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Ameliorative Effect of Nanoparticles with Trials for Treatment against Diabetic Hepatopathy Systemic Review

Rehab Mahmoud Kher-Eldin[1], Yara Sayed Abouelela[1], Fady Sayed Youssef[2]*, Hamdy Rizk[1] and Samer Mohamed Daghash[1]

[1]*Department of Anatomy and Embryology, Faculty of Veterinary Medicine, Cairo University, Giza, Egypt. Postal code: 12211*

[2]*Department of Pharmacology, Faculty of Veterinary Medicine, Cairo University, Giza, Egypt. Postal code: 12211*

Abstract

BACKGROUND: Nanoparticles (NPs) are minute objects having a diameter ranging from 1 to 100 nm. They can be categorized into several classes according to their shapes, sizes, chemical, and physical properties. NPs used in numerous fields of biology and medicine as tissue engineering, drug delivery, regenerative medicine, furthermore as antimicrobial agents and for detection of biomolecules. To confirm the efficacy and stability of each nanomaterial it requires informational data about physico-chemical properties. Research on nanoparticles has been increased in the last recent years due to its medical ameliorative effect against different pathological and metabolic disorders. The field of bionanotechnology has synchronized with novel regenerative strategies. The high demand for providing suitable cure for diabetes increases the attention toward using various nanoparticles in treatment of diabetes and its complications. **Aim:** Our goal is to collect information regarding various nanoparticles showing anti-diabetic activity. **Methods**: We gathered detailed overview from recent research via different databases (PubMed, Taylors, Google Scholar, Elsevier, Egyptian Knowledge Bank, Springer Nature , Empase, ProQuest), as we focused on the antidiabetic NP papers throughout the Current millennium with special reference to their therapeutic results. Then the collected data were summarised in tables and analysed. And all figures were designed by us through Photoshop and PowerPoint. **Results:** In this review, we focused on the most common nanoparticles approaches for treatment of diabetic hepatopathy like; curcumin, gold (Au-NPs), silver (Ag-NPs), selenium (Se-NPs), zinc oxide (ZnO-NPs), nano-tyrosol, nano-cinnamon, nano-Stevia, as well as Polydatin loaded chitosan nanoparticles. We also summarize the results of the experiments after receiving nanomaterials through blood glucose level (BGL), insulin level, liver function enzymes (ALT, AST, and ALP), lipid profile (TG and TC), and gene expression of both (SOD2 and GPx4). **Conclusion**: The pharmacological and physiotherapy effects of different nanoparticles on diabetes mellitus considered as a very common physiological syndrome which having huge regenerative influence when comparing with other traditional approach for treatment of diabetic hepatopathy.

Keywords: Diabetes mellitus, STZ, Hyperglycaemia, Nanoparticles, Liver injury, Apoptosis.

Introduction

Nanotechnology is a recent science take major interest in the last 15 years, that applied by making small sub-micronic objects, undetectable by the naked eye. Nanoparticles (NPs) are believed as the structural masses of nanotechnology. The scale of their diameter from one to hundreds of nanometres [1-5].

Diagnostic and Therapeutic NPs are classified into two categories: (a) Organic nanoparticles (e.g., liposomes, polymeric, micelles, etc.) and (b) Inorganic nanoparticles (e.g., gold, selenium, silver, zinc oxide, etc.) [6,7].

NPs have many purposes in industrial and biomedical applications for diagnosis and treatment of disease as shown in Fig.(1), also used in drug delivery due to their small size giving them the ability to distribute therapeutics to areas of the body that other forms of drug cannot spread [8, 9].

Recently, Diabetes mellitus (DM) has become one of the most metabolic epidemic threats that cause acute and chronic complaints that directly affect health conditions, quality of life, and huge economic

*Corresponding author: Fady Sayed Youssef, Email: fadyalsalhany@cu.edu.eg , Tel.: 01094572140
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costs leading to mortality throughout the world [10,11]. Otherwise, the incidence of diabetes is due to multiple factors such as genetic and environmental causes. Furthermore overweight, consuming large amounts of food and drinks, insufficient physical activity and stress condition can develop diabetes [12, 13].

Hyperglycaemia is the main characteristic of different categories of DM (type1, 2, gestational diabetes (GDM), and other types of diabetes). It results from pancreatic beta cell destruction that causes a marked reduction of insulin secretion or insulin insufficiency. This squelae linked with an increase of reactive oxygen species exposure (ROS) and hepatic damage, as fatty liver infiltration and steatohepatitis, and increase susceptibility to liver cirrhosis [14].

Serious Metabolic consequences of diabetes are categorized as shown in Table (1) [15-17].

Material and Methods

Ethical approval

Ethical approval for this article from the ethics committees was not applicable because it was a review article and was conducted by gathering and analysing the previous studies.

Methods of collecting data

Our collected data was gathered from various databases (BMC, PubMed, Springer Nature, Egyptian Knowledge Bank, Empase, Elsevier, Medline, and ProQuest) over the last twenty years focusing on the effect of different nanoparticles on diabetic rats with special reference to its effect on the liver cells that have a wide scope data in this field. Also focusing on article about nanoparticles that are effective in curing of diabetes. Our review article was supported by figures to illustrate the data attractively, all figures were designed by us through PowerPoint and Photoshop software programs.

Results

Curcumin nanoparticle

Curcuminoids are the extracted active ingredients from turmeric which represent about 2-9% of it, which gives about 75% curcumin [18]. Curcumin is a bioactive component that originates from turmeric *taken out by solvent extraction method followed by column chromatography* [19].

Curcumin has antioxidant, anti-amyloid, neuroprotective, antineoplastic effect, furthermore immune-modulating, antimicrobial effects and shows antidepressant action by the release of dopamine and serotonin. Also, its significant in protection of the tissue so can be used in the treatment of bacterial and fungal diseases such as mange atopic dermatitis [20-22]. Curcumin is a natural anti-inflammatory agent that has been used for treating medical conditions for many years. Several experimental and pharmacologic trials have proved its efficacy as an anti-inflammatory agent.

