

## The Ameliorative Effects of Selenium Nanoparticles (SeNPs) on Diabetic Rat Model: A Narrative Review

(Kesan Amelioratif Selenium Nanozarah (SeNPs) pada Model Tikus Diabetik: Suatu Ulasan Naratif)

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### ABSTRACT

The emergence of nanotechnology has become more popular, and the progress had sparked much development in nanoparticle synthesis, including selenium. Studies associated with the therapeutic abilities and physicochemical properties of selenium nanoparticles (SeNPs) are rapidly growing and gaining interest from many researchers. This review discusses on the fundamental components of selenium, different approaches in synthesizing selenium nanoparticles, its remedial properties and potential in biomedical application. Herein, primary focus will be given to the action of selenium nanoparticles mechanism in improving diabetes mellitus symptoms and complications in animal studies. It is known that selenium is an important micronutrient found in humans, plants and animals that can be incorporated as selenoprotein in the human body. Analysis and comparison on the findings enlighten that SeNPs demonstrated ameliorative effect on diabetes complications due to their antidiabetic, antioxidant, anti-inflammatory and lipid-lowering characteristics.

Keywords: Antidiabetics; diabetes mellitus; green synthesis; nanoparticle; selenium

### ABSTRAK

Kemunculan nanoteknologi telah menjadi popular dan kemajuannya telah mencetus pelbagai perkembangan dalam sintesis nanozarah, termasuklah selenium. Kajian berkaitan dengan kebolehan terapeutik dan sifat fizikokimia selenium nanozarah (SeNPs) telah berkembang pesat dan mendapat tumpuan para penyelidik. Kajian ini membincangkan tentang komponen teras selenium, pendekatan berbeza dalam sintesis nanozarah selenium dan kebolehan pemulihan serta potensi dalam aplikasi bioperubatan. Di sini, penulisan menjurus kepada mekanisme selenium nanozarah dalam memperbaiki simptom dan komplikasi kencing manis dalam kajian yang bermodelkan haiwan. Umumnya, selenium merupakan mikronutrien penting yang terdapat pada manusia, tumbuhan dan haiwan yang digunakan sebagai selenoprotein dalam tubuh manusia. Analisis dan perbandingan pada beberapa penemuan menjelaskan bahawa SeNPs menunjukkan kesan penyembuhan ke atas komplikasi kencing manis kerana ciri antidiabetis, antioksidan, anti-radang dan penurunan lipid.

Kata kunci: Antidiabetis; kencing manis; nanozarah; selenium; sintesis hijau

## INTRODUCTION

Over the past years, worldwide chronic disease such as diabetes mellitus (DM) has garnered lots of attention due to the increase in their prevalence rate. In 2021, International Diabetes Federation (IDF) has reported 537 million cases of DM worldwide and is anticipated to increase by 46% to 783 million by the year 2045. According to IDF, most of the cases are contributed by type 2 diabetes mellitus (T2DM). Besides, it was estimated that a total of 462 million peoples are diagnosed with T2DM globally in the year 2017, which comprises of 6.28% from the universal population (Abdul et al. 2020).

T2DM is a heterogeneous disorder with chronic hyperglycaemia as the main feature (Elksnis et al. 2019). The main pathophysiology involves a complex interplay between  $\beta$ -cell dysfunction in the pancreas which leads to impaired insulin secretion and the development of insulin resistance or decreased insulin sensitivity in the organ such as liver and adipose tissue (Galicia-Garcia et al. 2020). Hyperglycaemia, which is the hallmark of T2DM is mainly contributed by lifestyle factors such as nutritional excess and physical inactivity in genetically predisposed individuals (Daryabor et al. 2020; Lamb & Goldstein 2008). This will set an initial triggering factor for the development of T2DM. At the cellular level, chronic hyperglycaemia causes an increase in activity of NADPH oxidase enzyme, adiposity, and mitochondrial production of reactive oxygen species (ROS) which leads to formation of oxidative stress (Fakhrudin, Alanazi & Jackson 2017). Various literature including clinical trials and animal studies have suggested the development of oxidative stress as one of the critical factors in the progression of T2DM and its complications (Jha et al. 2018; Oguntibeju 2019). The complications can get aggravated by the formation of advanced glycosylated products (AGEs) which forms by glucose auto-oxidation (Singh et al. 2014).

Another factor that promotes T2DM progression is inflammatory reactions. The triggers of inflammation are chronic exposure to high glucose in the blood circulation (glucotoxicity), apart from an increase in free fatty acids (FFA) (Galicia-Garcia et al. 2020). The adipocyte expansion leads to the release of the pro-inflammatory adipokines such as interleukin (IL)-6 and TNF- $\alpha$ . The rise in the inflammatory markers' levels together with an increase in ROS and AGEs production synergistically cause the activation of stress-signalling pathways which include JNK, protein kinase c (PKC), p38-MAPK, and IKK complex (Lamb & Goldstein 2008).

Additionally, diverse factors may contribute to the propagation of insulin resistance, so repression of these factors should be among the focal point to prevent and manage T2DM.

However, managing T2DM is not an easy feat. The current form of management is mainly by administration of oral hypoglycaemic agents (OHAs) as single or in combination with insulin to control the blood glucose level. These agents act by improving insulin release, decrease glucose production and enhance the peripheral glucose uptake and will target on insulin signalling pathways to reverse the progression of T2DM (Rehani et al. 2019). The issue with existing OHA or insulin is the side effects, particularly hypoglycaemia which lead to the discomfort or even health hazards to the patients. This resulted in less compliancy of the patient towards the medication given. Hence, various study has been conducted in searching for more holistic or alternative approach in managing T2DM which include utilization of plant extracts, plants active compounds or even the minerals and trace elements (Tran, Pham & Le 2020).

