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Identification of potential antioxidant indices by biogenic gold nanoparticles in hyperglycemic Wistar rats

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ABSTRACT

Oxidative stress is a crucial factor in diabetes, where the abnormal metabolic ambience leads to hyperglycemia resulting in the onset of several vascular complications. Under homeostasis, innate antioxidants efficiently inhibit the oxidative stress, thereby restrain further progression of diabetes. In the present study, a potential antioxidant marker was identified from hepatic tissue of diabetic Wistar rats after oral administration of biogenic gold nanoparticles (GNPs). Diabetic animals treated with GNPs showed increase in insulin level and subsequently reduced the concentration of blood glucose level to normal. Further, GNPs favoured to retain the hepatic enzymatic markers, serum lipid levels and followed by renal biochemical profile in the rats. In addition, GNPs treated rats displayed an elevated level of lipid peroxidation, superoxide dismutase, glutathione peroxidase, and catalase enzymatic activity. Consequently, GNPs treated rats showed diminished level of histological injury in the hepatic, renal, and pancreatic tissues. Taken together, these results suggested that among the several antioxidant enzymes, catalase elucidated the highest area under curve (AUC) with 0.80 accomplished by receiver operating characteristic (ROC) curve. Collectively, our findings enlighten that GNPs treated rat able to alleviate the hyperglycemic condition due to the enzymatic activity of catalase.

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1. Introduction

Diabetes mellitus is chronic metabolic disorder characterized by deficiency of insulin secretion, fluctuations in insulin resistance coupled with several genetic and life style factors (Alberti et al., 2005). Further, Genome – wide association studies showed individuals of South Asian population with increased susceptibility to this disorder (Kooner et al., 2011). Progression of this disorder favours the manifestation of oxidative stress due to high production of reactive oxygen species (ROS) and decrease the antioxidant defence system (Wright et al., 2006). Additionally, increased glucose fluctuation through polyol pathway indirectly produces ROS, but greatly contributes to overall redox imbalance, that leads to oxidative stress in cells (Lee and Chung, 1999). Besides, collapse of the antioxidant defence system is associated with lipid peroxidation and oxidative cellular injury resulting in the damaged metabolism of lipids, proteins, DNA, and also disorients the regular functioning of normal cells (Kaneto et al., 2010; Nowotny et al., 2015). This results in the subsequent glycation and oxidation reactions between reducing sugars and proteins and led to an intensification of advanced glycation end products (AGEs) (Ott et al., 2014). AGEs deplete AGE receptor-1 and sirtuin which result in reduced antioxidant defence, thereby promoting insulin resistance in hyperglycemic patients (Cai et al., 2012). In addition, plasma membrane localised receptors interact with AGEs, modifies the intracellular signalling and gene expression to release the pro-inflammatory molecules which are responsible for diabetic retinopathy, neuropathy, nephropathy, and cardiovascular complications (Singh et al., 2014).

Nowadays, glucose levels are maintained by dietary modification, physical exercise, insulin therapy and oral medication that are fraught with frustration and risk (American Diabetes Association, 2014). The limitations of the current allopathic drugs include taking the medicines throughout a life, expensive therapy with side effects like hypoglycemia, weight gain, gastrointestinal disturbances and liver toxicity (Brackett and Pharm, 2003). Diabetes based morbidity and mortality remain high even with optimal medical management. So, it is a challenging task to develop new compounds for the elimination of active ROS in the blood. To circumvent this state, identification of novel molecules and retaining those available eco-friendly colloids could help in the development of new

Abbreviations: AGEs, advanced glycation end products; GPx, glutathione peroxidase; ROC, receiver operating characteristic analysis; ROS, reactive oxygen species; SOD, superoxide dismutase.

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drugs for treating non-communicable diseases like diabetes (Davis et al., 2008). Fortunately, defensive enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) detoxifies ROS into two oxygen and water molecules (Tiwari et al., 2013). Mateas reported that antioxidants would enhance the gene expression of detoxifying enzyme (Mateas, 2000). Molecular bugs in insulin action and insulin resistance amended by antioxidant enzymes could initiate the IRS-1 dependent signalling (Henriksen, 2006). This is of great potential to improve the health care and also in opening a way for progressing cost effective methods for treating chronic diabetic complications. Nanoparticle research has become incredible during the last two decades because of their exclusive optical, physical, chemical, and magnetic properties when compared to the existing bulk solids (Kelly et al., 2003). Among the various synthetic methods, the solution phase synthesis involving the reduction of metal to metal ions by plant extracts has gained intense significance in recent years, because of the renewable, nontoxic nature of the plant polyphenols, eco-friendly aqueous medium, mild reaction condition and biocompatibility (Venkatachalam et al., 2013). The application of biogenic gold nanoparticles (GNPs) in various areas such as drug delivery, cancer diagnostics, biological sensors, nanomedicine, and diabetes are gaining momentum in recent years (Yohan et al., 2016; Azadbakht et al., 2015; Jain et al., 2014). Effectual anti-diabetic activity by biologically synthesised GNPs by regulating the oxidative stress was reported by Rahiman and Tantry (2012), but there exists a lacuna on the mechanism and downstream pathways through which GNPs influence the anti-oxidant systems and their reverse effect on hyperglycemic conditions. The secondary metabolites of *Couroupita guianensis* have been found to enhance anti-inflammatory and anti-diabetic activity (Somani et al., 2012), but had poor dissolution rates, less bio-availability and high dosage requirement.

