



## Glucagon Like Peptide 1 (GLP -1) Receptor Natural Agonist for the Treatment of Type 2 Diabetes Mellitus: A Review

Sana Khan<sup>1\*</sup>, Khan Neelam<sup>1</sup>, Sanjay Giri<sup>1</sup>, Manju Parmar<sup>1</sup>, Javed Khan Pathan<sup>2</sup>, Mansi Gehlod<sup>2</sup>

<sup>1</sup>Amaltas Institute of Pharmacy, Amaltas University, Dewas(M.P.), India

<sup>2</sup>Index Institute of Pharmacy, Malwanchal University, Indore (M.P.)

\*Corresponding Author: Sana Khan, Department of Pharmaceutical Chemistry University, Amaltas Institute of Pharmacy, India.

DOI: 10.31080/ASPS.2024.08.1053

Received: March 22, 2024

Published: March 27, 2024

© All rights are reserved by Khan Sana., et al.

### Abstract

Increase in prevalence of Diabetes Mellitus is a major public health problem. It is a progressive disorder which commonly requires multiple pharmacotherapies for managing blood glucose. Use of incretin based therapy is a potential solution for management of Type 2 DM. Glucagon-like peptide (GLP-1) is an incretin hormone which enhances serum insulin after food intake and it participates in glucose homeostasis and feeding behavior. Owing to high cost of treatment and general toxicity in long term use of GLP-1 agonist, hence there is review for GLP-1 receptor natural agonist which may enhance GLP-1 production. Recently, GLP-1 secretagogues activity of medicinal plants has been reported an increase in GLP-1 secretion by phytochemicals may help in management of T2DM with lesser side effects and low cost compared to the GLP-1 agonists of synthetic origin. Natural products have proven historically to be a promising pool of structures for drug discovery and a significant research effort has recently been undertaken to explore the GLP-1 activating potential of a wide range of natural products originating from traditionally used medicinal plants or dietary sources and they are a rich source for the discovery of novel GLP-1 activators. In this review, collection of GLP-1 activators from plant product that shows interaction with both catalytic site as well as secondary binding site of GLP-1 receptor were investigated and list of natural GLP-1 agonist was prepared which can be included in our dietary source. Thus almost 60% prevention of diabetes occur which is better than cure by synthetic drugs.

**Keywords:** Diabetes Mellitus; Secretagogues; Natural GLP-1 Agonist; Dietary Source; Prevention of Diabetes

### Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycaemia and it is also a multi factorial chronic health condition triggered by several genetic and environmental factors. Diabetes mellitus is defined as the "It is a group of metabolic diseases characterized by chronic hyperglycaemia (high blood sugar) leading to defects in insulin secretion and insulin action. It is a chronic metabolic disorder characterized by persistent of hyperglycaemia it may be due to impaired insulin secretion. Low level of an insulin achieve adequate response or resistance of target tissues, mainly in adipose tissue and low amount in liver at the level of insulin receptor, signal transduction system or effectors enzyme are respon-

sible for metabolic abnormalities. The severity of symptoms is due to type and duration of diabetes. As per the WHO, diabetes mellitus (DM) is defined as a hetero geneous metabolic disorder characterized by common cause of hyperglycaemia with disturbance of carbohydrates and protein metabolism [1].

### Type 2 diabetes mellitus

Type 2 DM comprise about 80% cases of diabetes mellitus. Type 2 diabetes mellitus is associated with a combination of resistance to insulin action and inadequate insulin secretory response. The various complications associated with diabetes mellitus include nephropathy, neuropathy, cardiovascular and renal complications

or food related disorders and so on. Also type 2 DM resulting hinder the individual's ability to use insulin [2].

### Glucagon-like peptide 1

A hyperglycaemic principle was demonstrated to be present in the pancreatic islets just two years after the discovery of insulin in 1921. It was named 'GLUCAGON' it is a single chain polypeptide containing 29 amino acids and it is secreted by alpha-cells of the islets of langerhans and commercially by recombinant DNA technology. Glucagon- Like peptide-1 (GLP-1) is an endogenous incretin and plays a significant role in glucose homeostasis. GLP-1 is a 30 amino acid containing peptide secreted from intestinal l-cells in response to food intake and it is liberated from pro-glucagon by the action of pro- hormone convertase, preproglucagon, precursor of many glucagon related peptide. It exists in two forms, GLP-1 (7-36)- NH<sub>2</sub> and GLP-1(7-37) Its secretion is post prandially induced and increases in proportion to the size of meal (10-30PM), although basal secretion of GLP-1 is observed even in the fasting state (5-10PM). GLP-1 is found in many organs including pancreas, brain, heart, kidney and GI tract a recent study revealed that it is exclusively expressed in the pancreatic beta-cells and rarely in alpha cells. The secretion of GLP -1 into the circulation is stimulated by ingestion of carbohydrate, protein and fat however, only the mechanism of action for glucose is beginning to be elucidated. GLP -1 is degraded by DDP-4 and the products GLP-1 are biologically, inactive [3].

