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# SYNERGISTIC NANOTHERAPEUTICS: UNITING INCRETIN-BASED AGENTS AND SGLT-2 INHIBITORS FOR TYPE-2 DIABETES

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## ABSTRACT

Treatment modification in terms of dose up-titration or supplementary medications is the key requirement for Type-2 diabetes mellitus (T2DM) patients who fails to achieve glycemic targets. This demands treatment strategies including multiple diabetes medications to attain glycemic regulation. Numerous aspects were allied with declining adherence and persistence, comprising polytherapy versus monotherapy régimes. Combination therapy is one strategy to improve adherence, as it is envisioned to condense pill encumbrance, regime intricacy, and costs. This review primarily emphasizes on the dual therapy comprising of incretin-based agents (dipeptidyl peptidase-IV (DPP-IV) inhibitors and sodium-glucose cotransporter-2 (SGLT-2) inhibitors for T2DM treatment. Their mode of action, basis of combination and clinical trial results in support of combining these drugs together for effective management of T2DM. By utilizing the concept of two different patho-physiological mechanisms against diabetes, a noteworthy drop in HbA1c level without any integral menace of hypoglycemia, is achieved by combining these drug categories together.

**Keywords: Type-2 diabetes mellitus (T2DM), sodium-glucose cotransporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-IV (DPP-IV) inhibitors, Nanoparticles, HbA1c, hypoglycemia**