Curcumin is effective in treating chronic conditions like rheumatoid arthritis, inflammatory bowel disease, Alzheimer's and malignancies. The anti-inflammatory and antilipolytic properties of curcumin appear in the prevention of fat accumulation in high-fatty diet (HFD) rats and reduced levels of tumour necrosis factor TNF and plasma-free fatty acid (FFA) [23]. In addition to its great effect on DM as an antihyperglycemic, antioxidant, and antiapoptotic effect through rise of G6PDH activity. The latter causes oxidative stress suppression as well as improves β-cell functions, prevent its damage, and declines insulin impedance. Although the beneficial roles of curcumin, its drawbacks are low solubility, low stability, rapid metabolization to inactive metabolites, low penetration power, and poor absorption in the free form in the gastrointestinal tract, this limitation can be solved by using adjuvants, conjugates, stabilizers, and liposomes to achieve the best absorption to reach a desirable level of nano curcumin [24] as shown in Fig. (2)

Nanoencapsulation [25] of curcumin is an effective technique to reduce hepatic inflammation in STZ-induced rats so it can pass through the blood barrier and give a nine-fold increase in the bioavailability of curcumin; it shows their potential effect on vascular complications of diabetes. They reported that nanocurcumin make a decrease in total cholesterol, body mass index, glycated haemoglobin, plasma triglycerides, plasma malondialdehyde (MDA), Tumor necrosis factor (TNF-α), interleukin 6(IL-6) levels, Very low-density lipoprotein (VLDL-c), low-density lipoprotein (LDL-c), High-density lipoprotein (HDL-c) and serum C reactive protein (CRP). Shown different experiment on antidiabetic effect of nano-curcumin in Table (2).

Gold nanoparticle (Au-NPs)

In the last few years, there has been an increase in attention on gold nanoparticles due to their small size with a large surface area that controls the electric character and its unique optical properties [34,35]. Gold nanoparticles (Au-NPs) have suppressing effects on antiglycation, transforming growth factor-β, and antiangiogenic and anti-inflammatory effects.

In addition to antioxidant and anti-hyperglycaemic effects of Au-NPs were noted in the amelioration of several disease conditions as in diabetes models, Alzheimer's disease, and wound healing [36].

AuNP treatment successfully interrupts different causes of diabetes in animal models and its complications. The review provides the probable applications of AuNPs, which can help to halt the prevalence of diabetes. As Shown in Table (3)

Silver Nanoparticles (AgNPs)

Nano-silver is considered a significant honourable metal that has numerous chemicals, optical, magnetic, physical as well as biological properties [44-46]. Which provides silver to act as an anticancer, antiviral, antioxidant [47], antibacterial (to sterilize the sites of infection) antifungal, in addition to its role as antidiabetic in table (4) [48,49]. The role of silver NPs explained in Fig. (3) and in detail the MOA is antidiabetic in Fig. (4).

Selenium Nanoparticles (Se-NPs)

Selenium is a necessary micromineral for people and boosts innate and acquired immune responses [55]**.** This exerts multiple pharmacological actions through its Integration into selenoproteins. The selenoproteins are essential enzymes for enterocyte and adipocyte differentiation [56,57]. One of the important selenoproteins as selenocysteine may help in understanding the biological changes between SeNPs and its numerous inorganic compounds [58,59]**.**

According to Hwang [60] Selenium nanoparticles (SeNPs) take great attention due to their low toxicity, biocompatible, and unique biological actions that can lessen hyperglycaemia and hyperlipidaemia. Explaining this effect of SeNPs in Fig. (5) and as antidiabetic in Table (5).

Zinc oxide nanoparticles (ZnO-NPs)

Zinc oxide nanoparticles (ZnO NPs) are considered one of the most important metal oxide nanoparticles. They are frequently used in many fields due to their characteristic mechanical and physicochemical properties and biocompatibility. They have been commonly used in biomedical applications, cosmetics, food industry, and electronics [72].

Uses of Nano-ZnO in the Biomedical field as anticancer, antioxidant, anti-inflammatory activities antibacterial ,and antidiabetic shown in details in Table (6) as well as drug delivery, biosensors, and cell imaging [73-76]with describing the role of nano-ZnO against hyperglycaemia in Table (7).

Cinnamon Nanoparticles

Many researchers explained that Cinnamon is one of the most common traditional herbs used for managing diabetes mellitus. Nano-cinnamon showed beneficial anti-diabetic effects through stimulation of β-cells and decreased Blood Glucose Levels by suppressing the reactive oxygen species (ROS) production [98-102].

In addition to the hypoglycaemic properties shown in Table (8), cinnamon has antibacterial, antioxidant, and anti-inflammatory properties. Furthermore, the inhibitory influence on pancreatic amylase and intestinal glucosidases [103,104].

Other nanoparticles:

Nano-tyrosol

Tyrosol has antioxidant, anti-inflammatory, and anti-diabetic effects as well as, it has neuroprotective, anti-cancer, and cardioprotective effects [109,110].

Nano-Stevia

Stevia is a natural traditional plant characterized by its sweet taste that affects the blood glucose level so we can use stevia in nano form in case of diabetes and other health problems such as high blood pressure, memory improvement, and anxiety [111-117].

PD-CSNPs (polydatin-loaded chitosan nanoparticles)

A recent investigation showed that CSNPs are favorable nanocarriers with nontoxic effects for PD delivery against T2DM [118].

PD has anti-inflammatory and antioxidant effects via controlling free radicals' production, and mitochondrial function as well as defends against heart, kidney damage and brain injury [119].

Conclusion

This review discusses the influence of several nanoparticles as antidiabetic, antilipolytic, antioxidant as well as inflammation reduction.

We gathered approximately 63 studies over the previous 24 years, 22 of which focused on zinc oxide nanoparticles, which are regarded the most utilized to regulate and cure diabetic hepatopathy (Fig. 6).

The declarations

Affirmation of ethical standards

Due to the fact that this article was a review article that drew on data from previous studies, no ethical approval was needed from the ethics committees.

The manuscript was read and approved by all authors who consented to participate.

The manuscript was read and approved by all authors prior to publication**.**

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Authorship contribution statement

The article idea was created by Daghash S and Rizk H. The research was designed by Rizk H and Rehab M. Kher-Eldin, the review data was collected, and the manuscript draft was revised by Fady S and Abouelela YS. The final version of the manuscript was reviewed and approved by all authors.

List of abbreviations:

DM	Diabetes Mellitus	STZ	Streptozotocin
T2DM	Type Two Diabetes Mellitus	G6PD	Glucose 6 Phosphate Dehydrogenase
T1DM	Type One Diabetes Mellitus	HFD	High Fat Diet
ROS	Reactive Oxygen Species	TNF	Tumor Necrosis Factor
GDM	Gestational Diabetes Mellitus	FFA	Free Fatty Acids
VLDL	Very Low-Density Lipoprotein	MDA	Malondialdehyde
CRP	C Reactive Protein	HDL	High-Density Lipoprotein
BUN	Blood Urea Nitrogen	GLUT4	Glucose Transport 4
SOD	Superoxide Dismutase	AMPK	AMP-Activated Protein Kinase
NP	Nanoparticles	PTP1B	Protein-Tyrosine Phosphatase 1B
LEA	Lower-Extremity Amputations	PAD	Peripheral Artery Disease
ESRD	End-Stage Renal Disease	NEFA	Non-Esterified Fatty Acids
INSR	Insulin Receptor	GLUT2	Glucose Transporter2

TABLE 1. Shows the main complications of diabetes

a) Microvascular Complications	Nephropathy reaches end-stage renal disease (ESRD), neuropathy, retinopathy, lower-extremity amputations (LEA), and liver disease.
b) Macrovascular Complications	Stroke, cardiovascular disease, peripheral artery disease (PAD) ,and atherosclerosis
c) Miscellaneous Complications	Cardiomyopathy, coronary artery disease, and hypertension.

