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ROLE OF NOVEL DRUG DELIVERY SYSTEMS IN INSULIN RESISTANCE

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ABSTRACT: Reduced sensitivity of muscles or tissues to insulin is known as insulin resistance. The non-pharmacological management of diabetes, which involves exercise and food modification, has been the primary emphasis of diabetic self-management. Pharmacological therapy includes combination products, phytoconstituents, and oral antihyperglycemics. The limitations of currently available drugs have caused the pharmacological and non-pharmacological methods of treating hyperglycaemia to constantly change. The goal of this review is to observe many cutting-edge medication delivery approaches for the treatment of insulin resistance (IR). The development of nanocarrier delivery methods has revolutionized drug administration by addressing concerns such as limited bioavailability of classic dose forms used in diabetes therapy. Through enhancing insulin delivery specificity to target tissues, these systems aim to reduce side effects and optimize treatment efficacy. Because insulin is administered to specific cellular sites via nanocarriers and nanoparticles, this technique strongly depends on nanotechnology. The anti-inflammatory and anti-insulin-resistant properties of phytonutrients in macrophages and adipocytes are enhanced by nanoformulations. An effective vehicle for phytochemicals to stop T2DM in its early stages is the nano-phytosome. Niosomes reduced the expression of Retinol Binding Protein 4 (RBP4), increased the expression of leptin, adiponectin secretion and AMP-activated protein kinase (AMPK), and glucose intolerance and improved insulin resistance. The technology's innovative approaches pave the way for more tailored and efficient treatments, offering those with insulin resistance hope for improved outcomes and a higher standard of living.

INTRODUCTION: A condition where there is decreased responsiveness in the insulin-targeting tissues to the high insulin levels is called as insulin resistance (IR). It is the cause of various modern diseases, such as atherosclerosis, nonalcoholic fatty liver disease (NAFLD), metabolic syndrome, and type 2 diabetes [1].

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Main clinical symptom of Type 2 diabetes (T2DM) is non-physiologic elevated plasma glucose- levels, which comes before insulin resistance (IR). Levels of insulin rise in case of prediabetes to satisfy normal insulin, which causes hyperglycemia-induced β-cell failure, chronic hyperinsulinemia, ultimately type 2 diabetes mellitus.

Remarkably, insulin-resistant tissues do not exhibit the glucose-regulating effects of the insulin at normal plasma-levels, including the suppression of HGP, cellular uptake of plasma glucose, lipolysis, net glycogen-synthesis [2]. These tissues are very essential for understanding the mechanisms of insulin resistance (IR) because of the skeletal

muscles that are the central tissue for insulin-stimulated glucose-clearance and adipose tissue and liver are qualitatively acute sites for glucose induced insulin-signalling.

Mechanisms of Insulin Resistance: Possible routes include genetic polymorphism, IRS proteins, PIP-3 kinase, and down regulation of the insulin receptor's tyrosine phosphorylation. Anomalies in GLUT 4 activity could also be involved [3].

Muscle: Decreased intracellular glucose translocation plays a major role in the deficiency of muscle glycogen synthesis observed in the insulin resistance [4]. While this is achieved at cost of the hyperinsulinemia in this hyperinsulinemic euglycemic clamp research, investigation found no differences in protein turnover among insulin-resistant (IR) Type 2 diabetes and the controls [5]. Impaired GLUT-4 translocation leads to the impaired insulin-mediated glucose transport, suggesting that muscle cells, adipocytes have main abnormalities in the insulin action [4].

Adipose Tissue: Adipose tissues secretes additional cytokines along with to free fatty-acids, and they show systemic-effects on insulin resistance (IR). The effects of the insulin resistance on the adipose tissues are comparable, but in liver, elevated free fatty-acid flow leads to enhance the synthesis of hepatic VLDLs [6]. Whereas compensatory hyperinsulinemia usually decrease the ketogenesis. Moreover, peripheral absorption of triglycerides from very low density lipoproteins is diminished due to of insulin resistance (IR) damages the lipoprotein-lipase activity as it is insulin-dependent. The documented hyper-triglyceridemia of insulin-resistance (IR) is an outcome of these processes [7].

