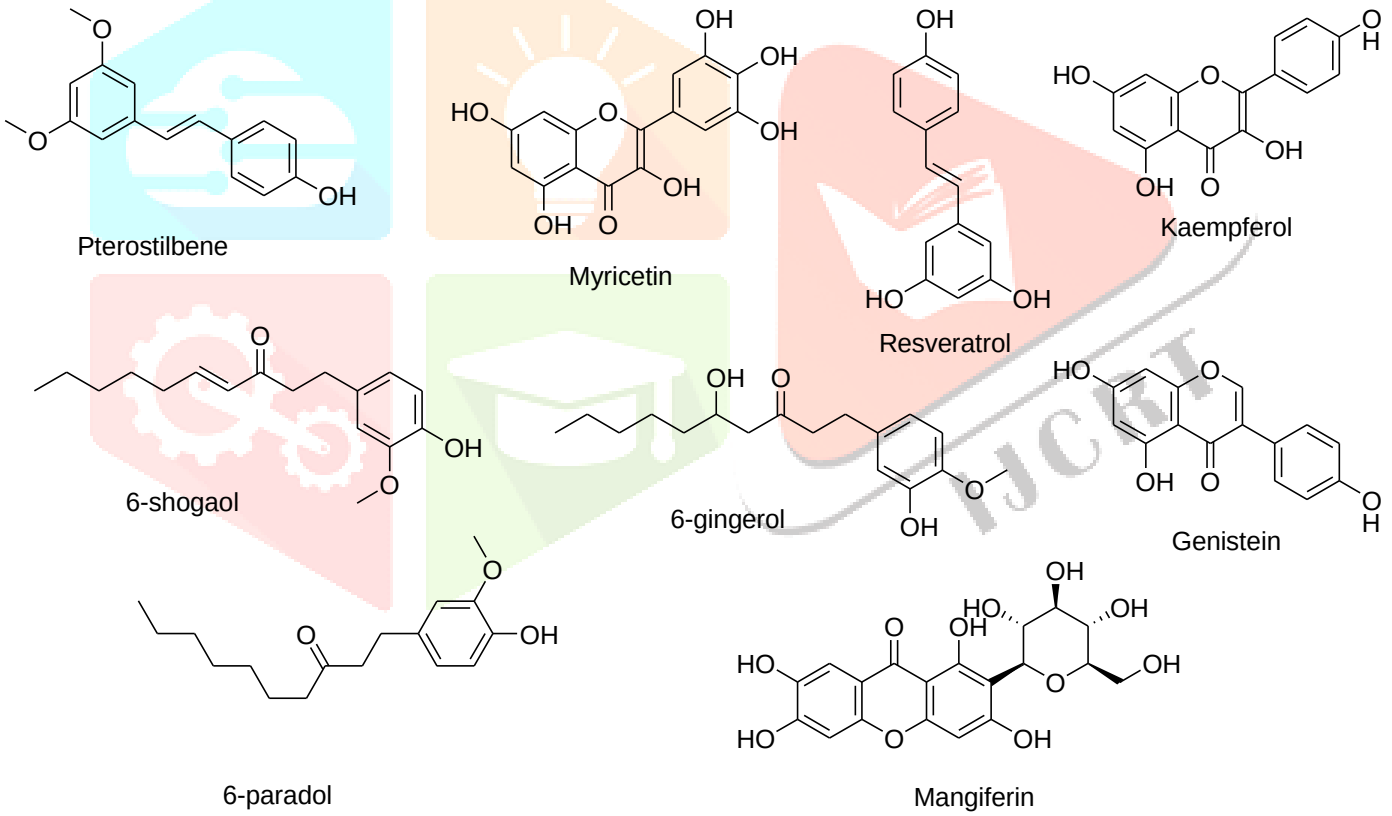
Table 2 Antidiabetic potential of phytochemicals (phenolic/ flavonoid) from medicinal plants and their mechanism of action.