TABLE 2. Summarize the mechanism of action of Nano-curcumin as antidiabetic material

Animal	MOA (role of curcumin)	Induction of diabetes	Treatment by Nano-curcumin	Result	References
Male rat	Anti-apoptotic and antidiabetic effects.	IP injection of 65 milligram per kilogram of STZ	Taken 50 and 300 milligram per kilogram) Per os for 30 days.	↑BGL, glycated haemoglobin, and insulin level. ↑pancreatic G6PDH activity and GSH level. ↓caspase-3 levels. ↑Pancreatic MDA and caspase-3 levels	**Kamel** [26]
Wistar rats	Hypoglycaemic and hypolipidemic	55 milligram per kilogram·b.w. of STZ	Given orally 300 milligram per kilogram·BW For 56 days	Dyslipidaemia ↓BGL and HBA1c. ↓MDA	**Patumraj** [27]
Wistar rats	Antioxidant, Antidiabetic and inhibitor of tumor initiation	45 milligram per kilogram·b.w. of STZ	0.5% curcumin in diet for 16 weeks	↑FBG, urine sugar, and urine volume. ↓ N-acetyl-β-D-glucosaminidase in liver, and Acid phosphatase activity	**Chougala** [28]
Male Wistar rats	Hypoglycaemic and hypolipidemic	IP injection of Nicotinamide (110 milligram per kilogram) and STZ (45 milligram per kilogram) in fasting rat.	(100 and 200 milligram per kilogram) given daily for 28 days	↓ lipid profile, insulin resistance, and serum level	**Shamsi-Goushki** [29]

Adult male Wister rats	antioxidant &antidiabetic	60 mg⁄kg b.w. of STZ	40-160 milligram per kilogram For 56 day Given orally	↑ALT AST LDH ALP and caspase-3 levels. ↓albumin Enzymes return to normal and albumin. ↓caspase-3 levels	**Ghosh** [30]
Adult female albino rats	Hypoglycaemic	STZ 50 milligram per kilogram b. wt.	15 mg/5 ml/kg/b.w.	↑gene expression of insulin and insulin receptor	**Gouda** [31]
Adult male Wistar albino rats	Hypoglycaemic	STZ 65 mg/ kg body weight	100 milligram per kilogram/day for a month	↓ blood glucose ↑ blood insulin level.	**Metawea** [32]

TABLE 3. Summarize the mechanism of action of AuNPs as antidiabetic material

Animal	MOA of AuNPs	Induction	Treatment by AuNPs	Result	References
Male albino rats	anti-diabetic	IP injection of Alloxan (150 milligram per kilogram b.w.)	AuNPs (0.25, 0.5, 0.75 and 1.0 milligram per kilogram b.w.) for 28 days	↓BGL, cholesterol and TG. ↑ Plasma insulin level.	**Venkatachalam** [35]
Male albino rats	hypoglycaemic	subcutaneous injection of STZ (6 mg/100 g b.w.)	(0.5 - 1 ml) AuNPs and 0.5 ml Ag for 21 days through gastric intubation.	↓BGL ↓ TG, total cholesterol, LDL. ↑HDL ↑serum insulin and glucokinase.	**Shaheen** [37]
Wistar albino rats	antidiabetic	alloxan (100 milligram per kilogram b.w.) T2DM	AuNPs (0.5 milligram per kilogram b.w.) given orally	↓BGL ↓cholesterol, triglycerides and LDL-c levels and ↑HDL-c levels	**Karthick** [38]
Adult Wistar rats	anti-diabetic	IP injection of STZ (55 milligram per kilogram b.w.)	AuNPs 10-20 milligram per kilogram b.w.	↓BGL and glycosylated haemoglobin. ↑insulin content ↓ AST, ALT, and ALP To the normal range. ↓serum creatinine ↓glucose-6-phosphatase, fructose 1,6-bisphosphatase function. ↑ hexokinase.	**Guo** [39]
Adult male Sprague–Dawley rats	hypoglycaemic	IP injection of STZ (45 milligram per kilogram) T2DM	AuNPs (2.5 milligram per kilogram) for 21 days	↓BGL ↓ PEPCK mRNA expression ↓ liver function enzymes	**Ayyoub** [39]
Wistar albino rats	antihyperglycemic	IP injection of STZ (70 milligram per kilogram b.w.) T2DM	AuNPs (200 milligram per kilogram) for 28 days	BGL restored to normal ↓ TC, TG, LDL, VLDL, and ↑HDL levels ↓ALP, ALT, and AST ↓Urea, uric acid, and creatinine	**Seetharaman** [41]
Wistar Albino rats	hypoglycaemic	Single IP injection of alloxan (100 milligram per kilogram b.w.) T2DM	AuNPs (0.5 milligram per kilogram b.w.) for 28 days.	↓ BGL ↓ Serum GPT, serum GOT, ALP, and creatinine. ↑insulin and total haemoglobin. ↓cholesterol, triglycerides, and LDL–c levels ↑HDL–c	**Dhas** [42]
Male albino		IP injection of	Au-nano	↓BGL	**Abdel-Halim**[43]

Western rats	hypoglycaemic + Antioxidant + hypolipidemic	STZ (60 milligram per kilogram b.w.) single dose	extract (2.58 ml/kg) with ethanolic B. variegata extract	↑insulin level ↓TC, TG, and LDL-c. ↑HDL-c. ↓AST, ALT, ALP, urea, and creatinine. ↑total protein. ↑antioxidant enzymes, GSH, and ↓TBARS levels.