### Glucagon- like peptide 1 (GLP-1) receptor agonist

Now a day GLP-1 receptor agonist are become a usefull tool for the treatment of Type -2 DM. GLP-1 receptor agonst are mainly two types.

- Short acting GLP-1 receptor agonist
- Long acting GLP-1 receptor agonist

#### Short acting GLP-1 receptor agonist

This type of agonist are characterized by Short - lived peaks in plasma drug concentrations following each injection, with intermittent periods of near- zero concentrations.

#### Long acting GLP-1 receptor agonist

Long acting GLP-1 receptor agonist are characterized by constantly elevated drug cocentartions in a range leading to sub-

stantial GLP-1 receptor stimulation and only minor fluctuations between injection, this definition does not rest on the injection frequency alone but on the pharmacokinetics [4].

### Experimental work

#### Natural GLP-1 receptor agonist

The plant kingdom is a good poential source for the discovery of novel medicines to treat numerous diseases including DM. Theis literature survey shows the use of plant and plant based therapy for the management of type-2 diabetes mellitus. In this work, a list of natural GLP-1 receptor agonist was prepared, that can be included in our diet for the prevention of type -2 DM.

#### Agave

- Biological name – Agave tequilana Gto.
- Synonyms – *Blue agave*, *Agave angustifolia*.

Agave is an important economic product of Jalisco, Mexico due to its role as the base ingredient of tequila. This belonging family Agavaceae and mostly obtained from dietary fiber, sugars or protein and lipids. Agave fructans induced GLP-1 and enhanced concentration of its precursors. Agave fructan is main phytochemicals. Recent data reported that this fructans extracted from chicory roots and regulate appetite or glucose metabolism and promoting GLP-1 production in colon. Its roots are used for induced GLP-1 Its main phytochemical is agave fructan. This is giving supplementation with 10% fructans in male C57BL/6J mice shows activity [5].

#### Barberry

- Biological name – *Berberis vulgaris*
- Synonyms – *Berberis acida* and European barberry.

Barberry is a shrub in the family *Berberidaceae* it produce edible but sharply acidic berries, which people in many countries eat as a tart and refreshing fruit. Its main phytochemical is berberine. On the giving 500 mg/kg of this in rat shows antidiabetic effect this is effect of berberine which is produced by increasing insulin secretion and stimulating glycolysis. Berberine also increases glucose transporter-4 (GLUT-4) and GLP-1 levels. The main part which is used is Roots and rhizomes [5].

#### Bitter hop

- Biological name – *Humulus lupulus*
- Synonyms – Hope, *Lupulus amarus*.

The common hop is a species of flowering plant in the hemp family *Cannabaceae*, native to Europe, western Asia and north America. It is bitter in taste, in particular bitter taste receptor has shown modulate secretion of different gut hormones mainly glucagon-like peptide which are involved in the regulation of glucose homeostasis. The chemical constituent present in bitter hop are humulone, lupulone, xanthohumol and Adlupulone. This involved endocrine cells of GIT and acting on it and potential therapeutic target of T2DM because of its stimulation of GLP-1 resulting in hypoglycemic effect [6].

### Bitter melon

- Biological name – *Momordica charantia*
- Synonyms – karela

Bitter melon is a tropical and subtropical vine of the family *Cucurbitaceae*, widely grown in Asia, Africa and Caribbean. It becomes more and more bitter as it ripens this is linked to lowering blood sugar, which some studies suggest means it can add in diabetes treatment mainly its fruit is used. The main phytochemicals is Karavilagenine E. In the research when 5000 mg/kg of bitter melon administered orally with a single dose of WES for 30 min, in mice shows higher serum GLP-1, insulin and lower glucose were observed including that WES stimulated GLP-1 secretion in vivo as well [7].