In recent year, numerous studies have been conducted to explore the utilisation of selenium nanoparticles (SeNPs) as modalities of intervention for wide range of diseases. SeNPs shows promising result in cancer and immunotherapy and various neurological diseases such as Alzheimer's disease, Parkinson's disease, cerebral ischemia and epilepsy owing to their anti-inflammatory, anti-apoptotic and antioxidant properties (Gao et al. 2020; Huang, Rose & Hoffmann 2012; Kuršvietienė et al. 2020; Roy et al. 1992). Due to the large surface area, nanoparticles can adsorb, fix and serve as carrier to other active agent. This property of SeNPs makes them fit as an alternative drug delivery system to enhance treatment efficacy while eliminating the deleterious side effects to normal tissue. In view of diabetes mellitus, different formulation of SeNPs reported to provide reno-protective effect (Saif-Elnasr, Abdel-Aziz & El-Batal 2019), serve as an active agent for diabetic wound healing (Ramya, Shanmugasundaram & Balagurunathan 2015) and provide protection against testicular damage in various pre-clinical studies (Hamza & Diab 2020).

An earlier review has highlighted the therapeutic potential of selenium nanoparticles. However, no review has been conducted yet to explore the effect of SeNPs in diabetes mellitus. Thus, we aimed to review the available literature on the effects of SeNPs on diabetes mellitus to better understand the potential to support its scientific use further.

## SELENIUM

Recent focus has shifted towards the minerals and traces compound utilization as complementary to be used in combination with standard treatment in managing T2DM (Dubey et al. 2020). Due to its abundance and availability, selenium is among the essential trace elements that has been actively studied (Kieliszek 2019). Selenium is one of the essential trace elements that belongs to group 16 in the periodic table and can be found abundantly in nature as well as in mammals. In humans, selenium mainly plays a role in modulation of the oxidative stress control, by acting as the co-enzyme of various catalytic sites in selenoproteins and enzymes (Kieliszek 2019). There are approximately 25 selenoproteins in the body that regulate the oxidoreductase activity and maintain the physiological redox balance (Tinggi 2008).

Selenium, in the form of selenocysteine moiety, forms the active centre for an enzyme such as glutathione peroxidase (GPx), selenoproteins P, and thyroxine 5-deiodinase to name a few (Ferro, Florindo & Santos 2021). The selenocysteine found in the GPx is an important antioxidant and acts as free-radical scavengers' agent. Another enzyme that contributes to the antioxidant effect is glutathione reductase. This enzyme can protect cells from the accumulation of peroxidase damage. Collectively, selenium possesses an integral part in maintaining the oxidative balance in the body as well as the enhancement of immune response (Huang et al. 2012).

Interestingly, selenium is also shown to cause a reduction in fasting plasma insulin level and insulin resistance index possibly due to its insulin-like action (Fontenelle et al. 2018; Jablonska et al. 2016). However, the effect of selenium in overcoming insulin resistance remain controversial as some studies found that it can dysregulated the redox and cause impaired in the insulin signalling cascade in high dose (Fontenelle et al. 2018). But, given in appropriate amount, selenium can be a powerful antioxidant agent. A longitudinal study done in 2019 showed selenium supplements able to decrease the blood levels of glucose, HbA1c, cholesterol, and LDL in T2DM patients after three and six-months commencement of the treatment (Karalis 2019). Similarly, a cross sectional study involving 5423 subjects, shows positive correlation between dietary selenium intake (average of 43.51 µg/day) and diabetes (Wei et al. 2015). Selenium supplementation also found to be an effective strategy for reducing insulin

resistance in patients with cardiometabolic diseases in the systematic review and meta-analysis done in 2022 (Ouyang et al. 2022).

However, despite the potential therapeutic effects, selenium possess narrow toxicity margin and administration should be maintained within the therapeutic dose range (Fontenelle et al. 2018). Excessive intakes of selenium could lead to diarrhoea, fatigue, hair loss, joint pain, nail discoloration or brittleness and nausea as reported in an outbreak in 2008 involving selenium supplements in the US (MacFarquhar 2010). Hence, intake of selenium should be maintaining around 55 µg/day as recommended daily doses.

Due to the toxicity issues with selenium, technology using nanoparticles has emerged to overcome these limitations and overall enhance the potential therapeutic effects. As compared to sodium selenium, selenium nanoparticles (SeNPs) have a greater advantage as they possess selenium effects, with better bioavailability, absorptive ability and less toxicity (Hosnedlova et al. 2018). The improvement in bioavailability can allow safe delivery of the therapeutic drugs while protecting the non-target tissue from the unwanted side effects. Due to its nano size, the concentration of SeNPs required to exert the similar effect is much lesser as compared to selenium and allow gradual release of the selenium from the particle surface. Zhang et al. (2001) reported, SeNPs with 20-60 nm in size exhibited seven-fold lesser acute toxicity compared to selenite in mice. Interestingly, Benko et al. (2012) reported SeNPs (100-500 nm) possess similar toxicity with selenite suggesting the size of the SeNPs imposed a crucial role in determining toxicity. There is also no SeNPs specific toxicity reported to date.

## METHODS OF SYNTHESIZING SELENIUM NANOPARTICLES

The nanoparticles (NPs) can be synthesized using either the top-down or bottom-up approaches (Bhardwaj et al. 2020). For the top-down approach, the principal involve is mainly by breaking down the bulk substance into smaller fragments by harnessing optimum external force onto it. In order to achieve this, techniques using physical, thermal, and chemical are utilised to generate ample amount of force and energy needed for the formation of NPs. While the top-down approach involves breaking down large material to smaller parts, the bottom-up approach works in opposite manner, where the smaller molecule, atom and gas will be fuse

and amass together, forming nanomaterial (Nadaroğlu, Güngör & İnce 2017). Similar to top-down approach of synthesizing NPs, physical and chemical methods can be utilised along with other unique approach which is the biological methods. The distinction between these approaches and techniques used in synthesizing NPs provides a variation in terms of the intended outcome and utilisation of the NPs.