TABLE 4. Summarize the mechanism of action of AgNPs as antidiabetic material

Animal	Effect of silver NPS	Induction	Treatment by AgNPs	Result	References
Male Wistar rat	anti - hyperlipidaemia + anti-hyperglycaemic	IP injection of STZ (40 milligram per kilogram)	given orally (100-200 milligram per kilogram /b.w.) of AgNPs for 14 days.	↓BG ↓TC, TG, and LDL levels. Insulin level Returned to normal	**Shanker** [50]
Male Wistar rats	anti-diabetic	IP injection of STZ (40 milligram per kilogram)	100-200 milligram per kilogram herbal-mediated silver nanoparticles (20 to 100 nm)	↓BGL ↓TC, TG, and LDL levels. ↑HDL levels. Insulin levels restored to normal level.	**Kalakotla**[51]
Male Wistar albino rat	antidiabetic	IP injection of alloxan)200 milligram per kilogram b. w.)	phytosynthesised silver NPs 10 milligram per kilogram/b.w. for 21 days.	↓BGL TC, and TG levels return to normal	**Sengottaiyan** [52]
Male Wistar albino rats	antihyperlipidemic + anti-hyperglycaemic	IP injection of STZ (70milligram per kilogram b.w.)	cinnamon silver nanoparticles (C-Ag-NPs) (25.0 and 50.0 milligram per kilogram b.w.) for one month	↓FBG. ↓TC, LDL, and, TG levels.	**El-Baz** [53]
Male Wistar albino rats	Antidiabetics improve the cell membrane structure and decrease endothelial dysfunction.	subcutaneously injected of STZ (6.0 mg/100g /b.w.)	given orally of docosahexaenoic acid loaded by silver nanoparticles (DHA/AgNPs) (10 milligram per kilogram b.w./day) for one month.	↓FBG. ↑asymmetric dimethylarginine and nitric oxide levels ↑omega-6 polyunsaturated fatty acids (PUFAs), ↓omega-3 PUFA	**Hussein** [54]

TABLE 5. Summarize the mechanism of action of se-NPs as antidiabetic material.

Animal	Role of Selenium NPS	Induction	Treatment by Se-NPs	Result	References
Adult male Wistar rats	anti-diabetic + anti-hyperlipidaemic	IP injection of 35 milligram per kilogram of STZ	Se-NPs (0.1 and 0.4 milligram per kilogram/b.w.)	↓ BGL ↓lipid profile ↑serum HDL-c level. ↑liver and kidney markers close to normal levels	**Abdulmalek and Balbaa** [61]
Rat	Antioxidant	IP injection of STZ 55 milligram per kilogram b.w.	0.1 mg of SeNPs/kg for 4 weeks	↓ oxidative stress markers (MDA), , lipid peroxidation, and nitric oxide (NO). ↑the activity of SOD, CAT, GPx, and GR ↑gene expression of both SOD2 and GPx4	**Dkhil** [62]
Mice	Antioxidant + anti-diabetic	IP injection of STZ 40 milligram per kilogram/b.w.	SeNPs (10 milligram per kilogram/day) for 6 weeks	↓BGL ↓ALT, AST, and ALP ↓MDA	**Gutiérrez**[63]
Male Wistar rats	hypoglycemic	IP injection of STZ 60 milligram per kilogram/b.w.	SeNPs (0.1, 0.2 and 0.4)milligram per kilogram/BW	↓ BGL ↓ Liver enzymes and kidney. ↓albumin,and creatinine	**Rezaei-Kelishadi** [64]
Male Wistar rat	hypoglycemic	IP injection of STZ 50 milligram per kilogram b.w.	Se-CNPs at a dose (3.5 milligram per kilogram b.wt.) given as 1 ml orally through intra-gastric tube daily for 45 days.	↓serum glucose level ↓TC, TG, LDL, VLDL, NEFA, urea, and creatinine level. ↓ALT and AST.	**Maksoud** [65]
Sprague Dawley rat	hypoglycemic + anti-hyperlipidaemic	IP injection of STZ 35 milligram per kilogram/b.w.	2 mg Se/kg orally through a feeding tube daily for 8 weeks.	↓ fasting BGL ↓ insulin level Liver enzymes returned to normal levels. ↓lipid profile (TC, TG, and LDL-c) and↑serum HDL-c level. The oxidants/antioxidants status near to the normal.	**Mohamed** [66]
Adult female Wistar rats	Hypoglycaemic	IP injection of STZ 45 milligram per kilogram b.w.	Se-NP stabilized in a liposome (0.1 milligram per kilogram b. w.) given orally for 21 days.	↓serum glucose ↓pancreatic MDA, nitric oxide (NO), (TNF-α), and prostaglandin F2α levels. ↑serum insulin, SOD, GPx, CAT, and glutathione reductase (GR).	**Ahmed**[67]
Albino male rats	Hypoglycaemic	IP injection of STZ 45 milligram per kilogram b.w.	0.5 mg/ml of SeNPs for one week. 40 and 50 nm	↓ BGL ↓pancreatic LPO. ↑GPx and GSH levels	**El-Borady** [68]
Adult male albino rats	Hypoglycaemic + anti-hyperlipidemic	IP injection of STZ 55 milligram per kilogram b.w.	0.1 mg of SeNPs/kg given orally for 28 days	↓ BGL ↓ Total lipid,TC , TG, LDL And G6PD. ↑malic enzyme, hexokinase, HDL, and glucose-6-phosphate dehydrogenase activity. ↓serum ALT, AST, and ALP ↓serum uric acid, urea, and creatinine	**Al-Quraishy** [69]
Male ICR mice	anti-diabetic +antioxidant +antilipidemic	intraperitoneal injection of STZ 100 milligram per kilogram bw	Intragastrically given 0.5,2 and 4 mg Se/kg/d for 30 days	↓BGL and insulin levels. ↓serum TG, TC,and LDL-Cand ↑HDL-C. ↑GSH-Px, SOD, CAT	**Zeng** [70]
Adult male Wistar rats	antioxidant	IP injection of STZ 55 milligram per kilogram	0.1 milligram per kilogram body weight	↑ GSH	**Fan** [71]

TABLE 6. Summarize the mechanism of action of Nano-ZnO as antidiabetic material.

Anti-diabetic effect of ZnO-NPs	↑ **Glucose tolerance** **Pancreatic functions** **Insulin sensitivity** **Glucose transporters & sensors**
	↓ **Oxidative stress** **Weight loss** **Inflammation** **Dyslipidaemia** **α-amylase and α-glucosidase activities**

TABLE 7.Describe the role of nano-Zno against hyperglycaemia.