These include leptin, plasminogen-activator inhibitor 1 (PAI-1), TNFα, IL-6, adiponectin (Adn), which are linked with the decreased and increased insulin resistance, respectively [8]. The insulin-signalling, endothelial function, lipolysis are compromised by the TNFα, IL-6. The way that different adipose tissue storage react to the insulin varies. The Adipocytes derived from persons with diabetes and insulin resistance (IR) exhibit decreased GLUT 4 translocation, compromised intracellular-signalling through decreased expression of the IRS-1 gene, protein, defective PIP-3 kinase and Akt (protein kinase B) in response to the insulin [9].

Liver: All the lipid portions are impacted by some lipid defects linked to insulin resistance. Their characteristics include decreased HDL, cholesterol, tiny dense low density lipoprotein particles, increased postprandial triglyceride-rich residual lipoproteins, and elevated fasting triglyceride levels. In the insulin-resistant atherogenic dyslipidemia, an excess of apo B and enhanced synthesis of VLDL, triglycerides in the response to enhanced supply of free fatty-acids to the liver. This contains apo B-containing VLDL particles. Decreased high density lipoprotein particle size is linked to decreased cholesterol, HDL levels, which are separate risk-factor for cardiovascular disease (CVD) in the atherogenic dyslipidemia. Exchange of triglycerides, VLDL for the cholesterol-esters in the HDL and LDL through the cholesterol-ester transfer protein is related to low high density lipoprotein (HDL) particle size. High density lipo protein (HDL) and Low density lipo protein (LDL) are decreased in size and the cholesterol when triglycerides in them hydrolyze [10]. Because of their higher percentage of apo B and increased oxidation susceptibility, small dense LDL particles have been found to be additional atherogenic.

Novel Drug Delivery System: The efficacy of the conventional drug delivery methods can be compromised by incorrect or else inadequate dosing, the drug metabolism may cause potency to decline or the effects to change, and the target - specificity can be lacking [11]. Due to there advantages in the lowering dosage frequency, improving bioavailability, preventing degradation in an acidic stomach environment, and providing tailored therapeutic efficacy with fewer adverse effects, the field of novel drug delivery systems (NDDSs) has lately grew popularity [12]. While several Novel drug delivery systems are being studied to treat other diseases, only a small number are stated to treat type 2 diabetes [13].

These are classified as following:

1. Particulate system:

(i) Microparticulate system

(ii) Nanoparticulate system

2. Vesicular system:

(i) Liposomes

(ii) Niosomes

The particulate system contains the little structures which can carry drugs inside the cells and also when ligands are coupled to the certain receptors, the molecules are recognized by receptors. As a result, thes are thought to be the most ideal delivery systems for anti-diabetic medications. Targeted drug release at intended location is done by microparticle-based treatment. By adjusting drug's release-rate and these systems preserve the drug's concentration in the plasma. Due to the smaller-size and the higher-surface to volume-ratio, microparticles are used to improve the dissolving of the insoluble medications [14]. Microparticulate systems are transported transcellularly *via* endocytosis mediated by receptors or carriers. Since microparticles are too large to pass through mucosal membrane tight junctions to enter the cells by the paracellular transport and nanoparticulate systems have a higher intracellular absorption than themicro particulate systems [15]. Microparticulate systems are transported transcellularly by receptor- or carrier-mediated endocytosis. Microparticles are too large to pass through a tight-connections in a mucosal membrane to enter the cells by paracellular transport; in contrast, nanoparticulate-systems have an increased the intracellular absorption than that microparticulate-systems [16].

Conventional dosage forms exhibit increase in dosage and poor availability, instability, first pass effect, drug level fluctuations in the plasma, and rapid release of medication. Three NDDS will lessen the issues. Due to rising environmental performance of the human-made NDDS and growing awareness of their possible consequences on the human health and the environmental sustainability, NDDS are presently of attention.