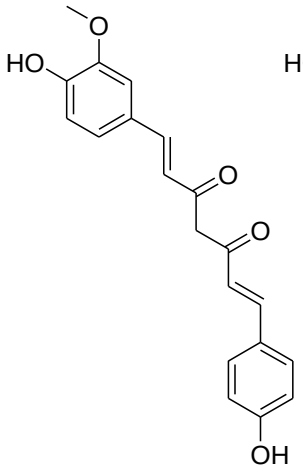
Phytochemicals	Plant source	Mechanism of action	Reference
Kaempferol	*Anethum graveolens*	Prevents the pathological progress of obesity-insulin resistance-β Cells apoptosis-diabetes. IR, insulin resistance	Yang Yan et al., 2022
Genistein	Lupinus	Enhance β-cell proliferation and reduce apoptosis	Gilbert ER. et al., 2013
Mangiferin	*Mangifera indica*	Suppresses the activation of peroxisome proliferator-activated receptor	Imran M. et al., 2017
Piceatannol	*Callistemon rigidus*	Suppression in the activity of α- amylase.	Kobayashi K. et al., 2006
Scirpusin B	*Callistemon rigidus*	Regulation of α-amylase in mouse GIT. Suppression in the activity of α- amylase.	Kobayashi K. et al., 2006
Chamaemeloside	*Chamaemelum nobile*	Potential suppression in the production of hepatic glucose, as such, reduced gluconeogenesis. Potential effects on intestinal absorption, hepatic or peripheral disposal of glucose as well	König GM. Et al., 1998
Pyrogallol	*Cinnamomum verum* J. Presl	Renovation of beta cells	Singh N. et al., 2021
Bisdemethoxycurcumin, Curcumin, Demethoxycurcumin	*Curcuma longa*	Inhibition of α-glucosidase activity	Lekshmi PC. et al., 2012
Acacetin	*Lobelia chinensis* Lour.	Promotion of secretion of insulin, improvement of insulin resistance, and stimulation of the utilization of glucose by acting on GSK3B, MAPK, INR, and dipeptidyl peptidase-4 (DPP4)	Ge Q. et al., 2020
Coumarins	*Aegle marmelos* Correa	Stimulation of insulin secretion from beta cells of the isles of Langerhans	Ruhil S. et al., 2011
Quercetin	*Matricaria chamomilla* L.	Quercetin moderately inhibited the enzymatic activity of sucrase	Kato A. et al., 2011
		Halted sorbitol from accumulating in erythrocytes	

	Moringa oleifera Lam.	Aiding the restoration of the normal histological structure of the pancreas	Muhammad HI. et al., 2016
		Blocking the transport of fructose and glucose by GLUT2 in the brain and promoting the translocation and expression of GLUT4 in skeletal muscle	Villarruel-López A. et al., 2018
	Vitis vinifera	Improvement of the expression of adiponectin in white adipose tissue and blood concentration, despite an inhibition of poly (ADP-ribose) polymerase γ expression followed by improved insulin sensitivity. Inhibition of glucose uptake at glucose transporters level	Wein S. et al., 2010, and Aguirre L. et al., 2011
Luteolin	*Matricaria chamomilla* L.	Halted sorbitol from accumulating in erythrocytes	Kato A. et al., 2011
Esculetin, Umbelliferone	*Matricaria chamomilla* L.	Esculetin showed moderate inhibition in the enzymatic activity of sucrase	Kato A. et al., 2011
		Esculetin and umbelliferone halted sorbitol from accumulating in erythrocytes	
Isoquercitrin, Astragalin	*Morus alba* L.	Inhibition α-glucosidase activity	Tian S. et al., 2016
Valoneic acid dilactone	*Punica granatum* L.	Inhibition of the activity of aldose reductase and protein tyrosine phosphatase 1B (PTP1B). Improvement in insulin secretion from pancreatic β cells or its release from the bound form along with insulin-mimetic actions or amended glucose utilization technique	Jain V. et al., 2012
Karanjin	*Pongamia pinnata* (L.) Pierre	Inhibition of PTPase-1B	Tamrakar AK. et al., 2008
Pongamol	*Pongamia pinnata* (L.) Pierre	Inhibition of PTPase-1B	Tamrakar AK. et al., 2008
Silychristin A	*Silybum marianum* (L.) Gaertn	Improvement of the function of β-cells along with glucose-lowering effect by protecting the β-cells from oxidative stress-induced damage and blocking the activity of α-glucosidase enzyme	Qin N. et al., 2017
Mangiferin	*Swertia chirayita* Buch Ham.	Exhibition of glucosidase and 2,2-diphenyl-1-picrylhydrazyl radical inhibitory action	Sekar V. et al., 2020
Pterostilbene	*Vitis vinifera* L.	Promising inhibitory efficacy on both normal and mutant models of the kir6.2 channel which is encoded by the KCNJ11 gene, whose mutation causes congenital hyperinsulinism	Nassiri-Asl M. et al., 2009
Myricetin	*Vitis vinifera* L.	Promotion of glucose uptake in liver and soleus muscles as well as hepatic glycogen synthase, halting advanced glycation end products in diabetic condition	Pandey KB. et al., 2014
		Improvement of insulin resistance	Ong KC. et al., 2000
		Human pancreatic alpha-amylase inhibition	Liu I-M. et al., 2007
Resveratrol	*Vitis vinifera* L.	Stimulation of the transportation activity of intracellular glucose and promotion of glucose uptake	Pandey KB. et al., 2013
		Improvement in the expression of insulin-dependent glucose transporter (GLUT4)	Chi T-C. et al., 2007 and Penumathsa SV. et al., 2008
		Modulation of the function of sirtuin-1, which ameliorates homeostasis of whole-body glucose and insulin sensitivity	Penumathsa SV. et al., 2008
6-shogaol	*Zingiber officinale* Roscoe	Suppression of the development of diabetic complicacies and advanced glycation end products (AGEs) by arresting methylglyoxal, the precursor of	Zhu Y. et al., 2015 and