Animal	Role of Znonps	Induction	Treatment by zno-nps	Result	References
Adult Wistar rats	Antidiabetic	Inject in the tail vein (45 milligram per kilogram) And single IP injection of STZ (90 milligram per kilogram)	Given orally Zinc oxide nanoparticles (1, 3, and 10 milligram per kilogram) Once daily for 4 weeks	↓blood glucose levels and NEFA.	**Umrani and Paknikar** [77]
Male Sprague-Dawley rats	Anti-diabetic	Single IP injection of STZ at 70 milligram per kilogram	Zinc-crystallized insulin loaded in hydrophobically modified glycol chitosan (HGC) (insulin, 2 and 5 IU/kg, 1 ml/kg and equal Amount of NP) Insulin to HGC from 0.5:1 to 4:1.	↓BGL ↑ insulin level	**Jo** [78]
Zebrafish adults	Anti-diabetic	Induced with alloxan for diabetics (5, 25, 50, 100, 200, 300 & 400 mg/ml)	Zno nps 1 mg/ml	↓glucose levels	**Jeyabharathi** [79]
Male Wistar rats	Anti-diabetic	Intraperitoneal injected of Nicotinamide (230 milligram per kilogram body weight) Then STZ (65 milligram per kilogram body weight)	Zno nps 10 and 100 milligram per kilogram body weight by two routes of administration, oral and intraperitoneal	↑ insulin level, GLUT-2, and glucokinase. ↓BGL ↓oxidative stress	**Ibarra-Leal** [80]
Syrian albino mice	Anti-diabetic	IP injection Of alloxan (180 milligram per kilogram)	Zno nps (0.1 and 0.5milligram per kilogram IP)	↓blood glucose, TG, LDL, and TC levels ↑HDL	**Amiri** [81]
Male Wistar rats	Antidiabetic	IP injection Of STZ (50 milligram per kilogram)	Zno (1, 3, and 10 milligram per kilogram)	↓blood glucose Restored serum catalase ↑insulin levels, SOD	**Nazarizadeh and Asri-Rezaie** [82]

Male Wistar rats	Antidiabetic	Single intraperitoneal dose of STZ (60 milligram per kilogram/body weight (b.w.)	Zno nps (5 mg of Zn/kg b.wt) Daily single oral dose via gavage for one month	↓BG and ↑serum insulin ↓AST, LDH, and CK-MB levels ↓CT, TG, and LDL-ch levels ↑HDL-Ch	**Shaban** [83]
Male albino rats	Antidiabetic	Single intra peritoneal dose of streptozotocin (50 milligram per kilogram)	A single daily oral dose of 5-10 milligram per kilogram Zno nps for 30 days	↓BG, and MDA. ↑serum insulin levels	**Hussein**[84]
Male Wistar rats	Anti-diabetic	Single intraperitoneal injection of STZ (60 milligram per kilogram) Then after 15 minutes give nicotinamide (95 mg/ kg)	Zno nps at a low dose (1milligram per kilogram) Orally for 30 days	↓BG, and MDA. ↓TC, TG, LDL-c, and VLDL ↑serum insulin levels, SOD, GPX, and CAT, and HDL-c	**Kamal**[85]
Adult male albino rat	Anti-diabetic	Single intraperitoneal injection of STZ (50 milligram per kilogram)	Zno nps (10 mg/ kg body weight/day) by gastric tube	↓blood glucose ↑serum insulin levels ↓TNF-a, ,IL-1b and IL-6	**Wahba**[86]
Male Wistar rats	Antidiabetic	Rats fed a high-fat diet that was treated with a low dose of streptozotocin).	Zno nps at doses of 1, 3, and 10 milligram per kilogram/day Given orally	↓plasma glucose levels ↑serum insulin levels ↑hba1c levels Not induce a significant change in the serum lipid profile	**El-Gharbawy**[87]
Male adult albino rat	Anti-diabetic	Ip of 110 milligram per kilogram nicotinamide administration 15 min before IP 65 milligram per kilogram STZ injection	Zno nps (10 mg/ kg/orally/day)	↓serum glucose levels and ALT and AST. ↑serum insulin levels ↑HDL-c ↓TC, LDL-c, TG, and VLDL-c ↑sod, cat levels, and hepatic cpt1a mRNA expression levels	**Gadoa** [88]
Male Wister albino rats	Hypoglycaemic + Antioxidant	Intra-peritoneal injection of STZ (45 milligram per kilogram)	Oral daily dose of Zno nps (10 milligram per kilogram) for four weeks	↓serum glucose levels ↓glycosylated haemoglobin levels ↓TNF-α, and IL-6 ↑serum level of insulin, SOD and GPX	**Elassy** [89]
Male Wistar rats	Antidiabetic	Intraperitoneal injection of STZ (65 milligram per kilogram body weight) After 15 min give Nicotinamide (230 milligram per kilogram b.w.)	10 and 100milligram per kilogram Zno nps given Orally.	↓serum glucose levels. ↑serum level of insulin, (IR), and GLUT 2 ↓ROS.	**Virgen-Ortiz** [90]

Adult male Wister albino rat	Antioxidant	Subcutaneously at a dosage of (35milligram per kilogram b.w in 1ml saline solution Weekly for 8 weeks in rats	5 milligram per kilogram b.w. Of Zno nps daily through oral gavage	↓ALT, AST, ALP, and P53. ↑serum albumin, and total protein ↓hba1c, TNF-β, TG, and TC.	**Elmetwalli** [91]
Swiss albino mice	Antidiabetic, hypoglycaemic	Multiple intraperitoneal injection (45 milligram per kilogram body wt.) Of STZ for 5 consecutive days.	Zno nps is given 8 and 14 milligram per kilogram b.w.	↓ BGL ↑serum insulin levels	**Siddiqui** [92]
Male Wistar rats	Anti-diabetic	Single intraperitoneal dose of STZ 40-50 mg /kg	100 mg/ kg and 200 mg/ kg of Zno nps	↓blood glucose levels Level of insulin Return to normal.	**Shanker**[50]
Male albino rats	Antidiabetic	Single intraperitoneal injection of STZ by a dose (60 milligram per kilogram body weight)	10 milligram per kilogram body weight of Zno nps given orally daily for 3 weeks	↓blood glucose ↓ hba1c levels ↑ serum insulin and insulin receptor gene.	**Afify** [93]
Wistar rats	Antidiabetic + Antilipidemic	IP injection of 60 milligram per kilogram BW.	Combination of 500 milligram per kilogram ginger + 50 milligram per kilogram Zno-nps daily for 30 days.	↓FBG And TG levels. ↑ HDL ↓TC and LDL Levels.	**Hassanpour** [94]
Rat	Anti-diabetic Antioxidative	(6.0 mg/0.5 ml/100 g body weight) subcutaneously administrated	DHA-loaded Zno nps (10 milligram per kilogram b.w./day)	↑plasma insulin and sod ↓insulin resistance and blood glucose concentration ↓MDA and AOPP ↓ TC and TG Level.	**Hussein** [95]
Adult male Wister rats	Antidiabetic	Intraperitoneally injected by STZ (120 milligram per kilogram in sterile normal saline)	Zno nps (30 milligram per kilogram)	↑Insulin , glut2, and GCK expression ↓ AST, ALT and BGL. ↓TNFa	**Jobie**[96]
Male albino rats	Antidiabetic	Subcutaneously STZ (6.0 mg/0.5 ml/ 100 g body weight)	Zno nps (10 milligram per kilogram b.w./day orally) for30 days	↑insulin levels ↓blood glucose	**Hussein** [97]