Various approach and technique have been done in order to synthesize the SeNPs. One of the common route of synthesizing SeNPs is by using physical approach which involve laser ablation and facile microwave irradiation as reported in multiple studies (Panahi-Kalamuei, Salavati-Niasari & Hosseinpour-Mashkani 2014; Quintana et al. 2002). In this method, the SeNPs is produced by breaking down the large substance, as in the top-down approach mentioned earlier. Due to high energy consumption in synthesising SeNPs using the physical approach, focus have shifted towards utilization of other technique of synthesisation, such as chemical or biological methods.

In chemical methods, ascorbic acid is commonly use as source to reduce sodium selenite for the production the SeNPs. The utilisation of ascorbic acid or vitamin C as chemical agent of choice in multiple studies is mainly attributed to its properties with lower toxicity and better biocompatibility compared to other reducing chemical agents (Badgar & Prokisch 2021). However, previous research that used this method commonly tend to combine with other substance that will act as the capping or stabilising agent to further stabilised the SeNPs as an end-products (El-Borady et al. 2020; Mohamed et al. 2021). Other than ascorbic acid, utilisation or combination of selenium dioxide with sodium thiosulfate or acetone had been studied previously to synthesize the SeNPs which is known as the Riley oxidation (Lin and Wang 2005; Shah et al. 2010).

The green methods or biological approach of synthesising SeNPs has recently garners lots of attention. In this method, organisms such as bacteria or fungus or plant extract have been utilised as reducing agent in synthesising the SeNPs. In this bottom-up approach, biological constituents such as proteins or enzymes in the organism or the phytochemical compounds from the plants such as phenols, flavonoid and alkaloids will act as the reducing agent in the process for SeNPs synthesis (Nadaroğlu, Güngör & İnce 2017). Compared to the other two methods, biological approach tend to be more gentle to the environment as the physical

method release heat energy to the atmosphere in order to operates while chemical method might produce toxic and hazardous substance as by-product during the process of synthesisation which could affect the environment (Jadoun et al. 2021; Muniandy, Sasidharan & Lee 2019).

#### GREEN SYNTHESIS OF SELENIUM NANOPARTICLES

The use of biological organism in synthesizing SeNPs recently have shown promising results and becoming more popular choice especially in biomedical field. Microorganism such as bacteria, fungus and protozoa have been reported to successfully synthesized SeNPs in many studies (Abu-Elghait et al. 2021; Shoeibi & Mashreghi 2017). These microbes have shown to trap toxic metal and converted it into safe elemental NPs (El-Saadony et al. 2021). Some of the proposed NPs reduction activity in these organisms are attributed by the defensive mechanism and stress response of the microorganisms, leading to secretion of protective enzyme and proteins, peptide binding action and metal build up and excretion through the cell membrane (Ghosh et al. 2021). Bacteria-mediated NPs can be synthesized via both intracellular and extracellular techniques, although intracellular method is not preferred due to its complexity in yielding the SeNPs (Alam et al. 2020).

Previous report has shown that Gram-negative bacterial strain of *Pseudomonas aeruginosa* have successfully synthesized the SeNPs with the average size at 96 nm under the aerobic condition (Kora & Rastogi 2016). Other bacterial strain such as *Staphylococcus aureus*, *Escherichia coli*, *Lactobacillus casei* and *Rhodococcus aetherivorans* have also exhibit positive and promising result in mediating SeNPs synthesis (Medina Cruz, Mi & Webster 2018; Presentato et al. 2018; Xu et al. 2018). Study by Lian et al. (2019) showed that biogenesis of SeNPs by *Magnusiomyces ingens* strain depends directly to the concentration of the proteins produced by the yeast as it shows higher surface plasmon resonance peak at higher protein concentration. Supporting this finding, *Penicillium expansum*, *Penicillium chrysogenum*, *Mariannaea* sp. and *Fusarium* sp. have also shown promising result and been utilised in mycosynthesis of SeNPs for various biomedical purpose (Amin et al. 2021; Hashem et al. 2021; Zhang et al. 2019). Among these microorganism, protozoa species was not widely use to synthesize the SeNPs. However, there was a study reported on utilisation

of *Tetrahymena thermophila* SB210 strain has been accomplished to synthesized red amorphous SeNPs. They believed the reduction process is owing to the presence of glutathione which acted as antioxidant agent in the eukaryotic cells (Cui et al. 2016).

Among the biological method available, plant mediated synthesis shows better potential as green synthetic routes as it did not require complicated laboratory and resource for cell cultures that is essential for microorganism mediated synthesis. Microbial source for SeNPs synthesis may exhibit a few limitation that needed to be address such as the need of sterile environment, time consuming process due to microbial growth and other necessities of specific microbial species and strains (Azam & Suriya 2021). Plant as the main source of synthesising SeNPs also exist in abundant and filled with various potential phytochemical constituents that can act as both reducing and stabilizing agent (Rashid et al. 2022). Plant-mediated synthesis is deemed to be cost-effective, low toxic and environmental friendly as compared to other methods of synthesising SeNPs (Nasrollahzadeh et al. 2019). Previous studies have shown multiple plant-mediated green synthesis such as *Cleome droserifolia*, *Withania somnifera*, and *Allium sativum* are capable to synthesize SeNPs with various pharmacological purpose (Abdel Maksoud et al. 2020; Alagesan & Venugopal 2019; Satgurunathan, Bhavan & Komathi 2017). Additionally, study has shown a possible positive synergistic potential when use in combination with microorganisms where they fermented Lupin, which is a leguminous plant extract with *Aspergillus oryzae*, a filamentous mould to produce SeNPs with SPR peak at 510 nm assisted with gamma radiation (Mosallam et al. 2018). This show that there is potential in combining the biological methods to synthesize SeNPs.