Nanoformulations and Insulin Resistance: Main traditional drug classes for treatment of the hyperglycemia include sulfonylureas that increase discharge of the insulin from the pancreatic islets, the biguanides, which decreases production of the glucose in the liver, PPARγ agonists, which enhance the action of insulin, and the α-glucosidase inhibitors, which prevents absorption of the glucose in the stomach [17]. Those medication groups are moreover used along with other hypoglycemics or as monotherapy.

Disadvantages of the conventional medicines are:

1. Increased hypoglycaemia
2. Weight-gain
3. Decreased therapeutic efficacy due to a inappropriate or a ineffective dosage regimen
4. Decreased potency
5. Altered side-effects due to drug-metabolism
6. Lack of the target-specificity
7. Low permeability and solubility [18].

Even with introduction of favourable anti-hyperglycemic medications, decreasing major problems associated with the diabetes mellitus (DM) and improving the effectiveness of already existing treatments to confirm optimal glucose concentrations remain the main difficulties for effective diabetes care [19]. Under such circumstances, nanoformulations have a history of avoiding the problems mentioned above with the regard to the use the traditional-medications [20]. A number of the shortcomings of the current anti-diabetics can be addressed by nanoformulations, which increase the drug's solubility while also offering a host of other advantages like controlled the drug - release profile, accelerated onset of action, decreased dosage, life reduced patient variability, fewer side-effects, enhanced drug-delivery, extended drug-half-life and enhanced bioavailability [14]. Remarkably, other reports have indicated that the nanoformulations frequently function on the molecular level to enhance cellular drug-uptake, interfere with efflux-mechanisms like the target specific receptors or P-glycoprotein (P-gp) pump, all of which enhance the pharmacokinetics (PK) and pharmacodynamics (PD) profile of various anti-diabetic molecules [21].

Liposomes: Liposomes are bilayered, vesicles that are condensed as well as have an entirely enclosed in aqueous volume. A lipid bilayer membrane made

mostly of natural or synthetic phospholipids. Microparticulate or colloidal carriers, usually ranging from 0.05 to 5.0 μm in diameter, that arise naturally in aqueous media when these lipids hydrate [22].

Clodronate Liposomes: Vistrial adipose tissue macrophages (VATMs) were efficiently reduced by intraperitoneal (IP) injection of the clodronate liposomes, preventing the weight gain, hepatic steatosis fat-accumulation and insulin resistance (IR) caused by a high-fat diet. In a similar vein, clodronate liposomes enhanced insulin sensitivity and prevented mice from gaining weight after feeding them a high-fat diet [23].

Obesity caused by the high fat diet is commonly characterized by the disorders in metabolism of the fats and carbohydrates. To evaluate how removal of VATMs affects homeostasis of glucose and fat. Measurements of insulin, free- fatty acid, and glucose were done. According to those, it was detected that the rats receiving continuous clodronate liposome treatment, insulin, free fatty acids and low levels of fasting glucose were linked to the reduction of VATMs [24]. Remarkably, the same treatment did not alter the glucose levels or free fatty acids in animals that had previously been fed a high-fat diet. HOMA-IR verified that animals given clodronate liposomes had elevated insulin sensitivity.

A deposition of excess lipids in liver that is associated with visceral obesity. Excess lipid stored in liver results in an inflammatory response by further activating Kupffer cells, which are local macrophages. Furthermore, cell-autonomous insulin-signalling dysfunction is the frequently the outcome of ectopic-fat [25]. Because insulin does not prevent gluconeogenesis in the liver but instead increases lipid synthesis, insulin resistance (IR) in liver is selective [26]. Reduced expression of lipoogenesis and gluconeogenesis-related genes in a mouse liver following VATMs depletion reduced insulin resistance and lessened glucose intolerance.

Niosomes: These smallest structures are called lamellar ones, and are created by adding cholesterol, a nonionic-surfactant, and a charges-inducer to watery media, followed by hydration. Because of the hydrophillic and hydrophobic moiety architecture of the niosomes, the wide variety of pharmacological compounds can be involved. The capacity to minimize clearance from the body by slowing drug release of such agents is one of the significant benefits in clinical use, along with the potential to lessen systemic toxicity by encapsulating therapy medicines [27].