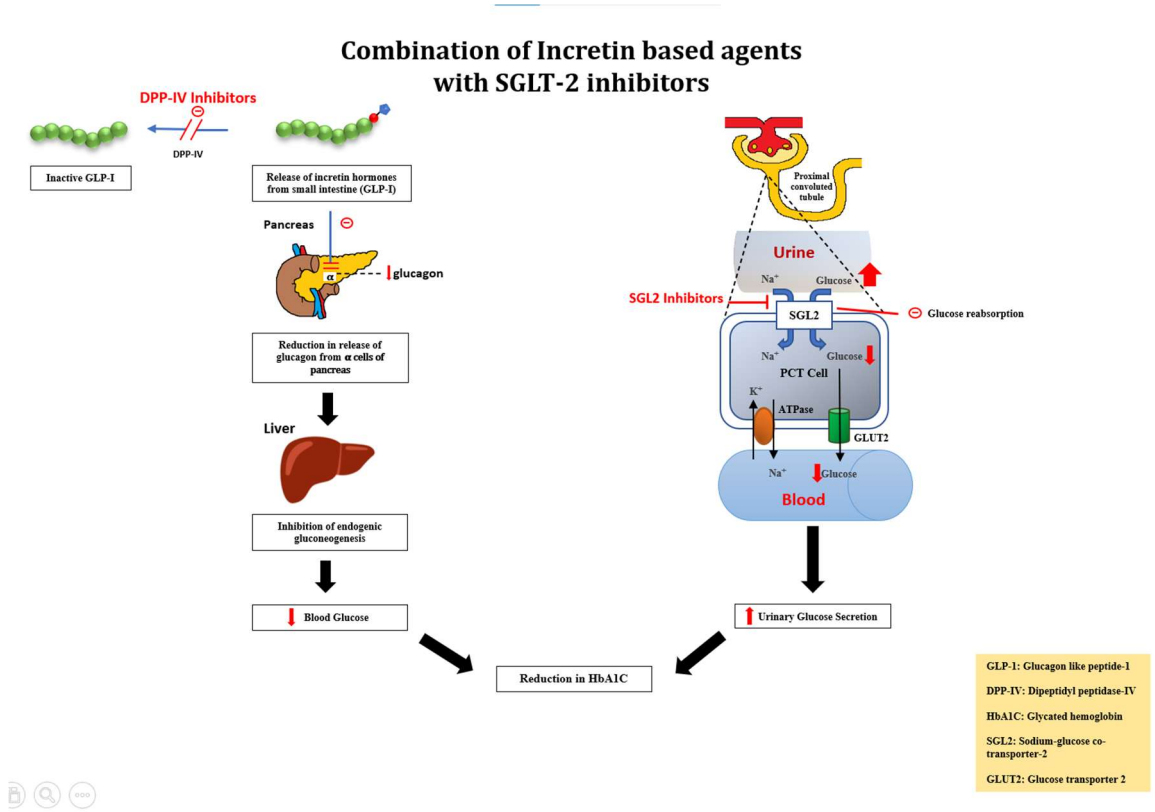


**Figure a: Graphical Abstract**

## INTRODUCTION

Type-2 diabetes mellitus (T2DM) is an advanced, multiple factors related to hereditary, metabolic and cardiovascular disease pertaining several pathophysiologic anomalies **[1]**.

Impaired or altered insulin secretion and altered insulin action are two chief pathological flaws of T2DM, which are results of pancreatic β-cell dysfunctioning and resistance to insulin respectively **[2]**. In conditions of predominant insulin resistance, β-cells collectively undergo a transformation leading to increase in insulin amount and reimbursement for the extreme and abnormal need of insulin. In such case, both fasting and meal plasma insulin concentrations are augmented classically. The plasma insulin concentration is inadequate to continue normal glucose homeostasis in comparison to the harshness of insulin resistance. Hence the ultimate consequence is insulin resistance and hyper insulinemia leading to impaired glucose tolerance **[3]**.

It has risen as global pandemic currently. Previously impaired insulin secretion and insulin resistance were considered as the

solitary cause of T2DM, but now several other factors or pathological conditions are considered equally responsible for causing the disease. These include- excessive alpha glucagon production, irregular incretin outcome, improved hepatic glucose production, augmented lipid breakdown, neurotransmitter dysfunction, abnormal renal management of hyperglycemia **[4]**. **Figure 1** represents pathophysiology of T2DM.