#### SELENIUM NANOPARTICLES THERAPEUTIC APPLICATIONS

Previous reports have shown that selenium possess multiple therapeutic potential such as anticancer, anti-inflammatory, antioxidant, antidiabetic, immune-regulating, anti-cholesterol, antimicrobial and repro-protective effects (Ferro, Florindo & Santos 2021). The use of SeNPs as a cancer preventing agent has been studied and exhibit promising result by causing anti-proliferative effect on breast cancer cell lines in dose dependant manner and have higher affinity towards

negatively charge cancer cells (Wadhvani et al. 2017). In a recent study, anti-inflammatory properties of SeNPs were evident when 6 and 24 hours of SeNPs treatment significantly moderated mRNA expressions of pro-inflammatory cytokines markers such as IL-1 $\beta$ , IL-6, IFN- $\gamma$ , IL-17, and TNF- $\alpha$  in colonic epithelial cells exposed to BPA toxicity (Pan et al. 2023). This activity can be exploited and utilised in improving treatment selection especially in managing inflammatory related diseases (Francis et al. 2020). Supplementation of SeNPs towards animal model have shown beneficial effect in increasing in immunity level by active expression of C3 and C4 biomarkers and humoral immune response via immunoglobulin level (Jin et al. 2021). Low level selenium as micronutrient in the body can cause reduction in T lymphocyte which it can lead to decrease in body immune level (Sadeghian, Kojouri & Mohebbi 2012).

Utilization of SeNPs as antimicrobial agents is trending in demand due to their ability to modify the microbial cell membrane, causing leakage and disruption of the DNA (Huang et al. 2016). Previous research showed effective bactericidal action on both Gram-positive and Gram-negative bacteria with slightly lower inhibition on Gram-negative species and significant inhibition on fungi such as *Candida albicans* (Lara et al. 2018; Wang et al. 2019). Thus, application of SeNPs may prevent pathogenic microbes related disease such as candidiasis, superbug infection and malaria. As reported by Guo et al. (2020), nano selenium manages to control hyperlipidemia and vascular injury in atherosclerotic mice by enhancing the hepatic cholesterol metabolism and reducing the tissue damage from oxidative stress. This can potentially alleviate the burden of cardiovascular diseases as hyperlipidemia associated with diabetes mellitus is a well-known as modifiable risk factor for ischemic and cerebrovascular heart diseases (Wan et al. 2021).

#### SELENIUM NANOPARTICLES EFFECTS ON DIABETIC ANIMAL MODEL

##### BIOCHEMICAL ANALYSIS

Diabetes mellitus is commonly characterised by high plasma glucose level and decrease in normal insulin level. This symptoms occur due to increase in ROS in the body, causing irreversible damage and changes to the pancreatic tissue, affecting the insulin production and glucose uptake to the cell (Abdel Maksoud et al. 2020).

TABLE 1. Summary of SeNPs effects in studies with diabetic animal model

Diabetic animal model	Treatment dosage	Study duration	Major outcomes	References
Male albino rats induced with 45 mg/kg STZ	0.5 mL of 1 mg/mL	7 days	↓ Blood glucose, LPO, NO ↑ Insulin, GSH, GPx activity and gene expression Restoration of islet of Langerhans and insulin immunoreactivity	(El-Borady et al. 2020)
Male ICR mice induced 100 mg/kg STZ	0.5 mg/kg 2 mg/kg 4 mg/kg	30 days	↓ Blood glucose, MDA, TG, TC, LDL-C ↑ Body weight, GSH-Px, SOD, CAT, HDL-C	(Zeng et al. 2018)
Male Swiss albino rats pups from diabetic parents (100 mg/kg Alloxan-induced)	5 mg/kg, twice per week	30 days	↓ Blood glucose, Urea, Creatinine, MDA ↑ Albumin, GSH ↑ Partial recovery of pancreatic and kidney cells	(Hassan et al. 2021)
Male Sprague-Dawley rats fed with HFD and treated with 35 mg/kg STZ	2 mg/kg	60 days	↓ Blood glucose, MDA, TP, Albumin ↑ Body weight, insulin, HDL-C, SOD, CAT, GSH ↓ ALP, AST, ALT, GGT ↓ TNF- $\alpha$ , IL-6, IL-1 $\beta$ , Troponin 1, CK-MB	(Mohamed et al. 2021)
Male Sprague-Dawley rats treated with 55 mg/kg STZ	0.5 mg/kg	4 weeks	↓ Plasma creatinine, BUN, MDA ↑ Body weight, GSH, Recovery of glomerular injury ↑ HSP, SIRT-1, Bax protein	(Kumar et al. 2014)
Male Wistar rats induced with 50 mg/kg STZ	3.5 mg/kg	45 days	↓ Blood glucose, ALT, AST, Urea, Creatinine ↑ Insulin, HDL ↓ TC, TG, VLDL, LDL, NEFA Normalization of pancreatic islet with mild hypertrophy	(Abdel Maksoud et al. 2020)
Male Wistar rats induced with HFD/STZ at 35 mg/kg	0.1 mg/kg 0.4 mg/kg	8 weeks	↓ Blood glucose, ALT, AST, GGT, ALP, Total bilirubin ↑ Body weight, insulin, TP, Albumin ↓ Creatinine, Urea, Uric acid, AGE ↓ MDA, NO, XO ↑ T-SOD, CAT, GPx, GR, GST, GSH, TAC, AHR	(Abdulmalek and Balbaa 2019)
Male Sprague-Dawley induced with HFD/STZ at 35 mg/kg	2 mg/kg	8 weeks	↑ SOD, CAT, TAC, GSH ↓ MDA, TNF- $\alpha$ , IL-6, IL-1 $\beta$ ↓ Kim 1, albumin, $\beta$ 2-microglobulin, BUN Mild nephroprotective effect	(Khater et al. 2021)
Goto-Kakizaki (Diabetic) rats	125 mg/kg	2 weeks	↓ MDA, ROS ↑ SOD, GSH	(Deng et al. 2019)