Numerous (hydrophilic, lipophilic, and amphiphilic) substances can be captured by niosomes. The distinct composition of pharmaceuticals). It is simple to keep an eye on niosome characteristics including type, flow, and size. Alteration to the production techniques and structural makeup. Niosomes can be given orally, parenterally, or administratively, among other ways. Accessible in a range of forms, including topical, semisolids, powders, or solutions [28].

Extracts of Anthocyanins Packed inside Non-ionic Niosomes: Anthocyanins-loaded niosomes (ACN/Nios) showed enhanced glucose tolerance and the insulin sensitivity [29]. There was no significant difference in the levels of low-density lipoproteins (LDL) and triacylglycerol (TAG), high-density lipoproteins (HDL) between the treatment groups. On the other hand, mice administered ACN/Nios showed a considerable drop in total cholesterol (CT). Serum levels of adiponectin were unaffected by the treatments. On the other hand, leptin concentrations in mice given ACN/Nios dramatically dropped.

Some of the obesity-related metabolic anomalies were corrected by administering ACN/Nios. Furthermore, among adipose tissue of obese mice, anthocyanin loaded into niosomes decrease production of pro-inflammatory cytokines. Function of Anthocyanin loaded niosomes in T2DM and metabolic syndrome prevention as well as treatment. Through many pathways, ACNs were proved for improving glucose tolerance, dyslipidemia, glycemia, and reverse IR while also protecting β-cell activity [30].

In Muscle as well as adipose tissue, ACNs upregulate PPARγ activation and control GLUT4 upregulation and translocation. They down regulates of retinol-binding protein 4 (RBP4) and up regulates AMP-activated protein kinase, leptin, as well as adiponectin secretion.

Moreover, they prevent the action of pancreatic α-amylase and intestinal α-glucosidase, which lowers the absorption of carbohydrates and simulates calorie restriction. Similarly, ACN's anti-inflammatory properties are linked to decreased levels of the MCP-1, TNF-α and IL6 in the adipose tissue, most likely through altering the AMPK pathway [31]. The presence of ACNs in niosomes indicates their biological activity. Because the animal group treated with ACN-Nios experienced a reduction in fasting blood glucose and the insulin amount and also glucose and insulin intolerance, these nanoparticles appear to improve the bioavailability of ACNs [32]. These findings imply that reversal of the systemic insulin resistance (IR) developed in the animal model is considerably impacted by therapy with the ACN/Nios formulation [33].

Phytosome: Phytosomes were a vesicular delivery system for phytoelectric substances found in herbal extracts and lipid-binding (one molecular phyto-constituent bonded to at least one molecular phospholipid). Phytosomes prevent vital components found in herbal extracts from degrading. Gut bacteria that have increased absorption and digestive secretions offers enhanced biological, pharmacokinetic, and pharmacological properties and enchanced availability. Parameters of a traditional herbal extract [34].

Increased absorption of phospholipid complexes. Improved absorption in the GIT. Enhanced bioavailability is linked fors better treatment outcomes. Minimal dose is necessary for high bioavailability. Increased steadiness. Elevated lipophilicity [22].

Chrysin-Loaded Phytosomes (CP): In C2C12 myotubes, CP increased glucose absorption by upregulating the expression of the GLUT4 and PPAR γ genes [35]. There's a HOMA-IR enhancement in CP, chrysin as well as metformin groups. Those finding suggests the CP, opposed to the chrysin supplementation, were more successful in increasing insulin sensitivity. Both Fasting Blood Glucose and HOMA-IR given a major difference in the CP group [36]. A qRT-PCR used to check the changes in mRNA expression of GLUT4 as well as HK2, and the PPARγ. Metformin as well as CP therapy dramatically resulted in up regulation of the GLUT4 gene[3 7]. Insulin resistance is caused due to PPARγ malfunction, which has an insulin-sensitizing impact [38]. The CP group's skeletal muscle showed an increase in GLUT4 plasma translocations. The aforementioned finding proposes that the amelioration of insulin resistance brought about by CP was because of heightened GLUT-4 translocation and insulin-sensitivity within skeletal muscle [39]. FBG levels and glucose tolerance considerably enhanced by Chrysin phytosomes supplementation. Biomarkers of insulin resistance (IR) surrogate, HOMA IR was decreased, and the insulin levels of Chrysin phytosomes treated subjects were dramatically reduced as well. Chrysin phytosomes increased absorption of glucose of skeletal muscle while suppressing gluconeogenesis through the down regulation of PEPCK [40].

