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Review Article

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Drug Discovery and Development of Semaglutide and Tirzepatide from the Gila monsters (*Heloderma spp*)

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Abstract

The archetypical venomous lizard species are the helodermatids, the Gila monsters (Heloderma suspectum), and the beaded lizards (Heloderma horridum). Biological significance: The helodermatid lizards are the classical venomous lizards, and the pharmacological potential of the venom from these species has been known for years; best illustrated by the identification of exendin-4, which is now used in the treatment of type 2 diabetes. Heloderma venoms contain a complex mixture of biologically active proteins and enzymes, many of which are similar to those found in snakes. Exendin-4, a glucagon-like peptide-1 (GLP-1) receptor agonist, was derived from Heloderma venom and has been developed into the diabetes drug exenatide.

The potent effect of exendin-4 in stimulating insulin secretion has shown that it mimics glucagon-like peptide-1 (GLP-1), in most if not all of its actions. Thus, like GLP-1, exendin-4 inhibits glucagon secretion and stimulates insulin synthesis. Research into extendin-4 yielded semaglutide and tirzepatide. Both semaglutide and tirzepatide are well-known as (GLP-1) receptor agonists widely studied and used to manage type 2 diabetes. The journey of drug discovery to develop anti-obesity drugs began with identifying the role of GLP-1 receptor agonists in appetite control. Tirzepatide can lead to more pronounced weight loss compared to semaglutide, but the real mechanisms underlying their extraordinary effectiveness in weight loss lie in their effects on the brain. The gastrointestinal tract contains specialized cells that measure the quantities and qualities of incoming food (as well as the absence of food) and communicate this with the rest of the body, including the brain. The brain starts the process of releasing digestive juices and even causes insulin levels to rise.

Keywords: Gila, Monster, *Heloderma*, Diabetes type 2, Obesity, Weight, Loss

1. Introduction

The tablets were found in what was once known as the 'cradle of civilization' in the ancient remains of the city of Assur in Iraq. Written in an ancient language invented by Sumerians called cuneiform script, the tablets tell the story of a doctor in training. The tablets speak about a combination of medical practices (potentially handed down to the Greeks) and magical rituals [1]. Clay tablets from Mesopotamia dating from 2600 B.C. "humanity's earliest written records" describe the healing powers of several plant species, including licorice, myrrh, and poppy capsule latex [2]. The surviving Mesopotamian medical records consist of roughly 1000 cuneiform tablets, of which 660 medical tablets. About 420 tablets from other sites also survived, including the excavation from a medical practitioner's private house, and some Middle Assyrian and Middle Babylonia texts [3]. Now and then, scientists develop treatments that end up being even more popular for another entirely. Viagra, originally for high blood pressure, is nowadays used for erectile dysfunction, or the infamous thalidomide, a dangerous morning sickness treatment that is now a valuable cancer treatment [4].

2. Materials and Methods

This work is a systematic review of the employed literature research approach to investigate and examine: Gila Monster, *Heloderma* spp. diabetes type 2, weight loss, and obesity. To link common knowledge with modern discoveries, additional research was carried out using the mentioned specific keywords in the title or abstract of articles through Medline/PubMed (Medical Literature Analysis and Retrieval System Online), Embase (Excerpta Medica), Scielo (Scientific Electronic Library Online) databases, PubMed, Google Scholar, CAS Sc Finder, Scopus, the FDA official website, the EMA official website, and the official website

of the related Pharmaceutical Companies. Relevant literature was collected and screened until the end of January 2025.

However, let us see the journey of drug discovery for various compounds used for the treatment of different diseases:

2.1 Nitroglycerine

Nitroglycerine was discovered in 1847 and first noted the 'violent headache' produced by minute quantities of Nitroglycerine on the tongue. Nitroglycerine was tested in 1849 by healthy volunteers, observing that headache was caused with 'such precision'. Pursued nitroglycerine is a good candidate as a homeopathic remedy for headaches [5]. Alfred Nobel in 1851 recognized the potential of nitroglycerine [6]. During the mid-19th century, scientists in Britain took an interest in the newly discovered amyl nitrite, and nitroglycerine in 1867, was recognized as a powerful vasodilator used to relieve angina symptoms by dilating the blood vessels and improving blood flow to the heart [7,8].