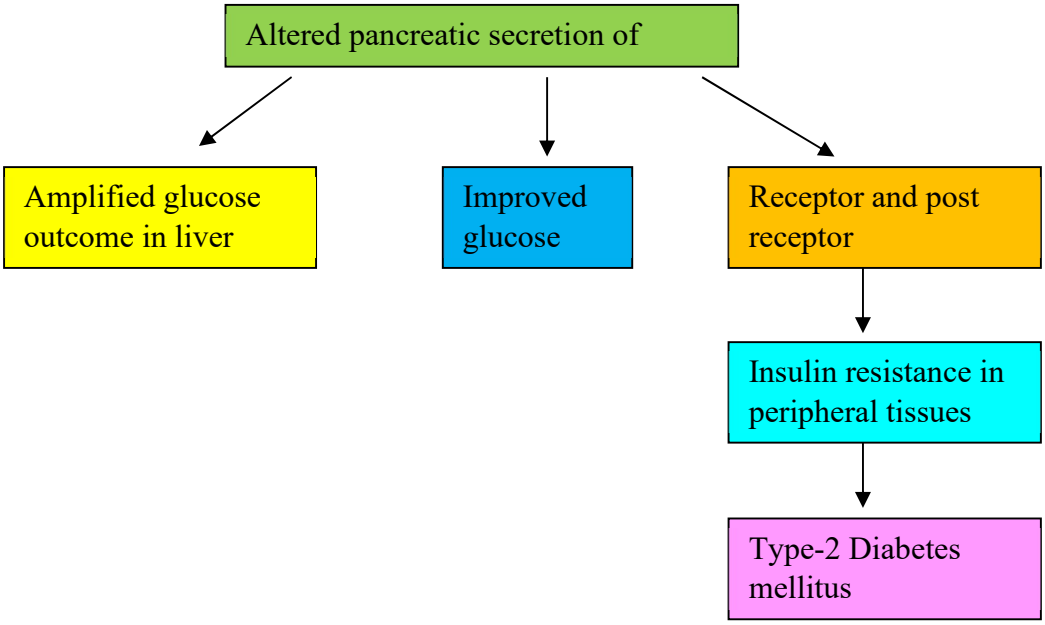


**Figure 1: Pathophysiology of Type-2 diabetes mellitus**

Nearly half of diabetic adult patients are unable to attain the endorsed glucose regulation, hence demanding treatment modification (i.e., up-titration of dose or additional medications). Studies demonstrate that polypharmacy in diabetes can be associated with poor medication adherence and persistence. Poor adherence has been associated with loss of glycemic control and increased risk of hospitalization and mortality, as well as increased costs in patients with type 2 diabetes mellitus **[5]**. All these pros have encouraged the preliminary use of combination therapy along with added hostile initial therapy as they retain the A1C from intensifying much above the target range **[6]**. The early initiation of combination remedy is suggested by many scientists for T2DM, which results in sustained decrease in glycated hemoglobin HbA1c levels by correcting the allied pathophysiologic anomalies. The use of low-dose combined therapy results in greater glycemic control with les side effects as compared to the high dosed of the monotherapy **[7]**. The prime objective of T2DM treatment strategies must be to reserve

or recover proper functioning of pancreatic β-cell, decrease insulin resistance with safety and weight neutral characteristics along with a treasured outcome on cardiovascular risk facets **[8]**.

**COMBINATION STRATEGY FOR T2DM**

The combination therapy should include drugs possessing complementary mechanisms of action, so that the incidence of compensatory mechanisms can be prevented and HbA1c goals can be achieved using additive effects of combined drugs **[6]**. Combination therapy is one strategy to improve adherence in type-2 diabetes mellitus, as it is intended to reduce pill burden, regimen complexity, and costs **[9]**.

Preferably, a combination of hypoglycemic agents must discourse multiple pathophysiologic trails through complementary mechanisms without any integral risk of weight gain, hypoglycemia and cardiovascular complications. It must be safe to use at all stages of diabetes, imparting adequate efficacy and well tolerability and should also offer patient compliance and enhanced dosage adherence in terms of oral, single-dose pill with once-a-day dosing frequency **[10]**.

Extent of hyperglycemia, properties of hypoglycemic agents as well as co-morbidity condition affects the treatment strategy of T2DM.

As T2DM is a progressive disease because it is known to intensify innumerable complications and comorbidities all over a patient's lifetime. Apart from the morbidities due to T2DM, various specific chronic conditions like cardio vascular disease, renal disease, blindness, heart stroke, myocardial infarction etc. may be caused as a result of T2DM **[11]**. Cardiovascular diseases may be precisely observed in diabetic patients with hepatic disease due to metabolic anomalies **[12]**. Hence it becomes necessary to include combined therapy as treatment strategy since the diabetic patients have many complications like hypertension, dyslipidemia and other comorbidities which demands polypharmacy **[13-15]**. Patients are unwillingly bound to take multiple medications in such conditions, even before the antidiabetic therapy is initiated. To overcome such problem, combination therapy or fixed dose combination treatment strategy is a coherent approach for maintaining HbA1c levels along with the omission of heavy-pill burden of the patients **[16]**.

Maintaining glycemic control is directly linked with extenuating menace. Lower morbidities have been reported in patients with HbA1c 7% or less **[30]**. Financial burden

can be minimized by adequately maintaining glycemic control **[17]**.

**COMBINATION OF INCRETIN-BASED THERAPY WITH SGLT-2 INHIBITORS**

Inhibition of the enzyme linked deprivation of endogenic incretin hormones (active glucagon-like peptide [GLP]-1 and glucose-dependent insulinotropic polypeptide [GIP]) by Dipeptidyl peptidase -IV (DPP-IV) or CD26 inhibitors is the key mechanism of incretin-based therapy. Such inhibition results in elevated GLP-1 and GIP concentration in blood-plasma, that further kindle insulin ooze from pancreatic β-cells and impede glucagon release from pancreatic α-cells, which ultimately leads to inhibition of endogenic gluconeogenesis and subsequent drop in plasma glucose level. This property of DPP-IV inhibitors is responsible for interfering with the plasma concentration of biologically active peptides as well as the peptide GLP-1 and is contemplated to be capable drugs for the management of diabetes mellitus. Examples of DPP-IV inhibitors are sitagliptin, saxagliptin, linagliptin, gemigliptin and alogliptin. Though, Incretin-based agents proved to pose a lower risk of hypoglycemia during fasting which apprehended traditional set of population in India and other countries too and presenting major challenges for physicians **[18]**. Their ample pros make it suitable for treating hyperglycemic conditions.