Gymnema Inodorum Phytosomes (GIE Phytosomes): Insulin-resistant adipocytes are subject to an anti-insulin resistance action by GIE nanophytosomes. By stimulating adipocyte inflammation through Toll-like receptor 4, lipopolysaccharide (LPS) can mimic insulin resistance in human obesity by disrupting the uptake of glucose into adipocytes through the insulin-dependent glucose transporter type 4 (GLUT4) [41]. Lipid cells has ability for absorbing glucose is reduced as a result of damage to Glucose transporter 4 (GLUT4) [42]. The LPS-induced adipose cells model's insulin sensitivity was increased by GIE. Following treatment with GIE, LPS-induced adipocytes showed a notable elevation in the uptake of the glucose by the cells [43].

Alternatively, the phytosome carrier may transport the insulin-mimetic chemicals in the GIE into cells by influencing GLUT4s' embedding on adipocyte cell membranes [44]. As a amount of the glucose absorbed through inflammatory adipocytes rose to the similar level as the subjects receiving insulin treatment, a reduced dosage of Gymnema inodorum extract appears to have antiinsulin-resistance effects. Low amount of glucose was transferred by cells, and lipid breakdown was enhanced [45].

Exosomes: Extracellular vesicles (EV) called exosomes transfer the signal molecules from the

donor to receiving cells [46]. Exosome cargo loading, which includes proteins, RNA and DNA47. Can affect recipient tissues and the organs, which are crucial in the genesis of disease.

Mesenchymal Stem Cells Derived Exosomes: Exosomes derived from human umbilical cord mesenchymal stem cells (hucMSC-ex) have been shown to potentially treat type 2 diabetes. They discovered that giving mice with type 2 diabetes an injection of hucMSC-ex considerably reduced their hyperglycemia. By enhancing the stimulation of p-IRS-1 andthe p-AKT and inhibiting the release ofthe proinflammatory- cytokines, which may prevent the stimulationof insulin signalling pathway, HucMSC-ex may improve insulin sensitivity [48].

By influencing GLUT4 and other enzymes involved in glucose metabolism's membrane translocation, these exosomes may enhance skeletal muscle's absorption of glucose and glycolysis [49]. By enhancing insulin signalling, hucMSC-ex improved hepatic glycogen production by up regulating the expression of glycogen synthase and p-GSK3β. Moreover, hucMSCex has the ability to prevent STZ-induced β cell death in addition to stimulating insulin secretion[50]. Exosomes from hUC-MSCs elevates the expression of SIRT-1 as well as adiponectin that enhances insulin sensitivity in human adipocytes [51]. Insulin sensitivity was enhanced by injecting exosomes produced from lean mice's macrophages, which stimulated the peroxisome proliferator-activated receptor (PPAR)-γ [52]. Exosomes' positive effects on insulin resistance most likely stem from their ability to regulate adipocytokines [53].

Nanoparticles: Nanoparticles are defined as nano-objects having all external dimensions in the nanoscale, where the longest and shortest axis' lengths do not significantly differ from one another. When there is a significant difference in dimensions, usually greater than three times [54]. Natural, synthetic, and semi-synthetic polymers make up the Colloidal Framework for Drug Delivery Nanoparticles (NP). The diameter of NP particles ranges from 10 nm to 1,000 nm in size [55].

Gadofullerene Nanoparticles: In diabetic mice, the mRNA expressions of Akt2 and Ampk were clearly down-regulated, whereas in GFNP therapy both are markedly increased. The AKT and AMPK signalling pathways to interpret GFNPs' potential anti-T2DM action [56]. In diabetic mice treated with GFNP, AMPK phosphorylation was increased in the Western blot (WB) but down regulated in other tissues. After receiving GFNP therapy, the mRNA expressions of two upstream signalling molecules Akt2, Irs2, and Pi3k were markedly elevated [57].