### Black chokeberry

- Biological name – *Aronia melanocarpa*
- Synonyms – *Aronia nigra*

Black chokeberry is a species of shrubs in the rose family native to eastern north America, ranging from Canada to central United States and belonging to the family *Rosaceae* it having glossy dark green leaves. These fruits are richest source of polyphenols and anthocyanins and its chemical constituents are malic acid, quinic acid and ascorbic acid and its active compound used for studies is Cyanidin 3,5-diglucoside and its juice is used. When IC<sub>50</sub> of 5.5 μm is used for in vitro it resulting DPP-4 inhibition and increases GLP-1 levels by acting on this receptors [8].

### Black currant

- Biological name – *Ribes nigrum*
- Synonyms – *Ribes olidum*

Black currant is a deciduous shrub in the family *Grossulariaceae*, rich in vitamin C and polyphenols. Chemical constituents of *Ribes nigrum* are glucose, fructose, malic acid and citric acid. The main active constituent is Delphinidin 3-rutinoside. When 5 mg/kg of *Ribes nigrum* fruit is given with 1 mg/kg delphinidin 3-rutinoside is administered in GLUT ag cells it stimulates GLP-1 and insulin secretion [8].

### China mangolia

- Biological name – *Anemarrhena asphodeloides*
- Synonyms – Zhi mu

*Anemarrhena asphodeloides* fulfills the categories of bitter tasting medicinal plants and have been reported to stimulate GLP-1 secretion and mainly supports healthy blood glucose levels. *Anemarrhena* is plant genus in family *Asparagaceae* china mangolia. Its rhizome is used in traditional Chinese medicine and also shows the properties like diuretic, laxative and others. *Anemarrhena* contains Steroidal saponins, flavonoids, phenylpropanoids, benzophenones and alkaloids. Its model for study is Human L cell line [8].

### Chinese throughwax

- Biological name – *Bupleurum falcatum*
- Synonyms – *Bupleurum*

*Bupleurum falcatum* has been used traditionally as a medicinal herb in Korean medicine from family *Apiaceae*. It promotes GLP-1 secretion and the possibility that the medicinal herb can be used as a therapeutic agent of diabetes mellitus. It decreased blood glucose levels and it also stimulates GLP-1 secretion through G-Mediated pathway and insulin secretion through the modulation of the ATP-dependent potassium channel, increasing the calcium influx from intercellular stores. This is treated NCI-H716 cells with three concentrations 100, 200, and 500 μg/ml in db/db mice and GLP-1 secretion was increased dose dependently all concentrations increased GLP-1 secretion and had significance in human L cell line [9].

### Chinese yam

- Biological name – *Dioscorea polystachya*
- Synonyms - Dioscorea batatas

Chinese yam is species of flowering plant, this belongs to *Dioscoreaceae* family. Its yam is unique as the tubers can be eaten raw. The main active compound of chinese yam is Allantoin which is administered in STZ- treated Spraguedawley rats in 2 mg/kg concentration in the form of iv and it results increases release of GLP-1 [8].

### Cinnamon tre

- Biological name – *Cinnamomum zeylanicum*
- Synonyms - Cinnamon

Cinnamon is a small evergreen tree belonging to the family *Lauraceae*, it is currently marketed as a remedy for glucose intolerance, DM and dyslipidaemia. Intergative medicine is a new concept that combines conventional treatment with evidence – based therapies. Cinnamaldehyde, cinnamate and cinnamic acid are the chemical constituent of cinnamon. Plexopathy demonstrated a dose dependent reduction of serum insulin concentrations and an increase in glucagon-like peptide 1 (GLP-1) with cinnamon treatment. It was also reported that the addition of 3 g of cinnamon to a rice meal in humans caused significant increase of GLP-1 levels with decreased serum insulin. Improved glucose transport across the cell membrane reduces the insulin resistance and this probably accounts for the reduced insulin levels [10].

### Coffee

- Biological name – *Coffea arabica*
- Synonyms – Cocoa

Cacao tree is a small evergreen tree in the family *Malvaceae*. Its beans are used as coffee drink and it is one of the most commonly consumed drinks worldwide. It is basically obtained from cocoa plant known as *Theobroma cacao*. The active compound is caffeine that control glycemic and are known to reduce blood glucose levels in animal models. Coffee consumption might also mediate levels of GLP-1. In healthy fasted volunteers 400ml of decaffeinated coffee (equivalent to 2.5 mmol chlorogenic acid/l) results lowers the glycemic index of meals and increase GLP-1 [8].