2.2 Warfarin

In the year 1920s, a devastating bleeding disorder swept through North American cattle herds, began dying from a mysterious bleeding disorder. Focusing on the suspected spoiled hay in the animals' food supply. It turned out that the cause was the moldy sweet clover (*Melilotus officinalis and M. albus*) hay or silage the cattle were eating. The harmful compound in the mold that caused the bleeding, is called dicoumarol [9-11]. With support from the university, state, and Wisconsin Alumni Research Foundation (WARF), further research on this compound and its analogs led to the development of a new drug, they combined the acronym WARF with the last syllables of coumarin to come up with "warfarin", entered the market in 1948; but only sold as a rat poison, it was so effective at causing internal bleeding in rodents [12,13].

Researchers soon realized its potential therapeutic use in humans as an anticoagulant. The drug took off in 1955 after US President Dwight Eisenhower was successfully treated with it following a heart attack. A revolutionary new rat poison (warfarin) and blood thinner (warfarin sodium) are still widely used today [14-16].

2.3 Hirudin

Hirudin is the principal anticoagulant of the medicinal leech *Hirudo medicinalis*. Hirudin is a naturally occurring peptide (made up of 65 amino acids polypeptide with a molecular weight of about 7,000 Daltons), found in the salivary glands of medicinal leeches that has a blood anticoagulant property. Hirudin is now regarded as the treatment of choice for heparin-induced thrombocytopenia [17]. Hirudin is now produced by recombinant DNA techniques and is commercially available as lepirudin, bivalirudin, and desirudin are given to people at a high risk of getting blood clots -such as those with atrial fibrillation, a type of heart arrhythmia, if a blood clot jams up an artery, it can cause a stroke or heart attack [17, 18].

2.4 Blood Glucose Sugar

It has been known for more than 100 years that extracts of the intestinal tract enhance pancreatic endocrine secretion and produce hypoglycemia [19]. Human and animal studies have shown that the increase in insulin secretion in response to orally administered glucose is much greater than that of intravenous glucose [20]. In the 19th century, French physiologist Claude Barnard sought to explain why large amounts of glucose (blood glucose, or blood sugar, is the main sugar found in our blood) can be taken orally, whereas if glucose is given intravenously, small amounts overload the body's systems [21,22]. Bernard thinks that living creatures cannot be reduced to chemical and physical facts , he believes life is something unique and that it can be studied through its phenomena, and thus leading to laws based on the inner organs' functioning . He asserts, "There is an arrangement in the living being, a kind of regulated activity, which must never be neglected, because it is in truth the most striking characteristic of living beings" [23, 24].

2.5 Insulin

By 1920 Sir Frederick G. Banting, had already pinpointed clusters of cells in the pancreas, called islets, that produce insulin and worked out that it is these cells that are destroyed in type 1 diabetes [25]. In 1921 Banting, Charles Best, and John Macleod first got together to begin their research and set about figuring out how to remove insulin from a dog's pancreas [25,26]. A new researcher, James Collip, joined the group to work on purifying insulin so it would be safe enough to be tested in humans. With his help, a more concentrated and pure form of insulin was developed, this time from the pancreas of cattle [27]. Early of the year 1922, insulin was first used to treat a patient with diabetes, high blood sugar levels dropped, but he developed an abscess at the site of the injection and still had high levels of ketones. James Collip worked day and night on purifying the extract even further, and the patient was given a second injection. This time it was a complete success and the patient's blood sugar levels became near normal, with no obvious side effects. For the first time in history on 23 January 1922, type 1 diabetes was not a death sentence [25-29].