Ginger Nanoparticles: Insulin-resistant syndrome patients with chronic hyperinsulinemia cause Foxa2 to be inactivated [58]. And localized in the cytoplasm, which increases hepatic lipid build-up and insulin resistance. Insulin/PI3K/AKT-mediated phosphorylation at the threonine 156 (Thr156) site controls the expression of Foxa2 [59]. In rats given a high-fat diet, ginger-derived nanoparticles (GDNP) can prevent insulin resistance by re-establishing intestinal epithelial homeostasis and hepatic Foxa2 signalling. Because GDNP therapy inhibits Akt-1-mediated phosphorylation of Foxa2, it was able to restore Foxa2 expression that had been altered by the HFD [60].

TABLE 1: MECHANISM OF VARIOUS NOVEL DRUG DELIVERY SYSTEMS IN INSULIN RESISTANCE

Type of delivery system	Name of NDDS	Mechanism	Ref.
Liposome	Clodronate Liposomes	Lower blood glucose, insulin, fatty acids, reduced expression of genes involved in the gluconeogenesis as well as lipogenesis	26
Niosomes	Anthocyanin Extracts Loaded into Non-ionic Niosomes	Regulate the GLUT4 expression and the translocation and also increase PPARγ activation in the adipose tissue and the muscle cells. Up regulates the expression of AMP-activated protein kinase(AMPK), increse the secretion of leptin and adiponectin(Adn) and down regulates the expression of the retinol-binding protein 4 (RBP4).	33
Phytosome	Chrysin-Loaded Phytosomes	PPARγ and GLUT4 activation enhanced glucose uptake in C2C12 myotubes	40
	Gymnema inodorum phytosomes	regulate GLUT4 expression	45
Exosomes	Mesenchymal stem cell derived	increasing activation of p-IRS-1 , p-AKT and also preventing the secretion of proinflammatory-cytokines, by upregulating adiponectin and	

	exosomes	SIRT-1 expression, by activating peroxisome proliferator-activated receptor (PPAR)-γ	50
Nanoparticles	Gadofullerene Nanoparticles	Upregulation of phosphorylation of AMPK,. mRNA expressions of two upstream signalling molecules of Akt2, Irs2, and Pi3k were significantly up-regulated	57
	Ginger nanoparticles	by restoring homeostasis in gut epithelial and hepatic Foxa2 signalling	60

CONCLUSION: Effective management of diabetes and associated metabolic disorders is significantly hampered by insulin resistance (IR), which is stated as a diminished responsiveness of target tissues to the insulin. Low bioavailability, unpredictable pharmacokinetics, and the possibility of hypoglycemia are only a few of the drawbacks of conventional insulin therapy. By optimizing administration, absorption, distribution of insulin, novel drug delivery methods aim to overcome the obstacles. One of the most significant developments in this field is the creation of tailored drug delivery systems. By increasing the specificity of insulin administration to the intended tissues, these systems seek to maximize therapeutic efficacy while reducing adverse effects. This strategy heavily relies on nanotechnology, as insulin is delivered to targeted cellular locations using nanocarriers and nanoparticles. In addition to increasing insulin's bioavailability, this focused administration lowers the total amount needed, which may lessen the chance of hypoglycemia.

Investigating alternate administration routes is a crucial component of innovative medicine delivery strategies for insulin resistance. Although subcutaneous injections have been the conventional method of delivering insulin, research is currently being conducted on alternate delivery methods, including transdermal and oral. One of the major obstacles to effectively managing chronic illnesses may be overcome with the help of oral insulin delivery, which shows promise for increasing patient adherence. Research in this field is still focused on overcoming the obstacles associated with gastrointestinal breakdown and absorption. The new medication delivery approach for insulin resistance has the ability to completely change how this illness is treated. It ameolirates insulin's focused delivery, which reduces side effects while also increasing efficacy. The novel strategies demonstrated by this technology open the door to more individualized and effective therapies, giving those who suffer from insulin resistance hope for better results and an enhanced quality of life.

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