TABLE 8. Outlines various applications of cinnamon NPs as antidiabetic

Animal	Role	Induction	Treatment by nano Cinnamon	Result	References
Adult male Sprague Dawley rats	Antihyperglycemic	Intraperitoneal injection of STZ (70 milligram per kilogram)	3 gm Cinnamon cassia powder was soaked in 90 ml of boiled DW. Given orally	↓Blood glucose levels	**Elobeid** [105]
Wistar male rats	Anti-diabetic	Nicotinamide was injected at a dose of 230 milligram per kilogram intraperitoneally, followed by the injection of STZ at 65 milligram per kilogram 15 min later.	Cinnamon powder in hydrosol (0.5 g/10 ml) for 30 days	↓FBG, OGTT levels	**Huang and Chen**[106]
Male Wistar rats	Antihyperglycemic	Alloxan (120 milligram per kilogram, IP.)	T-CA suspension (80 milligram per kilogram, P.O for 30 days	BGL, TG, and TG at become normal level. ↓ALT, and AST	**Wang** [107]
Male rats	Antihyperglycemic	IP injection of STZ (35 milligram per kilogram)	80 mg/day For 30 days	↓fasting glucose, Hba1c Turns off LDL	**Hussein** [108]

TABLE 9. Describe the role of different NPs against hyperglycaemia.

Nanoparticles used	Animal	Role	Induction	Treatment	Result	References
Nano-tyrosol	Male Wistar rats	Hypoglycemic + Anti-inflammatory + Antioxidant	Single IP injection of STZ (50 milligram per kilogram/b.w.) T2DM	Nano-tyrosol 1 ml was given intra-gastrically at a dose of (20 milligram per kilogram/ b.w.) Given once daily for 30 days.	↓amount of apoptosis and collagen disposition ↑ total protein levels of insr ↑ sod activity ↑ glutathione-transferase	**Jafari-Rastegar** [110]
Nano-stevia	Male Wistar rats	Anti-apoptotic activity + attenuating complications of type 2DM.	Single-dose IP injection of STZ (50 milligram per kilogram/b. w.)	Nano-stevia Intra-gastrically treated with 1ml of nano-stevia (20 mg/ dl) given daily for one month.	↓ BGL ↓ insulin secretion and glucokinase (gck) expression ↑ Protein levels of insr and the expression of the mRNA levels of Pepck and gck genes. ↓apoptotic cells	**Mousavi-Niri** [120]

PD-csnps (Polydatin-loaded chitosan nanoparticles)	Male Wistar albino rats	hypoglycaemic	IP Injection of STZ (50 milligram per kilogram b.w.)	PD-csnps, (50 milligram per kilogram b.w.) of Polydatin via gastric intubation for 28 days	↓ HBa1c Improvement in hepatic glycogen	**Abdel-Moneim** [118]
PD csnps	Male Wistar albino rats	hypoglycaemic + Anti-inflammatory + Antioxidant	IP Injected of STZ (50 milligram per kilogram body weight)	PD csnps (50 milligram per kilogram /b.w.) given Daily for a month via gastric intubation.	↓BGL , lipid peroxidation in the liver ↑liver glycogen content, GSH, SOD, gpx, CAT, and G6PD ↓TNFa and interleukin1β mrnas ↓AST and ALT	**Abd El-Hameed**[119]

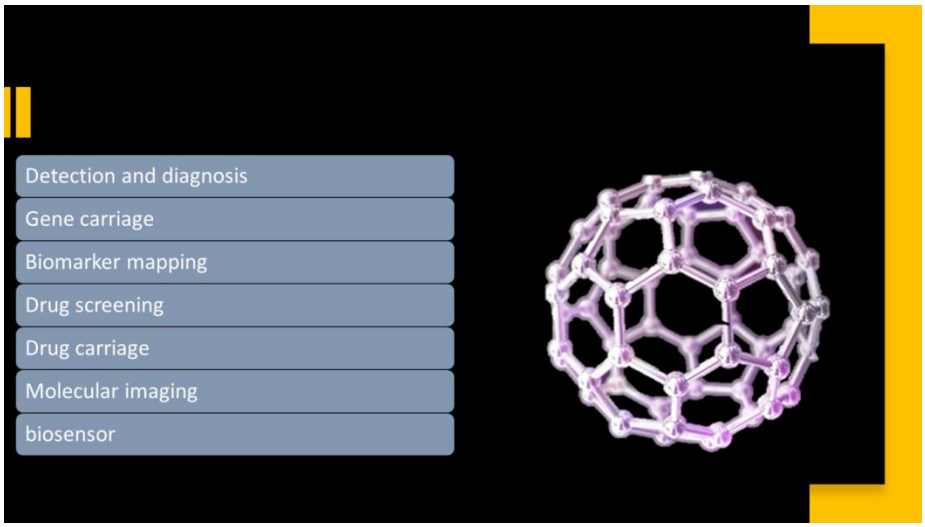

Fig. 1. Shows the different uses of nanoparticles.