2.6 Mustard Gas

Mustard gas was used as a biological weapon in World War I, the mustard gas destroyed lymphatic tissue and bone marrow. Later, Alfred Gilman began to study the effects of nitrogen mustard on lymphoma experiments in mice showed that topically applying nitrogen mustard caused tumors to shrink as a result, it might also be able to kill cancer cells in the lymph nodes [30-32]. The next step was a clinical application of mustard gas in a patient suffering from terminal stages of lymphosarcoma. Within two days, doctors noticed that his tumors were softer and by the end of treatment, they had disappeared [33]. Mustard gas was incorporated into multidrug chemotherapy for Hodgkin's disease and remains a potent agent against cancer today. It has also paved the way for similar chemotherapeutic agents that attack cancer cells [32,33].

2.7 Incretin

Incretin hormones are gut peptides released by nutrients from the gastrointestinal tract, two distinct gut hormones originally named gastric inhibitory polypeptide (GIP) later renamed

glucose-dependent insulinotropic polypeptide, and glucagon-like peptide 1(GLP-1) [34]. By raising circulating incretin levels, oral glucose provokes a higher insulin response than that resulting from intravenous glucose. The two most important incretin hormones are (GIP) (GLP-1) [35,36]. However, in addition to its insulinotropic effect, GLP-1 inhibits glucagon release, prolongs gastric emptying, and leads to an increase in the ability to control plasma glucose concentrations and induce weight loss [35]. The GIP and GLP-1 excited scientists, but they couldn't be used as medicines because they metabolized too quickly in the body, this meant there must be another hormone, whose discovery had to wait until the age of cloning in the 1980s. Cloning the GLP-1 gene by Svetlana Mojsov demonstrated it stimulated pancreatic insulin secretion at 1/100th of the concentration needed for GIP. So GLP-1 was identified as the other incretin responsible for people's insulin response [36].

2.8 Captopril

Snake venoms the Brazilian arrowhead viper (*Bothrops jararaca*) produces peptide inhibitors nonapeptide or teprotide of angiotensin-converting enzyme (ACE), a hormone that cleaves angiotensin I to generate angiotensin II and causes vasoconstriction and increased blood pressure [37]. In the late 1960s, researchers were studying this snake's venom and its effects on blood pressure, they were able to isolate a peptide from the venom, which could inhibit the enzyme (ACE) and lead to a decrease in blood pressure. This resulted in the development of a synthetic version of the peptide called captopril which was approved by FDA in 1981 [38, 39]. Captopril is a remarkably effective new antihypertensive drug designed and developed as a potent and specific inhibitor of angiotensin-converting enzyme, a zinc metallopeptidase that participates in the synthesis of a hypertensive peptide, angiotensin II, and in the degradation of a hypotensive peptide, bradykinin. Although captopril is rarely prescribed today, it led to the next generation of ACE inhibitors, such as enalapril, which are widely prescribed to treat high blood pressure and heart failure [38-41].

2.9 Ziconotide

The cone snails (*Conus magus*) are venomous marine mollusks that use small, structured peptide conotoxins for prey capture, defense, and competitor deterrence [42]. Because conotoxins discriminate between closely related subtypes of ion channels, they are widely used as pharmacological agents in ion channel research, and several have direct diagnostic and therapeutic potential [42,43]. Large conotoxin families can comprise hundreds or thousands of different peptides; most families have a corresponding ion channel family target. Different conotoxin families may have different ligand binding sites on the same ion channel target [44,45]. Ziconotide, a synthetic peptide initially isolated from *C. magus* in 1982 and approved by the FDA and EMA in 2004, is the first-line intrathecal method for individuals experiencing severe chronic pain refractory to other therapeutic measures. Ziconotide produces powerful analgesia by blocking N-type calcium channels in the spinal cord, which inhibits the release of pain-relevant neurotransmitters from the central terminals of primary afferent neurons [45,46]. However, despite possessing many favorable qualities, including the absence of tolerance development, respiratory depression, and withdrawal symptoms (largely due to the absence of a G-protein mediation mechanism), ziconotide's application is limited due to factors such as intrathecal administration and a narrow therapeutic window resulting from significant dose-related undesired effects of the central nervous system [47,48].