On the contrary, Sodium-glucose co-transporter-2 (SGLT-2) inhibitors act by inhibiting SGLT-2 (a low-alliance, high-throughput glucose transporter located in the renal proximal tubule), which is accountable for 90% of glucose reabsorption. Inhibition of SGLT-2 results in the reduction in blood glucose attributable to the rise in renal glucose elimination. SGLT-2 inhibitors also provide additional glucose regulation by permitting augmented insulin compassion and acceptance of glucose in the muscle cells, reduced gluconeogenesis and upgraded initial stage insulin release from the beta cells. Examples of SGLT-2 inhibitors include Empagliflozin, Canagliflozin, Dapagliflozin, Ipragliflozin, Sergliflozin etabonate (which was withdrawn post Phase II trials), Remogliflozin etabonate, Ertugliflozin, Luseogliflozin, Fogliflozin **[19]**.

Australia was the first country to introduce SGLT-2 inhibitors as antidiabetic agents. From various clinical studies it was concluded that regardless of background therapy, approximately 0.6 to 0.9% HbA1c reduction was reported with SGLT-2 inhibitors. Comparable results were achieved with incretin-based agents too **[20]**. Many studies confirmed that incidences of heart failure have

been markedly reduced (8.2/1000) as compared to the incretin-based agents alone **[21]**.

Remarkably, the probability of achieving HbA1c levels less than 7% is improved to the same degree by addition of an incretin-based agent to an SGLT-2 inhibitor or vice versa **[22]**.

Overall incretin-based agents and SGLT-2 inhibitors in combination therapy improves glycemic regulation and reduces body weight deprived of increasing the menace of hypoglycemia and urinary tract infection in patients with ineffectively controlled T2DM **[23]**. Some studies also proved that combination of incretin-based agents with SGLT-2 inhibitors lead to decreased urinary albumin excretion through reduction in blood pressure and improve a variety of metabolic parameters in a glucagon-independent manner **[24]**.

**Objectives of combining incretin-based therapy with SGLT-2 inhibitor**

1. To cut off the hypoglycemia menace in consort with significant furtherance of HbA1c. (As gliptins, alone reduces HbA1c and has a low risk of hypoglycemia. While gliflozins, improve HbA1c by causing glucosuria and ameliorating glucotoxicity).
2. To provide complementary or synergistic mechanisms of action for effective treatment of T2DM.
3. In patients who cannot tolerate metformin (e.g., those with hepatic impairment and gastrointestinal intolerances), DPP-IV inhibitors and SGLT-2 inhibitors are treatment alternatives as combined therapy that may be safely use at any stage of diabetes.
4. To formulate such a combination, that is suitable to use at all phases of the disease with well tolerability and no associated risk of low blood glucose level, cardiovascular events, or weight gain.
5. To offer patient compliance in terms of single-pill, once-daily administrable oral formulation, certainly rendering to better constancy **[5]**.
6. Optimizing the biopharmaceutical characters of combination therapy.
7. No need of dose adjustment and absence of noteworthy drug interactions make this combination reliable to co-administer **[25]**.