Reports from recent studies have shown SeNPs manage to alleviate the plasma glucose level and increased insulin production (Deng et al. 2017; El-Borady et al. 2020). The reduction of plasma glucose level is inversely proportional to the doses given as higher dose of SeNPs results in lower blood glucose level (Zeng et al. 2018). SeNPs believes to cause reduction in the plasma glucose level due to its insulin mimetic feature which helps regulates glucose metabolism and revive the insulin sensitivity and secretion (Hassan et al. 2021). Study by Mohamed et al. (2021) reported a decrease in hepatic protein such as albumin and total protein and elevated hepatic enzymes such as ALP, AST and ALT in diabetic rats were alleviate to normal level following administration of oral SeNPs supplementation in both combination therapy and monotherapy for 60 days. Another study on diabetic nephropathy in T2DM animal model shows lesser reduction of plasma glucose level. However, they have reported a reduction in plasma creatinine and blood urea nitrogen (BUN) with increase in the plasma albumin which signify reno-protective effect (Kumar et al. 2014).

Diabetes mellitus may also associate with dyslipidaemia with increased total cholesterol (TC), triglycerides (TGs), low-density lipoprotein (LDL) and decreased high-density lipoprotein (HDL) level (Nelson, Rochelau & Nicholls 2018). Intervention with SeNPs have shown to cause amelioration of the lipid profiles (Abdel Maksoud et al. 2020; Abdulmalek & Balbaa 2019; Khater et al. 2021; Zeng et al. 2018). In diabetes mellitus, the lack of insulin production or insulin resistance caused an influx of fatty acids into the liver which affect the lipid metabolism. Intervention with *Cleome droserifolia* mediated selenium nanoparticles (Se-CNPs) for 45 days were able to restore the dyslipidaemia in Streptozotocin-nicotinamide (STZ-NA) induced diabetic rats (Abdel Maksoud et al. 2020). They proposed that the flavonoid rich content in the Se-CNPs caused an inhibition towards cAMP dependent protein phosphokinase which caused an increase in phosphorylation process of the Hydroxy methyl glutaryl-CoA (HMG-CoA) reductase. HMG-CoA reductase is a critical enzyme responsible for conversion of HMG-CoA to mevalonic acid in the cholesterol biosynthesis. Due to the phosphorylation, HMG-CoA reductase will be kept in inactive state, causing reduction in the cholesterol production which explain the restored lipid profile in their findings.

Study done using chitosan-stabilized selenium nanoparticles (CTS-SeNPs) also exert the same anti-

hyperlipidemic findings (Mohamed et al. 2021). Mohamed et al. (2021) reported that the treatment with CTS-SeNPs exhibits a better result, compared to the positive control, metformin. The combination of the metformin and the CTS-SeNPs also given more potent result compared to monotherapy treatment, suggesting potential treatment strategy. This finding is supported by Abdulmalek and Balbaa (2019), where they found that the high dose of SeNPs combination with metformin gives better result in ameliorating dyslipidaemia in T2DM rat model.

The intervention with CTS-SeNPs in diabetic mice also exhibited similar finding with significant increase in HDL, decreased in LDL and cholesterol after intragastric administration of CTS-SeNPs for 30 days. They postulated that high HDL level promotes the migration of TG and TC from peripheral tissue to the liver for catabolism. The stabilization of SeNPs with chitosan were also found to cause a better anti-hyperlipidemic effect compared to the treatment with SeNPs alone (Zeng et al. 2018).

#### HISTOPATHOLOGY

Chronicity and complexity of diabetes mellitus could end up in damaging the organs if left without any intervention. Various literature reported the signs of inflammation with degenerative changes in the organs such as pancreas, liver, renal, reproductive organs and others in the diabetic animals model (Ahmadvand et al. 2017; Masarone et al. 2017). The defects in the histoarchitecture reflects the dysfunction of the organs which exacerbates the severity of diabetes mellitus. Treatment with SeNPs have shown to cause a restorative effects on the histological structures of the studied organs (Abdel Maksoud et al. 2020; Deng et al. 2019; Hassan et al. 2021).

The pancreatic  $\beta$ -cells are the main target for the oxidative stress and inflammation in diabetes mellitus. Additionally, it also has limited capacity to regenerate causing it to be more prone for destruction. In a study done by Deng et al. (2019), treatment with SeNPs for two weeks shown to cause significant increase in the amount of living  $\beta$ -cells in the islet of pancreas. Another study reported similar pancreatico-protective effects on the pup born from the diabetes mother treated with SeNPs for a month (Hassan et al. 2021). The histology findings showed more regular size islet of Langerhans compared to the rat pups born from non-treated mothers which shows irregularity in the islet shape and degeneration of the nuclei of the pancreas. SeNPs treatment also caused

lesser inflammation in the pancreatic tissue, evidence by lesser leukocyte infiltration and atrophy as reported by Abdel Maksoud et al. (2020). The overall histological findings following SeNPs treatments show its restorative effects on the islet of the pancreas which could help in improving the insulin release and overall blood glucose control.

The uncontrolled glucose level along with generation of ROS could end up with apoptosis and nephropathy. Diabetic nephropathy is one of the most common cause of end stage renal damage hence the protection towards renal is warranted in managing diabetes mellitus (Hojs et al. 2020). Reno-protective effect of SeNPs is also demonstrated by Kumar et al. (2014), as they reported glomerular hypertrophy and vacuolations were normalized following the treatment with SeNPs along with the improvement in renal profile value. This finding was further supported by Hassan et al. (2021), which demonstrated lesser lobulation and vacuolation in glomeruli with minimal edema in renal tubule of rat pups born from SeNPs-treated diabetic mother.