2.10. Trabectedin

Trabectedin is a marine tetrahydroisoquinoline alkaloid obtained from a Caribbean tunicate (Caribbean sea squirt) *Ecteinascidia turbinata,* an Atlantic-Mediterranean species growing in mangroves and coastal meadows [49]. The base structure, without the exocyclic isoquinoline group, is a well-known chemotype originally reported from microbes, where the compound classes are saframycins, naphthyridinomycins, safracins, and quinocarcins [50].

The antitumor activity of extracts from the ascidian *E. turbinata* had been reported as early as 1969 [51], but it was not until 1990 that the structures of the active components has been elucidated [52,53]. Preclinical and early clinical trials revealed the high cytotoxic activity of trabectedin against several resistant human tumors [54].

Trabectedin works by sticking to the DNA in cells and damaging it, this stops the cancer cells from growing and multiplying and the activity was observed in cases of soft tissue sarcoma that has spread to other parts of the body (advanced sarcoma) that had relapsed or were resistant to conventional therapy [55]. In 2015, the FDA US Food and approval for trabectedin (Yondelis®) for treating advanced soft-tissue cancers, such as liposarcoma and leiomyosarcoma in patients with advanced soft tissue sarcoma and relapsed ovarian cancer who failed to respond to chemotherapy [56].

2.11 Gila Monster (The story of Semaglutide and Tirzepatide)

There are two species of venomous lizards in the world, both species belong to the genus *Heloderma*, belonging to the family Helodermatidae, and are found in the Americas [57]. Two *Heloderma* species, *H. suspectum* (Gila monster) and *H. cinctum*, are found in the United States. The other species, *H. horridum* (Mexican beaded lizard), is significantly larger than other Helodermatids and occupies parts of Mexico and Guatemala [57,58].

H. horridum, which was first described in 1829 by Arend Wiegmann, and assigned the generic name *Trachyderma*, he changed it to *Heloderma* six months later, which means "studded skin", from the Ancient Greek words *hêlos* (the head of a nail or stud) and *derma*, meaning skin. The species belong to the order Squamata; class Reptilia belonging to the family Helodermatidae of the Kingdom Animalia [59].

Both species of *Heloderma* are slow, methodical predators. Their

large heads and muscular jaws yield a strong bite that is held while venom seeps into the wound. Many teeth have two grooves that conduct the venom, a nerve poison, from glands in the lower jaw. Fatalities to humans are rare [60,61]. Observation near shelters suggests that these *Heloderma* spp., have a structured social system [57,62].

Heloderma venoms contain a complex mixture of biologically active proteins and enzymes lethal, many of which are similar to those found in snake venom phospholipase A2 and five interesting bioactive peptides: vasoactive intestinal peptide analogs – helospectins I and II and helodermin and glucagon-like peptide-1 analogs exendins-3 and -4 which have been developed for the treatment of type 2 diabetes mellitus [63-65]. Unlike other venomous reptiles, these lizards use their venom for defensive purposes only. They cannot inject their venom, but rather infuse the venom as they bite, holding on tenaciously and chewing to allow the venom to mix with the saliva into the wound [66]. The toxicity has been attributed to a lethal component known as gilatoxin, a glycosylated serine protease with 40% homology with thrombin-like proteases from snake venoms [67]. The minimal toxic dose calculated for humans has been estimated at 8 mg of venom (dry weight). The venom yield of a Gila monster is 15 to 20 mg dry weight; however, the venom delivery system of the lizard is poor [68].