**Table 1: Comparison of incretin-based agents and SGLT-2 inhibitor [26]**

| Parameters | Incretin-based drugs/DPP-IV inhibitor | SGLT-2 inhibitor |
|---|---|---|
| Examples | sitagliptin, saxagliptin, linagliptin, gemigliptin and alogliptin | Canagliflozin, dapagliflozin, empagliflozin, Remogliflozin etabonate, Ertugliflozin, Luseogliflozin, Fogliflozin |
| Target organ | Gut | Kidney |
| Mode of action | Inhibition of deprivation of incretins i.e., GLP-1 and GIP | Inhibition of tubular reabsorption of glucose |
| Glucosuria | Unchanged/decreased (due to reduced hyperglycaemia) | Augmented (key outcome) |
| Caloric intake | Slightly reduced (GLP-1- related) | Slightly increased (compensatory) |
| Insulin ooze | Amplified (incretin effect, post-meal) | Reduced (economical effect) |
| Glucagon secretion | Reduced | Amplified |
| Endogenous glucose production | Reduced | Amplified |
| Bordering insulin compassion | Unaffected | Amplified |
| Fasting plasma glucose | Slightly reduced | Reduced |
| Postprandial plasma glucose | Reduced | Reduced |
| HbA1c | Reduced | Reduced |
| Body weight | Unaffected | Reduced |
| Systolic blood pressure | Unaffected | Reduced |
| Lipid profile | Almost unaffected | Almost unchanged |
| Serum uric acid | Unaffected | Reduced |
| Cardiovascular outcomes | Non-inferiority versus placebo | Preeminence versus placebo |
| Hospitalisation for heart failure | Amplified | Reduced |
| Mortality (cardiovascular and all-cause) | Unaffected | Reduced |
| Renal events | Not stated | Reduced |

**Table 2: Complementary pathways of SGLT-2 inhibitors and incretin-based [27]**

| Mediating Pathways | SGLT-2 Inhibitor | Incretin-based agents |
|---|---|---|
| Glucose-dependent insulin release | -- | Yes |
| Glucose-dependent decline in glucagon secretion | -- | Yes |
| Improved glucagon secretion | Yes | -- |
| Augmented glucosuria | Yes | -- |
| Improved β-cell sensitivity/function | Yes | Yes |
| Reduced glucotoxicity | Yes | -- |
| Impede incretin hormones' (GLP-1, GIP) deprivation | -- | Yes |

**Advantages of combining incretin-based therapy with SGLT-2 inhibitors [26]:**

1. Incretin-based therapy and SGLT-2 inhibitor combined remedies are more effective than individual therapies to regulate blood glucose, without deteriorating the safety contour.

2. Combination provides complementary or synergistic mechanisms of action for effective treatment of T2DM. These drugs do not interact with each other and hence no modification in pharmacokinetic and pharmacodynamic profile of drugs been observed. This is basically due to dissimilar

mode of action and boarding different paths in the pathological course.

3. This combination is usually well acceptable without any integrated menace of hypoglycemia [as no insulin secretion through SGLT-2 inhibitors **[28-29]** and glucose dependent insulin secretion through incretin-based agents **[30-32]**, cardiovascular events, or weight gain (SGLT-2 inhibitors are capable of promoting weight loss and incretin-based agents are weight unbiased **[33-36]**.

4. The addition of an incretin-based therapy (responsible for glucagon inhibition and stimulation of insulin release) may have the caliber to block the upsurge in endogenous glucose production and boost the glucose-lowering capacity of SGLT-2 inhibitor. Altogether, these conclusions recommend that the blend of incretin-based therapy with a SGLT-2 inhibitor would certainly offer added benefit to type-2 diabetic patients in attaining their glycemic goal.

5. No need of dose adjustment and absence of noteworthy drug interactions make this combination reliable to co-administer.

6. Combination of incretin-based agents with SGLT-2 inhibitors own promising efficiency and safety profile for T2DM treatment.

7. The well admissibility of this blend, specifically due to no integral menace of fattening and minimum peril of hypoglycemia, make this combination as a choice for initial remedy strengthening in T2DM.

8. The combination of SGLT-2 inhibitor plus incretin-based therapy has the caliber to produce a vigorous $HbA_{1c}$ reduction. This combination supports the findings that SGLT-2 inhibitor associated glucosuria is allied with an upsurge in the rate of endogenous glucose production (EGP), which further counterbalances the glucose-lowering outcome by around 50%. As incretin-based agents impede glucagon secretion and decrease EGP, consequently the combination of incretin-based agents plus SGLT-2 inhibitor would thwart the rise in EGP ensuing SGLT-2 inhibition and result in an additive, even synergetic effect to decrease $HbA_{1c}$.