### Gardenia

- Biological name – *Gardenia Jasminoides*
- Synonyms – Cape jasmine

Gardenia is an evergreen flowering plant, family *Rubiaceae*. The main chemical constituent of this plant is Geniposide. The main part is fruit, whose administration in insulin secreting cell lines (INS -1 cells), shows that the geniposides prevents the oxidative stress – induced in neuron apoptosis, and improved glucose stimulated insulin secretion by activating glucagon – like peptide 1 receptor [11].

### Ginger

- Biological name – *Zingiber officinale*
- Synonyms – *Rhizoma zingibere*

Ginger is a flowering plant and its rhizome and roots are widely used as a spice and a folk medicine, belonging to the family *Zingiberaceae*. Its chemical constituents are zingiberene, curcumene and gingerol. The main active compound is gingerol, its 200 mg/kg was given to diabetic mice for studies and it shows Activates GLP-1 and mediated insulin secretion [7].

### Guar gum

- Biological name – *Cyamopsis tetragonoloba*
- Synonyms – *Cordaea fabiformis*

Guar gum also called guaran, belonging to family *Fabaceae*. It contains polyphenol composition includes gallotannins, gallic acid and quinic acid. For studies of this three models was used and its extract was given. Firstly about 20&40 mg/kg guar gum was given in the human diet it reduces glucose absorption and insulin secretion and secondly about 7.6g per meal of guar gum was given to diabetic patients it results insulinemia and then third time high-fat supplemented with 10% guar gum /12 weeks was introduced in C57B mice and results short-chain fatty acids produced by colonic fermentation stimulate GLP-1 release, increasing glucose clearance [8].

### Hoodia extract

- Biological name - *Kalahari cactus*
- Synonyms – Bushman’s hat and *Hoodia Gordonii*

*H. gordonii* is a leafless spiny succulent plant supposed to have therapeutic properties in folk medicines, belonging *Apocynaceae* family. It is mainly appetite suppressant. The Gordonosides F is a steroid isolated from African cactiform *Hoodia gordonii*, which has been used for xhonomi bushmen as an anorexiant during hunting trips. It was observed that on oral administration of *H. gordonii* extract and its active compound Gordonosides F stimulated glucose dependent GLP-1 and insulin release showed a blood glucose lowering effect during OGTT. Hoodia contain steroid glycosides, fatty acids, plant sterols and polar organic material. Giving 1000 mg/kg extract and active compound Gordonosides F 200mg/kg in mice for OGTT and plasma insulin, plasma GLP-1 secretion increased. Isolated rat islets for GLP-1 stimulation shows anti-diabetic properties by acting on GLP-1 receptor agonist [15].

### Korean pine

- Biological name - *Pinus koraiensis*
- Synonyms – Korean pine

*Pinus koraiensis* is a species of pine known commonly as the Korean pine, belonging to the family *Pinaceae*. It is a member of the white pine group, *Pinus section Quinquefoliae*. Its phytochemicals are free fatty acids (FFA) and triglycerides (TG) and the main part of this plant is seed which used for studies. When the administration of 50 micro M Dose of each FFA of this plant in human females for study it shows GLP-1 was higher 60 min after pine nut administration, thus act as GLP-1 receptor agonist [8].

### Little dragon

- Biological name - *Artemisia dracunculul* L.
- Synonyms - Wild tarragon

*Artemisia dracunculul* also known as little dragon is a species of perennial herb in the sunflower family *Asteraceae*. The main part is leaves of this plant and the main chemical constituent is Tetralin. When 500mg/kg of Tarralin was given to KK-A (gamma mice) it

lowered the glucose levels and the extract was also shown to increase the binding of Glucagon – like peptide (GLP-1) to its receptor in vitro. In comparison to treatment with known anti-diabetic drugs decreased blood glucose concentrations [5].

### Mango

- Biological name – *Mangifera indica*
- Synonyms - Mango tree

*Mangifera indica* commonly known as mango is a species of flowering plant, *Anacardiaceae* family. The mango tree contains nutritional and phytochemical compounds like macronutrients (carbohydrates, proteins, amino acid and lipids) and leucine, valine and arginine or fatty acids. The study reported when the 320ug/ml of this studied in vitro model shows *mangifera indica* inhibits the DPP-4 and enhance GLP-1 for T2DM [5].