In the 1980s John Pisano, a researcher with a penchant for venoms, and a gastroenterologist Jean-Pierre Raufman were working with poisonous lizard venom of H. suspectum [57,63]. By the mid of 1990s, Pisano, Raufman, and John Eng identified a hormone-like molecule they called exendin-4, a polypeptide of 39 amino acid residues (Figure 1) showing 53% structural homology with GLP-1 [64-67]. Scientists found that the hormone in the Gila monster's saliva mimicked and the human hormone GLP-1 makes the lizard's venom suitable as the basis to treat type 2 diabetes [61, 67-68]. The hormone, exendin-4, works similarly to another hormone called Glucagon-like peptide-1(GLP-1), found in the digestive tract in humans that regulates blood glucose. However, exendin-4 degrades in the body much slower than GLP-1 [69,70]. Excitingly, exendin-4 was not quickly metabolized by the body, and so might be useful as a diabetic therapeutic [71,72]. Eng was convinced this would work, but pharmaceutical companies didn't want to give people hormones from a venomous lizard. Even the medical center where Eng was working wouldn't help fill the patent [73]. Eventually, Eng and Raufman convinced a small start-up called Amylin Pharmaceuticals. Amylin quickly showed synthetic exendin-4 rapidly normalized blood glucose in type 2 diabetic mice [63,74,75].

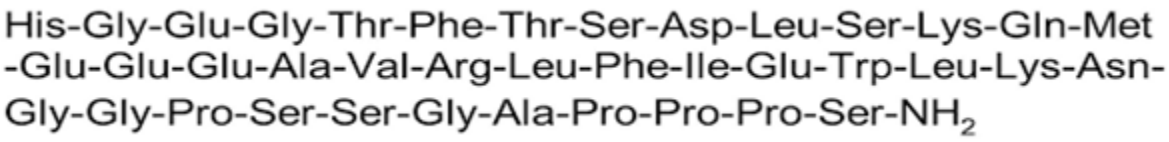

Figure 1: Exendin-4, a polypeptide of 39 amino acid residues.

2.12 Exendin-4

The use of snake venoms as medicinal has been recorded as far back as the Egyptian dynasties and they have long been found in texts of Chinese herbal lists as being used for specific remedies. Furthermore, the use of snake venoms in healing has been anecdotally passed from generation to generation among folk healers [76]. The discovery of biologically active toxins in animal venoms has led to a number of important scientific discoveries as well as serving as drug leads or drugs, several of which are on the market with numerous others in the approval pipeline [77, 78].

H. horridum and *H. suspectum* stimulates adenylyl cyclase activity and amylase release from guinea-pig dispersed pancreatic acini [62]. As helospectins and helodermin are members of the glucagon and secretin, which all contain a histidine residue at position 1, the venoms were screened chemically for other peptides with a similarly positioned histidine. This led to the isolation of the peptide designated exendin-3 from *H. horridum* venom and subsequently a very closely related peptide, exendin-4, from *H. suspectum* venom [79]. Researchers have cloned the cDNAs for exendin-3 and exendin-4 from small samples of lizard venom (*H. horridum* and *H. suspectum*, respectively) [80].

2.13 Actions of exendin-4

The studies of the potent effect of exendin-4 in stimulating insulin secretion in *vitro* and in *vivo*, have shown that it mimics GLP-1 in most if not all of its actions. Thus, like GLP-1, exendin-4 inhibits glucagon secretion and stimulates insulin synthesis [81-83].

Following the demonstration that exendin-4 reduced fasting and postprandial blood glucose in healthy volunteers, the peptide was shown to reduce blood glucose and improve β-cell sensitivity to glucose when given twice daily, subcutaneously for one month to patients with type 2 diabetes. This has been confirmed in many studies [84-87]. Exendin-4 then proved safe and effective in humans, leading (FDA) approval of exenatide, under the trade name Byetta in the year 2005 [88].

2.14 Exenatide

Research into extendin-4 yielded semaglutide, a derivative of the molecule but one that will stay in the body for far longer, producing the desired pharmacological effect. The development of exenatide, a synthetic exendin-4, represents an example of how the venom has developed a clinically useful agent, offering an entirely novel way to treat type 2 diabetes [89]. The development of the 'incretin concept' which hypothesized that hormones from the gut

contributed to insulin secretion in response to meals, led to the identification of (GLP-1) as an important incretin hormone [90].