In one-on-one study SGLT-2 inhibitors were found superior in reducing glycemic levels than incretin-based agents **[30, 37-39]**. {Study results are summarized below in **Table 3**).

**Table 3: SGLT-2 inhibitor and glycemic level reduction [30, 37-39]**

| S. No. | Drug/ Drugs in combination | Reduction in $HbA_{1c}$ |
|---|---|---|
| 1. | Saxagliptin | 0.9% |
| 2. | Dapagliflozin | 1.2% |
| 3. | Saxagliptin+Dapagliflozin | 1.5% |

9. The combination of incretin-based therapy and SGLT-2 inhibitors also has the competence to have advantageous effects on the kidney. Both categories of drugs have been testified to lower one of the causes of renal disorder i.e., urinary albumin excretion **[40-43]**.

10. A single-pill combination of an incretin-based therapy and a SGLT-2 inhibitor, would deliver numerous benefits over the individual medications, including a reduced pill burden, which could conceivably render into upgraded obedience.

11. Studies are being going on the use of these drugs as supplementary to insulin therapy in Type 1 Diabetes due to immunomodulatory outcome of incretin-based agents and renal action of SGLT-2 inhibitors **[44-45]**.

12. No need of dose titration which is a curse in anti-diabetic therapy.

**Limitation of combining incretin-based therapy with SGLT-2 inhibitors [34]:**

1. Practically, the reviving effect of the SGLT-2 inhibitor overseeds the restraining effect of the incretin-based therapy on endogenous glucose production and consequently most of the hypoglycemic effect of the incretin-based therapy is vanished. Additional studies are essential to evaluate this premise.

2. In the presence of magical antidiabetic drug Metformin and available combinations with metformin, these agents together are not so effective in lowering HbA1c to the extent of metformin and its combinations. Though metformin failure makes this combination suitable for candidates having metformin intolerance.

3. Each drug in these categories cannot be combined safely like vildagliptin has dosing frequency twice daily while the SGLT-2 inhibitors have dosing frequency once daily only.

4. Incretin-based agents can be used in all grades of renal inadequacy (however in some cases dose titration is needed), whereas the SGLT-2 inhibitors are restricted to some grades of renal failure. Combination of Linagliptin with SGLT-2 inhibitor is hypothetically supreme. Linagliptin + canagliflozin (Glomerular filtration rate 30 ml/min/1.73 $m^2$).

Linagliptin + dapagliflozin/empagliflozin (Glomerular filtration rate 60 ml/min/1.73 $m^2$). of Saxagliptin + Dapagliflozin (Glomerular filtration rate of 60 ml/min/1.73 $m^2$ and not beyond)

5. The high cost of the combined therapy is also one of the keys restrain to its use.

The FDA approved available combinations of incretin-based agents and SGLT-2 inhibitors are presented in **Figure 2**.