#### OXIDATIVE STRESS

Oxidative stress plays a vital role in initiating as well as propagating the DM as well as its complications. Oxidative stress is a result of the overproduction of ROS which supersedes the antioxidant defence system (Sakamula, Yata & Thong-Asa 2021). ROS are highly bioactive molecules containing one or more unpaired electron(s) that have high oxidising potencies due to their ability to donate extra electrons which could result in molecular and cellular damage (Lamb & Goldstein 2008). In diabetes, ROS mainly formed by excessive activity of the mitochondrial electron transfer chain and one of the membrane-bound enzymes, NADPH oxidase (Fakhruddin, Alanazi & Jackson 2017). The problem with ROS is that it can further cause deterioration of the cell by causing activation of stress signalling pathways. This includes JNK, protein kinase c (PKC), p38-MAPK, and the IKK complex (Lamb & Goldstein 2008; Zhang et al. 2016). On top of that, the adipocyte expansion which is common association in T2DM released the pro-inflammatory adipokines such as interleukin (IL)-6 and TNF- $\alpha$  (Burhans et al. 2019). These generate more inflammation which exacerbates ROS production and creates a vicious cycle of cellular damage. If no appropriate intervention is taken, development of  $\beta$ -cells and vascular dysfunctions, as well as insulin resistance

will further exacerbates hyperglycaemia and T2DM conditions.

The antioxidant is needed to scavenge the ROS or even break the chain reaction to yield fewer toxic radicals. To date, endogenous antioxidants can be found from enzymatic or non-enzymatic sources. The first-line defence of enzymatic antioxidants includes glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase whereas non-enzymatic antioxidants include glutathione, ascorbate, and  $\alpha$ -tocopherol, and vitamin A, C & E (Ighodaro & Akinloye 2018; Kurutas 2016). In T2DM, the ROS-antioxidants balanced is disturbed due to overproduction of the ROS. Among all, superoxide radicals ( $O_2^{\cdot-}$ ) has been identified as the primary ROS as it can interact with other molecules to generate secondary ROS such as hydrogen peroxide ( $H_2O_2$ ) (Zorov, Juhaszova & Sollott 2014). To neutralize this, cell utilised both enzymatic and non-enzymatic sources of antioxidants to maintain the redox balance. However, chronic utilization of antioxidant defence mechanisms that get exhausted over time may lead to detrimental effects in T2DM.

Studies have shown that T2DM patients with nephropathy possess lower levels of plasma antioxidant enzymes indicating the overwhelming activity of the antioxidant defence system (Hojs et al. 2020). Thus, it is reported that the administration of antioxidant agents in T2DM is able to restore and minimize the progression of the complications. Currently, various exogenous antioxidant agents have been introduced in the market as a supplementary to oxidative stress-driven diseases (Liu et al. 2018; Tan et al. 2018). In a study done in 2015, the administration of antioxidants such as vitamin C, vitamin E, linoleic acid, and acetylcysteine have shown to improve insulin sensitivity in diabetic patients. Additionally, a few antioxidant drugs have been approved in the market to be use as the treatment for diseases such as ischaemic stroke, osteoarthritis and diabetic neuropathy (Neha et al. 2019). However, the issue with the available antioxidants in the market is the limited bioavailability due to difficulties in crossing the cell membrane and absorption as well high degradation to end-product which limit their effect (Ikram et al. 2021). This limitation can be minimized by the utilization of SeNPs as it possess better stability and bioavailability resulting in better control of the disease outcome (Ferro, Florindo & Santos 2021; Hosnedlova et al. 2018). Various animal studies have shown that SeNPs succeeded to improve oxidative stress induced from hyperglycaemia (El-Borady et al. 2020; Hassan et al. 2021; Khater et al. 2021).



ROS such as hydrogen peroxide showed to significantly increase in T2DM due to depletion of antioxidant enzyme such as GPx which is the main antioxidant enzyme that catalyse the conversion of hydrogen peroxide to water with the aid of GSH as the electron donor. A study done with polyvinylpyrrolidone (PVP) capped SeNPs reported a significant increase in GPx activity in the treatment group as compared to the control diabetic rats (El-Borady et al. 2020). The increase in GPx activity is believed to be related with the role of selenium as selenoprotein which is essential in the expression of GPx. As the GPx activity is elevated, the GSH antioxidant activity also directly increase, further reducing the oxidative stress towards the diabetic model. This results were supported by Khater et al., when diabetic nephropathy rats showed an improvement on the GSH level after the treatment with chitosan-stabilized SeNPs for 8 weeks (Khater et al. 2021). Apart from that, the level of other antioxidant enzyme such as superoxide dismutase (SOD) was also restored following an administration of SeNPs in diabetic rats (Deng et al. 2019).

Free radical generation in diabetic condition caused high rates of lipid peroxidation which could lead to uncontrol oxidative damage towards the cells. Malondialdehyde (MDA) is the by-product of lipid peroxidation which acts as the main biomarkers indicating the severity of the oxidative stress (Kumar et al. 2014). Previous report from Hassan et al. (2021) have shown that treatment of low dose SeNPs was able to significantly reduced the MDA level which may indicates the amelioration of ROS generation and lowering rate of lipid peroxidation.

The efficacy of SeNPs as promising antioxidant agent mainly due to its capacity to increase the level of antioxidant enzyme specifically GPx, prevent the accumulation of free radical and decrease the oxidative damage towards the cells and tissues (Sentkowska & Pырzyńska 2022). Moreover, the pharmacokinetics properties of SeNPs deemed to have better bioavailability for distribution of small molecules to their desired organ, in order to increase their systemic circulation period, precise tissue targeting or prolong the therapeutic window (Yuan et al. 2019). Smaller nanoparticle sizes reported to have better antioxidant activity since it has more surface area for free radical interaction (Chaudhary, Chauhan & Kumar 2019).