Chemistry

Exenatide is a 39-amino acid peptide amide. Exenatide has the empirical formula C184H282N50O60S and a molecular weight of 4186.6 Daltons. The amino acid sequence for exenatide is shown in Figure 2 [91].

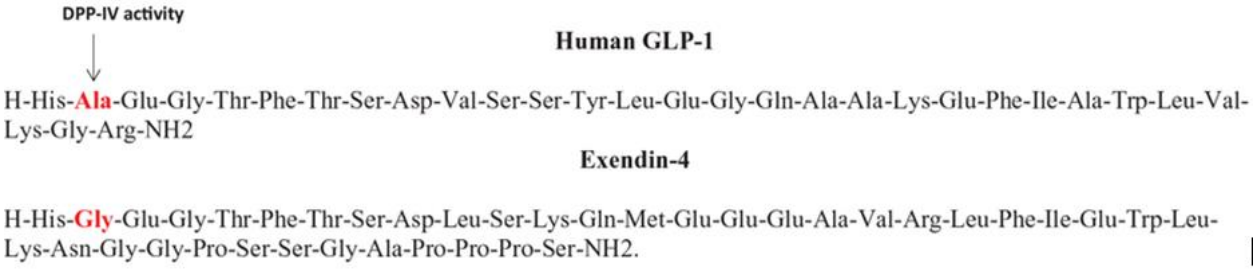

Figure 2: The amino acid sequence of exenatide in comparison to native GLP-1. The key amino acid substitution at position 2 that confers full resistance to DPP-4 in exenatide is highlighted.

GLP-1 not only increases insulin secretion but increases β-cell proliferation and survival, suppresses glucagon secretion, delays gastric emptying, and suppresses appetite, all of these actions contributing to a potential anti-diabetic effect. However, GLP-1 has a very short half due to its rapid breakdown by dipeptidyl peptidase IV and ectopeptidases [92].

Exenatide enhanced glucose-dependent insulin secretion, suppressed inappropriately elevated glucagon secretion, slowed gastric emptying, reduced body weight, enhanced satiety, and preserved pancreatic β-cell function [93,94].

The ability of exendin-4, like GLP-1, to stimulate insulin secretion in a glucose-dependent manner minimizes the risk of producing clinically important hypoglycemia, compared with that associated with other agents that stimulate insulin release, such as sulphonylureas [94]. Nausea, vomiting, and diarrhea were the most common adverse events reported with exenatide therapy. Exenatide is not associated with hypoglycemia, which may provide advantages over adding insulin to sulfonylurea or metformin [95]. Exenatide (Byetta), was approved by the FDA in 2024. First generic of once-daily GLP-1 injection to lower blood sugar in patients with type 2 diabetes [96].

2.15 Liraglutide (Victoza)

Liraglutide (Victoza) was the first generic referencing the 1 (GLP-1) receptor agonists that was initially approved for adults with type 2 diabetes in 2010, with an expanded indication in 2019 including children and adolescents aged 10 to 17 years. The FDA, in 2024, approved to improve glycemic control in patients aged 10 years and older with type 2 diabetes [97].

Chemistry

Liraglutide is a long-acting naturally occurring human GLP-1 analog with 97% amino acid homology to the human endogenous GLP-1. This 97% homology was achieved by substituting arginine for lysine at position 34 of endogenous GLP-1 , the addition of a glutamic acid-spaced palmitic acid to the ε-amino group of lysine in position 26 Figure 3 [98]. Liraglutide precursor is produced using recombinant DNA technology in yeast Saccharomyces cerevisiae [99].