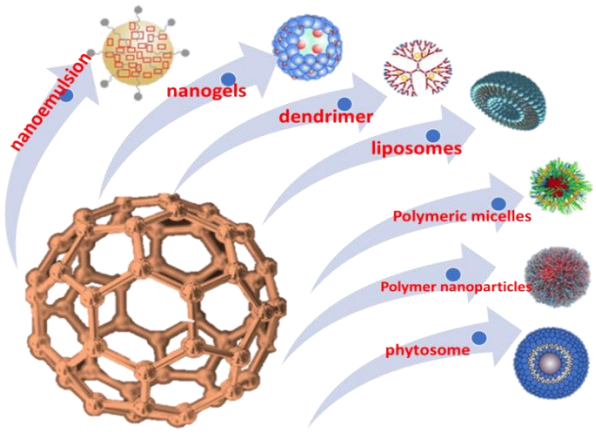

Fig. 2. Various ways to deliver the nanoparticles to the body

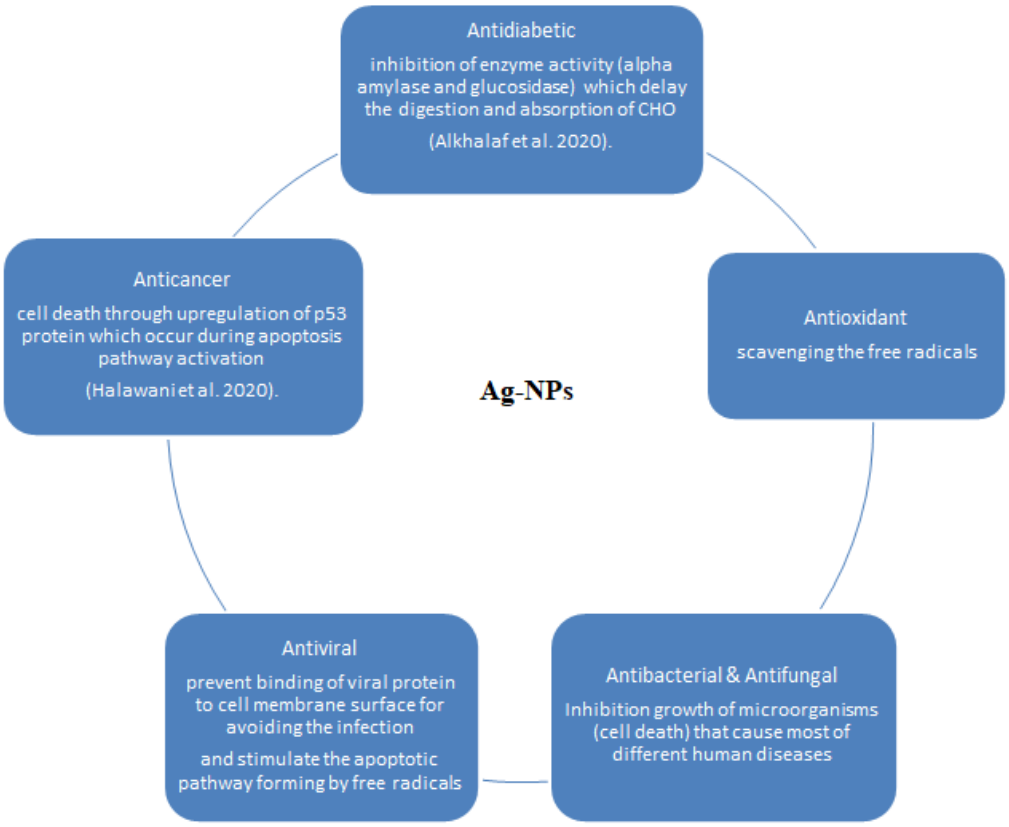

Fig. 3. Show in detail the role and MOA of Ag-NPs.

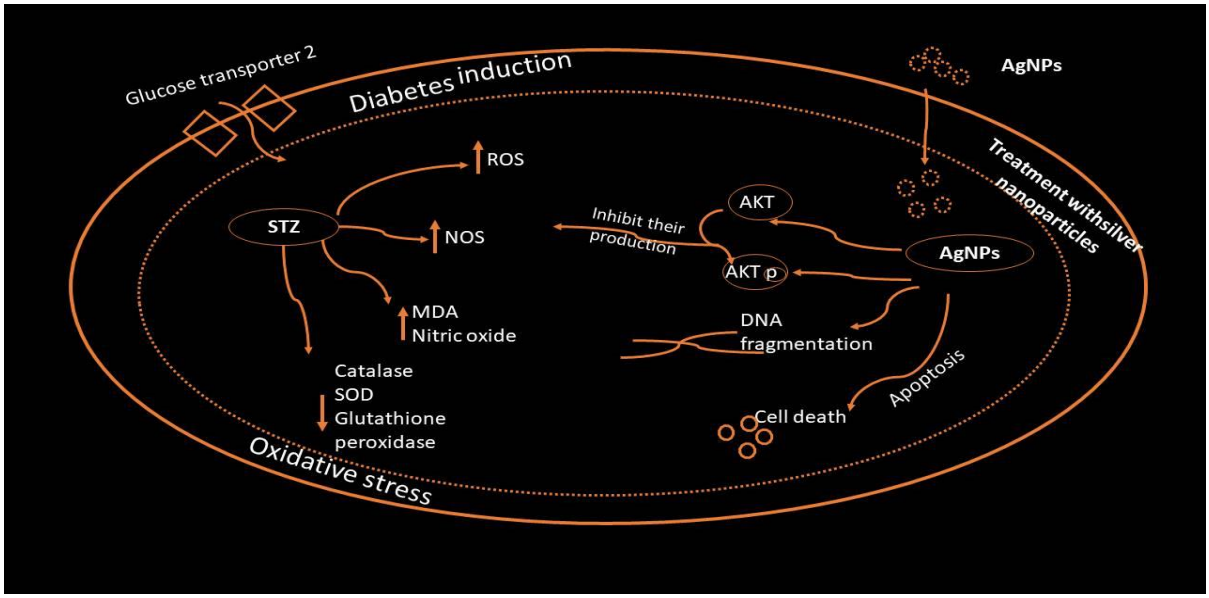

Fig. 4. Shows diabetes induced by STZ & mechanism of action of antidiabetic AgNPs

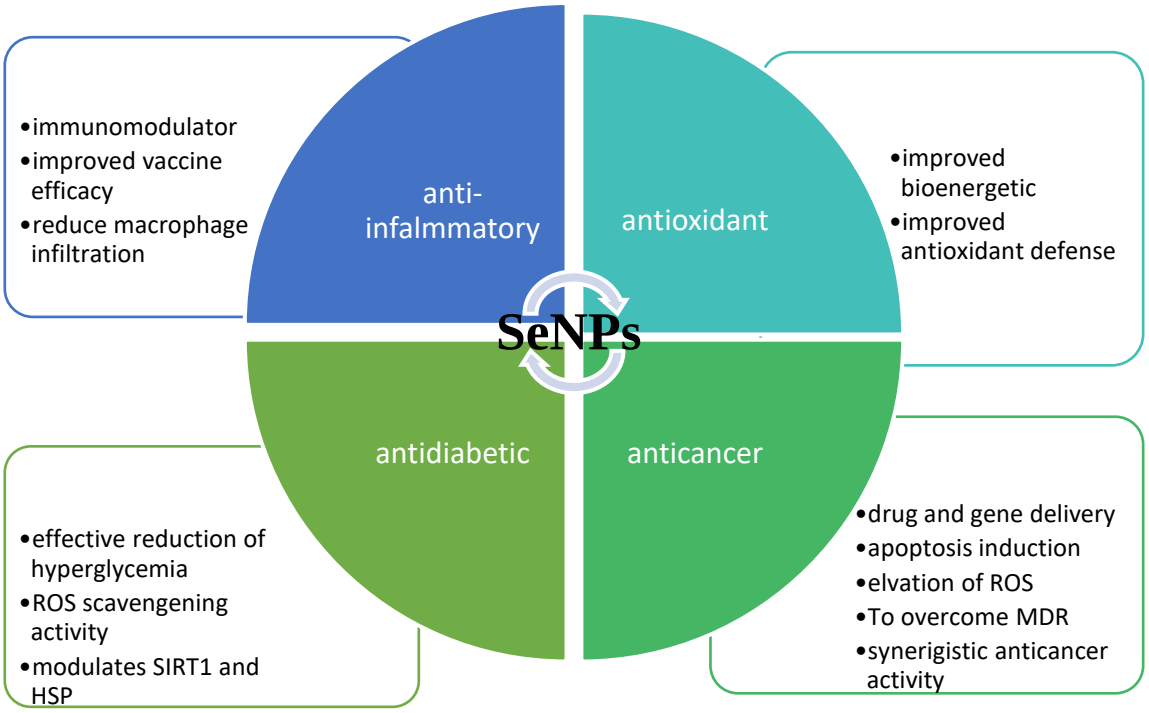

Fig. 5. A detailed overview of the role of SeNPs and how to act.