#### INFLAMMATION AND APOPTOSIS

Diabetes induced-oxidative damage consecutively triggers inflammation that mediate the degenerative and necrotic changes of tissues in the body. It is long recognized that pro-inflammatory molecules such as that interleukin 6 (IL-6), interleukin-1beta (IL-1 $\beta$ ) and tumor necrosis factor (TNF- $\alpha$ ) were significantly elevated in diabetic humans and experimental models (Wellen 2005). These pro-inflammatory molecules play important roles in metabolic inflammation via impairing serine phosphorylation of insulin receptor substrate 1 (IRS-1) which regulates insulin receptor signalling and consequently modulate insulin action (Langlais et al. 2011). Recent studies reported that IL-1 $\beta$ , IL-6 and TNF- $\alpha$  were found to be significantly reduced in blood serum as well as in renal tissue of STZ-induced diabetic rats treated with chitosan stabilized nanoparticles (Ch-SeNPs). This may relate to the SeNPs potential to significantly downregulate the gene and protein expression of inflammatory chemokines, as well as repressing the activation of MAPK and NF $\kappa$ B pathways which are crucial for cellular inflammatory responses (Ruan et al. 2002).

Interestingly, both studies highlighted that the anti-inflammatory effect were more prominent when Ch-SeNPs were administered in combination with Metformin rather than the monotherapy of Ch-SeNPs alone (Khater et al. 2021; Mohamed et al. 2021). Diabetic patients that received the standard antidiabetic drug Metformin were previously reported to exhibit decrease in pro-inflammatory markers and reduction of ROS production while the benefits of non-insulin antidiabetic drugs in are yet be defined (Festa et al. 2002; Frandsen et al. 2016). It is anticipated that combination therapy of both commercial medicine and plant derived active compounds to be a highly effective therapeutic strategy in managing diabetes by lowering the undesirable side effects associated with the synthetic drugs and reduce the risk of developing common complications related to diabetes (Prabhakar, Kumar & Doble 2014).

The generation of ROS and pro-inflammatory cytokines induced by hyperglycemia further lead to leakage of cytochrome-c and activation of apoptosis cascade. The extrinsic pathway of apoptosis is initiated by the binding of Fas ligand to death receptors, leading to the receptor multimerization and formation of a caspase-activating complex. While the intrinsic pathway of apoptosis arises from B-cell lymphoma 2 (BCL-2)

regulated pathway with expression of both pro-apoptotic and anti-apoptotic signals (Bredesen 2000). Following apoptotic stimuli, the ratio of BCL-2-associated X protein (BAX) and BCL-2 determines cell survival or death where upregulation of BAX expression, as well as down-regulation of BCL-2, has been shown to promote cell death in diabetic models (Ronco et al. 2002).

Previous study has reported that oral administration of Ch-SeNPs in diabetic rats significantly reverse the expression of BAX and BCL-2 in their liver tissue (Mohamed et al. 2021). Similar pattern was also found in the kidney tissue of diabetic rats intraperitoneally administered with glutathione reduced-SeNPs (Kumar et al. 2014). Furthermore, the combined therapy of Metformin with Ch-SeNPs reduced the expression pattern of Caspase-3, BAX, Fas, Fas-L while upregulated the expression of BCL-2 closer to the control values as compared to the Ch-SeNPs monotherapy in the diabetic rats (Mohamed et al. 2021). Results from these studies could strongly indicate that SeNPs treatment may prevent activation of both the intrinsic and extrinsic pathways of apoptotic cell death induced by hyperglycemia.

The severity of diabetes induced apoptosis was further confirmed with the observation of numerous apoptotic cells with extensive DNA degradation via Terminal deoxynucleotidyl transferase dUTP Nick-End Labeling (TUNEL) assay on the kidney and pancreatic tissues of diabetic rats when compared to the normal rats (Deng et al. 2017; Kumar et al. 2014). However, treatment of glutathione reduced-SeNPs significantly ameliorated this condition in the kidney tissues of STZ-induced diabetic rats while treatment of insulin-loaded SeNPs (INS-SeNPs) showed to reduce the number of apoptotic cells by 15.3% in the pancreatic tissues of Goto-Kakizaki rat model of T2DM. Abnormal rate of apoptosis in pancreatic tissues leads to decline in  $\beta$ -cell proliferation and deterioration in Islet of Langerhans development which consequentially results in insulin deficiency in the diabetic individuals. Selenium has been previously reported to elicit insulin-mimetic effects via stimulating glucose uptake, activating serine/threonine kinases and phosphoinositide-3-kinase/protein kinase B signalling pathways (Ezaki 1990; Hei et al. 1998; Steinbrenner et al. 2010). With that in mind, the SeNPs derived from green synthesis show a great potential to enhance the survival of pancreatic  $\beta$ -cells and improve the function of pancreatic islet in diabetic model. Heat-shock proteins (HSP) have been reported to regulate apoptosis and cell death. Notably, HSP-70 which is a

stress induced molecular chaperone has been found to exert cytoprotective effects in diabetic condition where increased expression of HSP-70 upon SeNPs treatment protects the diabetic kidney tissues from apoptotic cell death (Martindale & Holbrook 2002; Shinohara et al. 2006). HSP-70 has been reported to bind to apoptotic protease activating factor-1 (Apaf-1) and prevent the assembly of a functional apoptosome complex (Beere et al. 2000). In 2009, a study elucidated the link between HSP-70 and Sirtuin 1 (SIRT-1), a member from Sirtuin family proteins. SIRT-1 can directly inhibit apoptosis and promotes cell survival via deacetylation p53 tumor suppressor protein and indirectly via deacetylation of Heat Shock Factor-1 (HSF-1). Activation of SIRT1 showed to prolong HSF1 binding to the Hsp70 promoter region and regulates its expression (Westerheide et al. 2009). Evidently, a study demonstrate the ability of SeNPs to elevate the levels of HSP-70 and revives SIRT-1 expression which consequentially prevent cells from undergoing apoptosis and promotes cell survival in diabetic kidney (Kumar et al. 2014). Figure 1 shows the summary on SeNPs mechanisms of action and its possible ameliorative effects on diabetic animal model.