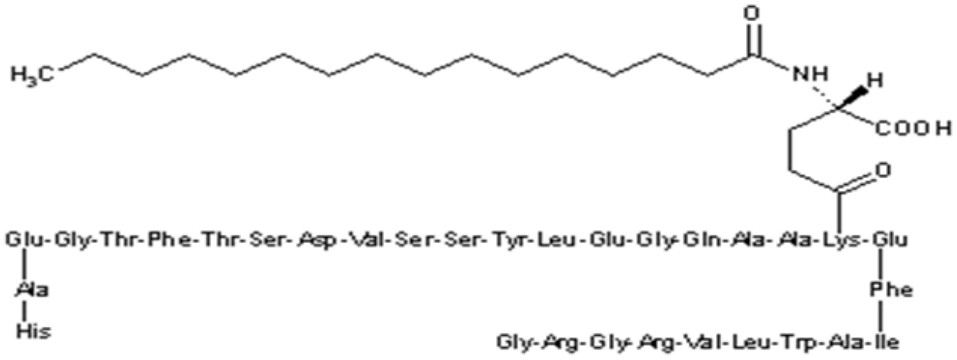

Figure 3: Liraglutide, a polypeptide of amino acid residues.

Endogenous GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4), and its insulin effect is short-lived. Liraglutide contains a fatty acid molecule that binds to albumin and prolongs the half-life of the structure [99]. Through the messenger intracellular cyclic adenosine monophosphate (cAMP), liraglutide causes insulin to be secreted in the presence of elevated glucose levels. Because of the receptor locations, liraglutide also inhibits glucagon secretion and delays gastric emptying [100,101].

2.16 What are Semaglutide and Tirzepatide?

Both semaglutide and tirzepatide are medications well known as glucagon-like peptide-1 (GLP-1) receptor agonists widely studied and used to manage type 2 diabetes [102]. These medications mimic the action of a hormone called GLP-1 receptor agonist which increases insulin secretion, decreases glucagon release, and slows gastric emptying. This combination helps lower blood sugar levels after meals and promotes fullness, which can contribute to reduced food intake [102-104].

Semaglutide enhances the body's natural ability to regulate blood sugar levels, making it easier for people with diabetes to maintain control over their condition [105]. Tirzepatide is a newer medication that combines the actions of GLP-1 and another hormone called glucose-dependent insulinotropic polypeptide (GIP). This dual-action approach makes tirzepatide unique and potentially more effective in managing blood sugar levels [106-108]. Tirzepatide has shown superior efficacy in lowering HbA1c levels compared to other GLP-1 receptor agonists, including semaglutide [109].

3. Mechanism of Action

Semaglutide works solely as a GLP-1 receptor agonist in the brain, causing less hunger and reduced cravings for food, meanwhile, tripeptide combines the actions of GLP-1 and GIP receptor agonists, providing a greater reduction in appetite than semaglutide alone [108].

3.1 Administration

These current drugs are big molecules (peptides) and for this reason, must be injected as they're not absorbed effectively in the gut. Both semaglutide and tirzepatide are administered via weekly subcutaneous injections [110]. Semaglutide is available as an oral that is used to treat Type 2 diabetes [111].

3.2 Side Effects

The safety profiles of tirzepatide and semaglutide were similar, both medications can cause gastrointestinal side effects, such as nausea, diarrhea and vomiting. However, the incidence and severity of these side effects can vary between individuals. There were no deaths [112, 113]. Tirzepatide's dual-action mechanism may result in a different side-effect profile compared to semaglutide. Tirzepatide tends to cause fewer gastrointestinal side effects (nausea and vomiting) compared to semaglutide [114].

3.3 From Gland Treatment to Semaglutide andTtirzepatide (Weight Loss)

Organotherapy (gland treatment) was hugely popular in the 1920s to 1940s. Physicians prescribed overweight people extracts of animal glands, ither eaten raw or dried in pill form or injected, to treat their supposedly "sluggish glands" [115,116]. There was no evidence underperforming glands usually caused excess weight or that gland extracts (thyroid in particular) were doing anything other than poisoning the body [115]. Fad diets, miracle diets, magic diets, and cult diets usually describe them as healthy diets with unusual properties but always through pseudoscientific arguments. However, it must be noted that there is not a diet better than eating less, moving more, and eating lots of fruits and vegetables [117].