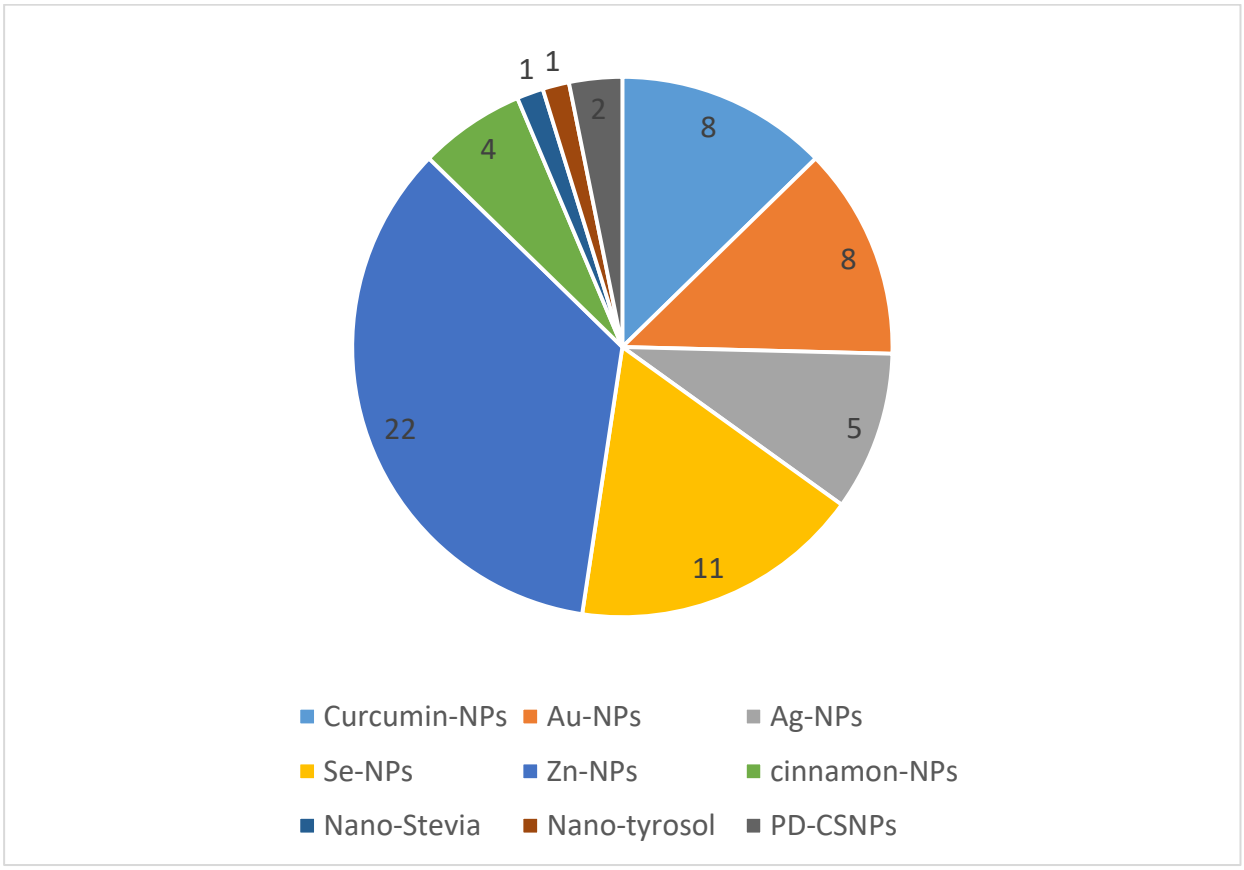

Fig. 6. Pie chart illustrate the distribution of nanoparticles among the collected researche

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التأثير التحسيني للجسيمات النانوية مع تجارب العلاج ضد اعتلال الكبد السكري- المراجعة الشاملة

رحاب محمود خير الدين [١]، يارا سيد أبو العلا [١]، فادي سيد يوسف [٢*]، حمدي رزق [١] وسامر محمد دغش [١]

[١] قسم التشريح و الأجنة، كلية الطب البيطري، جامعة القاهرة، ١٢٢١١ الجيزة، مصر.
[٢] قسم الأدوية، كلية الطب البيطري، جامعة القاهرة، ١٢٢١١ الجيزة، مصر.

الملخص

الجسيمات النانوية (NPs) هي أجسام دقيقة يتراوح قطرها من ١ إلى ١٠٠ نانومتر. يمكن تصنيفها إلى عدة مجموعات وفقًا لأشكالها وأحجامها وخصائصها الكيميائية والفيزيائية. تُستخدم الجسيمات النانوية في العديد من مجالات علم الأحياء والطب مثل هندسة الأنسجة، توزيع الأدوية، والطب التجديدي، علاوة على ذلك كعوامل مضادة للميكروبات وللكشف عن الجزيئات الحيوية. ولتأكيد فعالية واستقرار كل مادة نانوية، يتطلب الأمر بيانات معلوماتية حول خصائصها الفيزيائية والكيميائية. لقد تزايدت الأبحاث حول الجسيمات النانوية في السنوات الأخيرة بسبب تأثيرها الطبي المحسن ضد العديد من الاصابات المرضية وبعض مشاكل التمثيل الغذائي. مجال التكنولوجيا الحيوية يتطور ويتزامن مع استراتيجيات تجديدية جديدة. إن زيادة الطلب على توفير علاج مناسب لمرض السكري يزيد من الاهتمام باستخدام الجسيمات النانوية المختلفة في علاج مرض السكري ومضاعفاته.

الكلمات الدالة: داء السكري، ستربتوزوتوسين، ارتفاع السكر في الدم، الجسيمات النانوية، إصابة الكبد، موت الخلايا المبرمج.