#### DISCUSSIONS

Selenium can be found in different types of form and chemical properties. As an example, selenomethionine (SeMet) found to be the most common form of selenium supplementation thanks to its significant bioavailability and lesser toxicity as compared to other analogs (Wang, Zhang & Yu 2007). SeMet is a naturally occurring amino acids that can be found in common staple food diet believed to be influential in regulation of thyroid hormones (Combs et al. 2009). While inorganic form of selenium like sodium selenite and sodium selenate managed to show biological properties, their high toxicity compared to other selenium compound may lead to other complications (Takahashi, Suzuki & Ogra 2017). SeNPs is considered to be an elemental form of selenium ( $\text{Se}^0$ ) which have the dimensions of less than 100 nm in diameter. Nano-selenium have been reported to increase bioavailability of drugs and organ targeting agents due to its unique characteristics (El-Ramady et al. 2014). Previous reports showed that comparison of SeNPs with selenomethionine, SeNPs exhibit lower toxicity and has equal efficacy in upregulating the activities of selenium-containing enzymes (Wang, Zhang & Yu 2007). Under diabetic condition, there is substantial decrease on antioxidant defense which can be compensate by

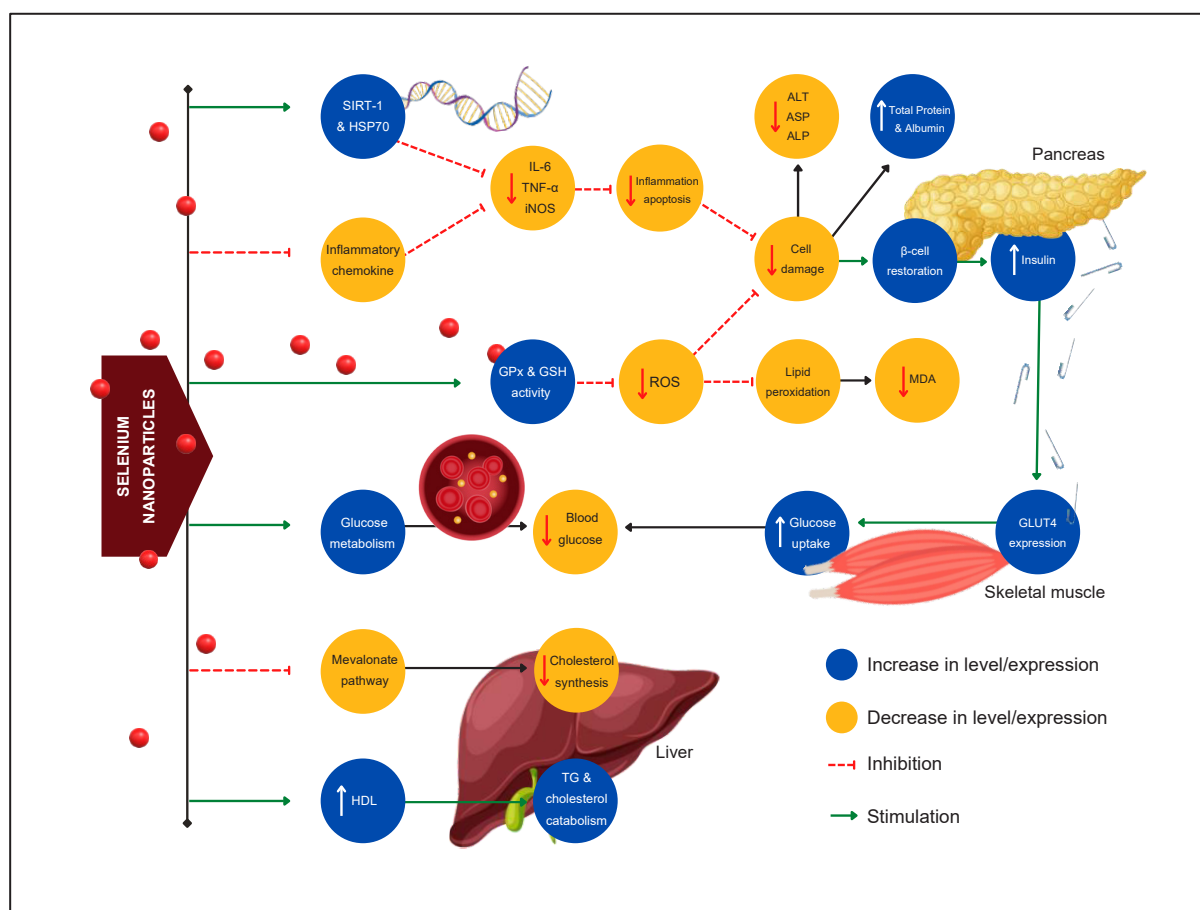


FIGURE 1. SeNPs mechanisms of action on diabetic animal model

increasing selenium-containing enzyme like GPx. Thus, SeNPs with lower toxicity as an alternative antidiabetic agent would be better in order to avoid any adverse effect and complications.

#### CONCLUSION

This review article demonstrates the therapeutic potential of SeNPs that could be used as a complement or adjuvant for the management of DM and its complications. Various techniques of SeNPs preparations have been studied to provide the optimum therapeutic strategies in management of DM. SeNPs exhibits multifactorial activities that target several tissues such as antioxidant, anti-inflammatory and antiapoptotic which are essential in improving the physiological damage and changes in diabetes mellitus. Regardless, the toxicity level of SeNPs must be considered and explored more before any applications. Additionally, the studies conducted so far

are mainly conducted in *in vitro* or *in vivo* setting, thus, more comprehensive research should be done to replicate and fill in the gaps before safely introduced SeNPs in patients with DM.

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