Scientists were found to have the remarkable and unexpected side effects of significant weight loss of both medications, semaglutide and tirzepatide [118,119]. The journey to develop the treatment began with identifying the role of GLP-1 receptor agonists in appetite control. Tirzepatide can lead to more pronounced weight loss compared to semaglutide, but the real mechanisms underlying their extraordinary effectiveness in weight loss lie in their effects on the brain [118]. The gastrointestinal tract contains specialized cells that measure the quantities and qualities of incoming food (as well as the absence of food) and communicate this with the rest of the body, including the brain. Brain starts the process of releasing digestive juices and even causes insulin levels to rise [119].

Both semaglutide and tirzepatide act on areas of the brain, including parts of the hypothalamus that regulate hunger, fullness, and cravings to turn off hunger signaling to a degree, which results in a state of negative energy balance that helps the majority of patients lose weight [120-123].

3.4 Ozempic® (Semaglutide)

In clinical trials, exenatide formulations reduced hyperglycemia in patients with type 2 diabetes mellitus and were associated with weight loss. The blockbuster drug Ozempic® was originally developed to treat type 2 diabetes, a condition that results in too much glucose, or sugar, in the blood. This is because the body can't effectively use the insulin it produces [124].

It binds to GLP-1 receptors and stimulates insulin release from the pancreas when needed. It slows down how fast food travels through the digestive tract. This can help people to feel fuller for longer, reduce how much they eat, and lead to weight loss [128, 129]. Ozempic should not be used together or with any other GLP-1 or GIP receptor agonists. It is given as weekly injections under the skin (subcutaneously) in the stomach area (abdomen), thigh, or upper arm [125,126].

Liraglutide, approved as Victoza in 2010 by the FDA, for for weight loss than Byetta (typically 10% weight-loss), but still needed daily injections [127]. Due to its safety profile and weight-loss efficacy (of around 15%), a higher dose of semaglutide the FDA approval as Wegovy® in 2021 as a stand-alone obesity treatment, injected

subcutaneously (under the skin) in the abdomen, thigh, or upper arm [128]. The oral form of semaglutide has not been studied for weight loss, but it does not result in weight loss comparable to the injectable forms [129]. Researchers managed to reformulate semaglutide so some would make it through the stomach [131].

Tirzepatide is sold under the brand name Mounjaro® for type 2 diabetes treatment [79,102], and Zepbound for weight loss in 2024, the FDA for the treatment of moderate to severe obstructive sleep apnea (OSA) in adults with obesity, to be used in combination with a reduced-calorie diet and increased physical activity (124). Mounjaro lowered hemoglobin A1C levels more than Ozempic over 3 months [124,1125]. People taking Mounjaro also lost more weight than those taking Ozempic). studied as Zepbound) also showed it to be more effective than Ozempic for weight loss (typically 18% of body weight), making it an attractive option for patients seeking weight management benefits [115].

In March 2024, the FDA approved a new indication for use for Wegovy (semaglutide) injection to reduce the risk of cardiovascular death, heart attack, and stroke in adults with cardiovascular disease and either obesity or overweight [132].

4. Conclusion

Tirzepatide and semaglutide are GLP-1 receptor agonists and mimic the actions of GLP-1 for type 2 diabetes treatment. They affect the area of the brain that controls hunger and delay the time it takes for food to travel through the gastrointestinal tract, making them ideal drugs for weight loss. Tirzepatide also mimics the action of another hormone, GIP. Although it is not fully understood what GIP does, it is believed to enhance the effects of GLP-1, resulting in greater weight loss.

Disclaimer (Artificial Intelligence)

The authors declare that they have no generative AI Technologies that have been used during the writing or editing of this manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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