### Mate tea

- Biological name- *Ilex paraguariensis*
- Synonyms – Yerba mate

Mate tea is a plant Mate tea a plant is species of the holly genus belonging to the family *Aquifoliaceae*, its aqueous extract made from the leaves of the plant. The chemical constituent of this plant are Matesaponin, 3,5-O-dicaffeoyl-D-quinic acid, mate saponin. When a 50 and 100 mg/kg/d of the drug given to male mice it shows the effect on GLP-1 and a acute administration of major constituents of mate showed significant increases in GLP-1 levels. Compounds (3,5-Odicaffeoyl-D-quinic acid and matesaponin 2, respectively) and the (linolenic acid) showed significant increases in GLP-1 levels [13].

### Myricetin

- Biological name - *Myrica rubra*
- Synonyms - Myricetin

Evidence suggests that myricetin having anti-diabetic properties that are mediated via regulation of the transport of glucose through the function of glucose transporter 2. Myricetin is a glucose-dependent insulin secretagogue this is similar to those GLP-1 including the inhibition of beta cells apoptosis, glucoregulation

and the prevention of hypoglycemia belonging family *Myricaceae*. It is a flavanoid extracted from the leaves of myrica of myrica rubra. It is also a flavonoid containing and its chemical constituent is protein, polyphenols, arabinose and myricetin. Subcutaneously injections giving on male wistar rats 250 ug/kg body weight was administered orally results for insulin secretion assay and this shows anti-diabetic properties acting on GLP-1 receptor agonist. In humans 250ug/kg body weight orally reduced 2 injections each day reported human model studies [14].

### Olive oil

- Biological name – *Olea European* linn.
- Synonyms – Indian olive

Olive oil is a fixed oil obtained by expression of ripe fruits of olea European linn, belonging to family *Oleaceae*. This is a traditional tree crop, by pressing whole olives and extracting the oil. The composition of olive oil varies with the time of harvest and extraction process. It consist mainly oleic acid, palmitic acid, linoleic acid and monounsaturated fatty acid and acting components is oligo fructose. This mainly regulates GLP-1 homeostasis by acting on a GLP-1 receptor agonist [12].

### Phlomooides rotata

- Biological source – *Phlomooides rotata*
- Synonyms – Phlomooides

This is a flowering plant belonging family *Lamiaceae*. This plant is used as a folk restorative medicine against tuberculosis, pulmonary, cardiovascular disease and rheumatoid arthritis. The chemical constituent of this plants are luteolin, isoorientin and chlorogenic acid. The active compound use for administration was Shanzhiside methylester that was given to wistar rats for allodynia test and its concentration is about 10, 30, 100 and 300ug intrathecal and it act on GLP-1 receptor as an agonist [8].

### Plantago indica

- Biological name – *Plantago indica*
- Synonyms – *Plantago arenaria*

*Plantago indica* belongs to family *Plantaginaceae*. This plant contains a number of effective chemical constituents including fla-

vonoids, alkaloids, terpenoids and phenolic acid derivatives iridoid glycosides which contributes to its exerting specific therapeutic effect. So, for trials its fiber-enriched meal was used and 23gm per meal was given to Healthy young adults and it shows decreases glycemia and increase postprandial GLP-1 [8].

### Panax ginseng

- Biological name – *Asian Ginseng*
- Synonyms – Korean Ginseng

Panax ginseng belongs to family *Araliaceae*, its act on sweet taste receptors expressed in enteroendocrine L cells. In vitro studies using human and mouse enteroendocrine cells demonstrated that this stimulate GLP-1 secretion. Several ginsenosides such as Rb1, Rb2, Re, C-K and Rg3, were reported to have anti-diabetic and anti-obesity effects. Ginsenosides, triterpenoid, gintonin and saponin are found abundantly in panax Ginseng. Long term intraperitoneal injection of Rb1 (10 mg/kg) showed drastically decreased food intake and body weight and shows effect on GLP-1 receptor agonist. Intraperitoneal injection of Re (20 mg/kg) for 12 days reduced fasting blood glucose levels in ob/ob mice [17].

### Pomelo

- Biological name – *Citrus maxima*
- Synonyms – Pummelo

*Citrus maxima* are the largest citrus fruit from the family *Rutaceae*. It is a natural non-hybrid citrus fruit. The extract of dried fruit was used for the studies; its chemical constituents are Naringenin, osthol and DDPH. Its 70% Ethanol extract of 300, 600 and 1200 mg/kg administered in genetically obese Zucker rats, shows Decrease of circulating GLP-1 on acting as GLP-1 receptors [16,18].