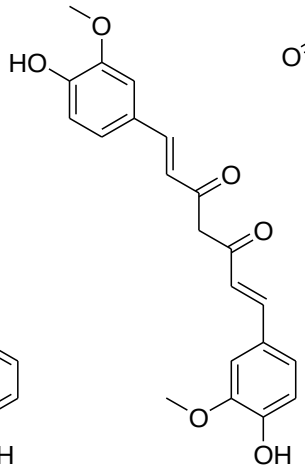
		AGEs, arrest of Nϵ-carboxymethyl-lysine (CML), a marker of AGEs through activation of Nrf2.	Sampath C. et al., 2017
		Facilitation of glucose consumption by increasing AMPK phosphorylation in 3T3-L1 adipocytes and C2C12 myotubes	Wei C-K. et al., 2017
6-gingerol	*Zingiber officinale* Roscoe	Aided glucose-stimulated insulin secretion and improved glucose tolerance by upraising glucagon-like peptide 1 (GLP-1). 6-gingerol also galvanized glycogen synthase 1 and increased glucose transporter type 4 (GLUT4) cell membrane presentations which amplified skeletal muscles' glycogen storage	Samad MB. et al., 2017
		Suppressing the development of diabetic complications and advanced glycation end products (AGEs) by arresting methylglyoxal, the precursor of AGEs, arrest of Nϵ-carboxymethyl-lysine (CML), a marker of AGEs through activation of Nrf2.	Zhu Y. et al., 2015 and Sampath C. et al., 2017
6-paradol	*Zingiber officinale* Roscoe	Facilitation of glucose consumption by increasing AMPK phosphorylation in 3T3-L1 adipocytes and C2C12 myotubes	Wei C-K. et al., 2017

Figure 2 chemical structure of Phytoconstituents for the treatment/manage type 2 diabetes

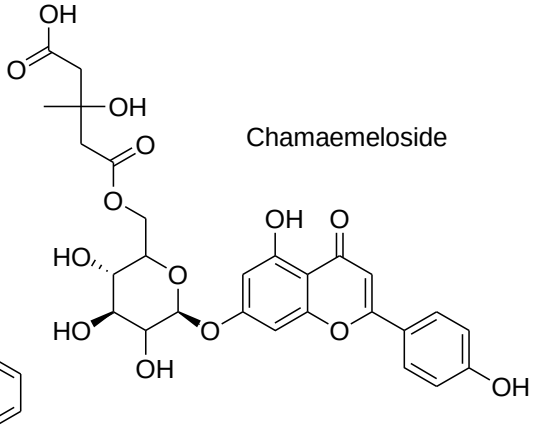




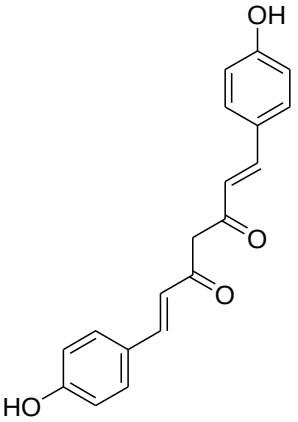
Demethoxycurcumin



Curcumin



Chamaemeloside



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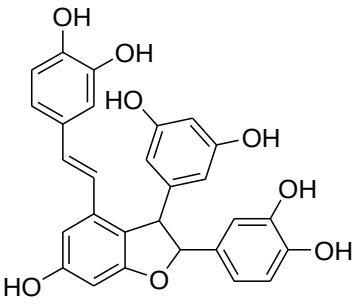
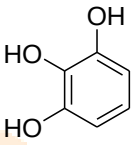
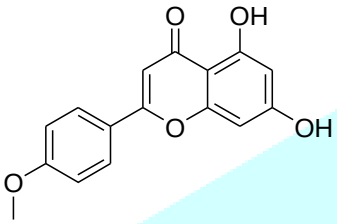