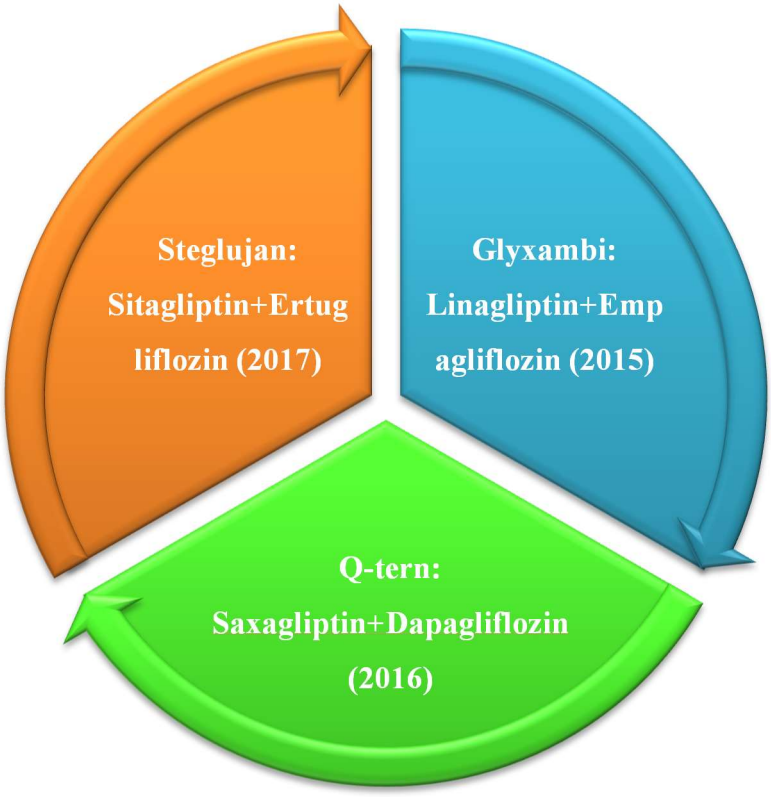


**Figure 2: FDA approved available combinations of incretin-based agents and SGLT-2 inhibitors**

## SYNERGISTIC NANOTHERAPEUTICS

Keeping in mind the advantages of nano-delivery system, various plant-based as well as allopathic drug based nanoparticulate anti-diabetic therapy has been formulated either as single therapy or combination therapy. Nanoparticles containing turmeric, berberin, ursolic acid, silymarin, quercetin etc. are some examples of plant-based nanoparticles, while insulin, metformin, GLP-1, glitazones etc. based nanoparticles have also been synthesized with better drug loading, bioavailability, safety and efficacy. Incorporation of nano-delivery into conventional anti-diabetic therapy resolves the major cons like fast drug-release into the blood stream and low bioavailability associated with conventional therapy.

Owing to their unique characteristics, the application of nano size system has been reported in variety of fields **[46-49]**. An effective nano drug delivery must have stability, non-toxicity, biodegradability, lack of immunogenicity and thrombogenicity and readily escaped by reticuloendothelial system. Nanomedicines provides multiple advantages such as improved permeability of poorly water soluble drugs, transcytosis of drugs across the tight intestinal barrier, targeting of drugs to the specific part of the

gastrointestinal tract, upsurged efficacy, tolerability, specificity and therapeutic index of drugs and improved oral absorption of proteins and peptides **[50-52]**. Several nano-particle based drug delivery for insulin delivery have been formulated using natural, synthetic polymeric system as well as inorganic nanosystems **[53-59]**. Some of the examples include chitosan based nanoparticles **[60-63]**, alginate based nanoparticles **[64-65]**, dextran based nanoparticles, synthetic polymeric nanoparticles (PLGA based nanoparticles, PLA based nanoparticlesv **[66]**, PAA based nanoparticles) **[67-70]** etc.

All these advanced nano-techniques improve the bioavailability of oral anti diabetic drugs by various mechanisms discussed earlier.

The entire review supports the dual therapy of incretin-based agents with SGLT-2 inhibitors. As it is having numerous advantages which subsides few disadvantages of the therapy. In a groundbreaking advancement, the authors have harnessed the power of nanotherapeutics to fuse Sitagliptin and empagliflozin into a potent combination **[71]**. The synergy observed the effects of individual drug products. This novel pairing not only offers enhanced therapeutic benefits but also proves to be a cost-effective breakthrough, making a significant stride in the pursuit of comprehensive T2D management.

## CONCLUSION

The combination of Incretin based agents along with novel SGLT-2 inhibitors may emerge as a model combined therapy for T2DM. These drugs do not interact with each other and hence no modification in pharmacokinetic and pharmacodynamic profile of drugs been observed. This is basically due to dissimilar mode of action and boarding different paths in the pathological course. The well admissibility of this blend, specifically due to no integral menace of fattening and minimum peril of hypoglycemia, makes this combination as a choice for primary treatment strengthening in T2DM. Hence the combined therapy may deliver the best effects with minimum adverse effects.

In nutshell, incretin-based agents and SGLT-2 inhibitors in combination therapy improves glycemic regulation and reduces body weight deprived of increasing the peril of hypoglycemia and urinary tract infection in patients with ineffectively controlled T2DM. Further research in this direction will aid this combination as first choice treatment strategy for T2DM.

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