### Conclusion

Natural products prove to be a rich source for the discovery of novel GLP-1 activators and many structurally diverse agonists of these receptors were recently identified from traditionally used medicinal plants or food sources. Interestingly, the majority of identified natural compounds are agonist of GLP-1 receptor which either act as partial or full agonist. Many extracts from medicinal plants reported in the literature act as GLP-1 activators are so far not thoroughly investigated. The identification of their active con-

stituents might provide further interesting ligands in the future. In this study, collection of plant products that have been demonstrated to prevent and treat type 2 diabetes via the regulation of insulin resistance and beta-cell function the actions, mechanisms and therapeutic potential of plant compounds or extracts, gives new insights into the advantage of herbal therapy.

In this review collection of GLP-1 activator from plant product was done and attempt had been made to overcome from this problem by preparing a list and detail description of natural GLP-1 activators obtains from plant source.

Finally, a range of GLP-1 activators from natural products and plant extracts were recently described that bear a good potential to be further explored for therapeutic effectiveness as well as to be studied as potential dietary supplements to counteract the metabolic syndrome and type 2 diabetes.

### Bibliography

- Colip JB. "Delayed manifestation of the physiological effects of insulin following the administration of certain pancreatic extracts". *American Journal* 63 (1923): 391.
- American Diabetes Association (ADA). "Classification and diagnosis of diabetes: standards of medical care in diabetes". *Diabetes Care* 42.5 (2019): 13-28.
- Manandhar B and Ahn JM. "Glucagon-like peptide-1 (GLP-1) Analogs: Recent Advances, new possibilities and therapeutic implications". 58.3 (2015): 1020-1037.
- Michael A., et al. "GLP-1 receptor agonists in the treatment of type 2 diabetes – state of the art". *Molecular Metabolism* 46 (2021): 101102.
- Singh R., et al. "GLP-1 secretagogues potential of medicinal plants in management of diabetes". *Journal of Pharmacognosy and Phytochemistry* 4.1 (2021): 197-202.
- Barrea L., et al. "Could hop- derived bitter compounds improve glucose homeostasis by stimulating the secretion of GLP-1". *Critical Reviews in Food Science and Nutrition* 59.3 (2021): 528-535.
- Rios JL., et al. "Modulation of diabetes by natural products and medicinal plants via incertins". 85 (2019): 825-839.
- Kim KS., et al. "Medicinal plants Qua Glucagon-Like peptide -1 Secretagogue via Intestinal Nutrient Sensors". 25 (2015): 9.
- Shin MH., et al. "Hexane Fractions of Bupleurum falcatum L. Stimulates Glucagon-Like Peptide-1 Secretion through G-Mediated pathway". 13 (2014).
- Medagama AB. "The glycemic outcomes of cinnamon, a review of the experimental evidence and clinical trials". *Nutritional Journal* 14 (2015): 108.
- Zhang W., et al. "The emerging possibility of the use of geniposide in the treatment of cerebral diseases: A review". *Chinese Medicine* 28 (2021): 16-86.
- Chang CLT., et al. "Herbal Therapies for Type 2 Diabetes Mellitus: Chemistry, Biology and potential Applications of Selected Plants and compounds". Hindawi publishing (2013): 33.
- Hussein GME., et al. "Mate tea (Ilex paraguariensis) promotes satiety and body weight lowering in mice: involvement of glucagon-like peptide-1". *Biological and Pharmaceutical Bulletin* 34.12 (2011): 1849-1855.
- Li Ying., et al. "Myricetin: a potent approach for the treatment of type 2 diabetes as a natural class B GPCR agonist". *FASEB* 31.6 (2019): 2603-2611.
- Ucellatore A., et al. "Composition Review of short acting and Low acting Glucagon- like peptide-1 Receptor agonists". *Diabetes Therapy* 6.3 (2015): 39-56.
- Choi EK., et al. "Hexane fraction of citrus aurantium L. stimulates glucagon-like peptide-1 (GLP-1) secretion via membrane depolarization in NCI-H716 cells". *BioChip Journal* 192.6 (2012): 41-47.
- Hinnen D., et al. "Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes". 30.3 (2017): 202-210.
- Nauck AM., et al. "GLP-1 receptor agonist in the treatment of type 2 diabetes". *State of Aet Article* 46 (2021): 101102.