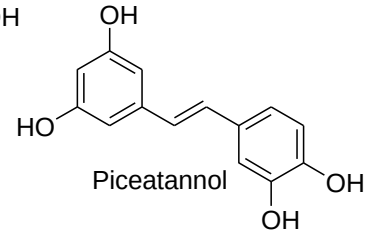
Scirpusin B



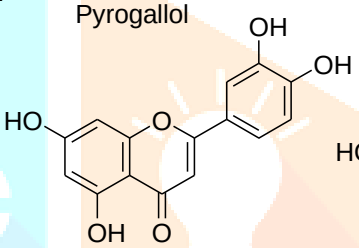
Pyrogallol



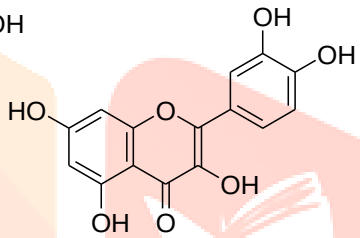
Acacetin



Piceatannol



Luteolin



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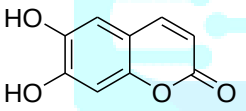
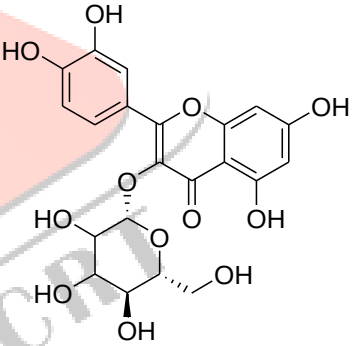
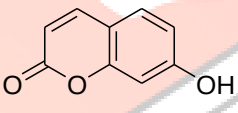


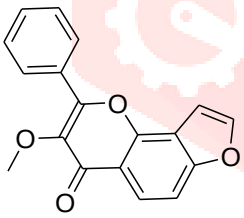
Esculetin



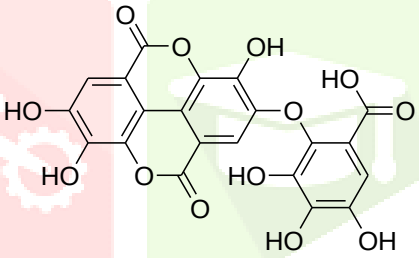
Isoquercitrin



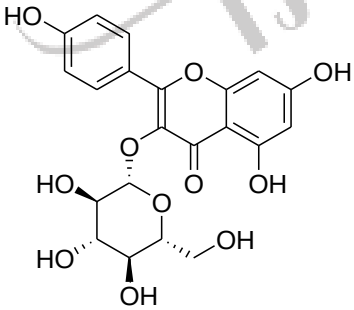
Umbelliferone



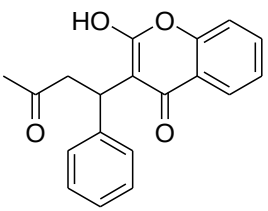
Karanjin



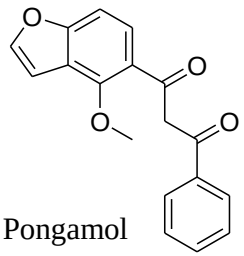
Valoneic acid dilactone



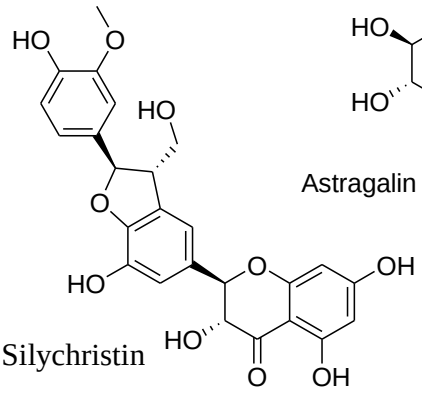
Astragalin



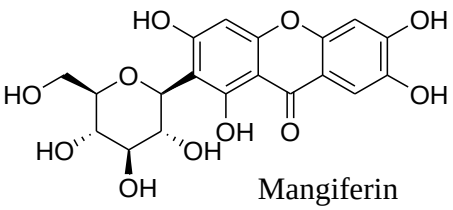
Coumarins



Pongamol



Silychristin



Mangiferin

1.8 CONCLUSION: Nowadays type 2 diabetes is a most common problem and its complications affect the lifestyle. Several treatment options are available in both synthetic and herbal origin. Both of the options are excellent for the management of diabetes. This review provides the synthetic as well as phytoconstituents involved in the multitargeted management of type 2 diabetes.

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