So, an effort was made to overcome the above – mentioned drawbacks by the biogenic synthesis of *C. guianensis* coated GNPs. The current study also intended to identify the potential antioxidant enzyme marker that is influenced by the GNPs in diabetic rats.

2. Materials and methods

2.1. Preparation of C. guianensis leaf extract

About 400 mg of finely dried and ground powder of *C. guianensis* was taken in a beaker containing 200 mL of deionised water and heated for 30 min at 90 °C in a temperature controlled water bath, then filtered through cellulose nitrate membrane filter paper and stored in a refrigerator until use. Freshly prepared extracts were used throughout the work.

2.2. Synthesis and characterization of GNPs

Chloroauric acid $(HAuCl)_4$ (100 mL of 0.001 M) was added to 200 mL of freshly prepared extract and stirred thoroughly at ambient condition. In addition of *C. guianensis* extract to $HAuCl_4$ solution resulted in visual color change from color less to purple within 5 min.

UV–vis spectroscopy was used for recording spectra between 200 and 800 nm against double distilled water as blank. The particle size, distribution and ex-situ stability were estimated in GNPs by zeta sizer (Horiba Scientific SZ-100, UK) and operated at an angle of 90°. After reduction, GNPs were collected by centrifugation of reaction mixture at 10,000 rpm, purified, dried and subjected to X-ray diffraction analysis and other studies. GNPs were coated on XRD grid and spectra were recorded in the 2θ region from 10° to 90° with a scanning rate of 4° min^{-1} and with a step size increase of 0.02° using Bruker D8 advance. Diffractometer with Cu *K*α radiation (λ = 1.54 Å). The GNPs were pelletized with KBr and then spectra were recorded using JASCO FT-IR 4100 instrument in the diffuse transmittance mode at a resolution of 4 cm^{-1}. The morphology and size of the bio-reduced GNPs was visualized by placing a drop of sonicated well- dispersed sample on Cu grid using PHILIPS CM 200 HR-TEM at an acceleration voltage of 20–200 kV with 2.4 Å a resolution. The SEM-EDAX was taken for the determination of the purity of GNPs formed. The spectra of *C. guianensis* leaf powder were recorded to determine the functional groups involved in vibrational bonding with the surface of the GNPs.

2.3. Selection of animals

All the experiments on animals were carried out as per the guidelines of the institutional animal ethics committee (VIT/IAEC/10th/March 14th/NO. 34). Female Wister rats weighing 150–200 g were obtained from the animal house at VIT University, Vellore, India. This study was conducted on female rats for the period of 5–6 weeks, housed in polycarbonate cages (six mice per cage) at room temperature of 25 ± 2 °C with 12 h-light and 12 h-dark cycles. The rats were given free access to pelleted food and water. The animals were allowed to acclimatize to the laboratory environment and then they were randomly subjected to the experiment.

2.4. Experimental design

Forty-two female Wistar rats (150–200 g bw) were used in this experiment. The rats were divided into seven groups, each group comprised of six rats. Group 1-comprised of normal control rats which were given distilled water only (NC), group 2-normal rats were given aqueous extract of *C. guianensis* (100 mg (kg bw)$^{-1}$) dissolved in 12 mL of double distilled water via oral gavage tube for 28 days (CP), group 3 normal rats were given phytochemically synthesized GNPs suspended in deionized water at a dosage of 2.5 mg (kg bw)$^{-1}$ per day using SONICS VCX 500 model sonicator by oral gavage tube for 28 days (CN). Effective inhibitor dosage (EC_{50}) 2.5 mg (kg bw)$^{-1}$ per day of GNP is given orally to reduce the blood glucose level (Barathmanikanth et al., 2010). Diabetes was induced by administering an intraperitoneal injection of a freshly prepared solution of streptozotocin (STZ) (60 mg (kg bw)$^{-1}$) as per the protocol reported by the Al-Amin et al. (2006) to the overnight fasted rats of group 4, group 5, group 6 and group 7. The blood glucose values were measured to be above 250 mg dL^{-1} on the third day after STZ injection thus confirming the induction of diabetes in Wistar rats. Once the hyperglycemic status was confirmed the treatment was initiated on the 4th day after STZ injection and it was assumed as a 1st day of treatment. Group 4- diabetic rats without any treatment considered as diabetic control (DC), group 5-diabetic rats were treated with the aqueous extract of *C. guianensis* (100 mg (kg bw)$^{-1}$) dissolved in 12 mL of double distilled water, given daily via gavage tube for 28 days (DP), group 6-diabetic rats were treated with phytochemically synthesized GNP (2.5 mg (kg bw)$^{-1}$) given continuously via gastric intubation for 28 days (DN) and group 7-diabetic rats were treated with glibenclamide 0.5 mg (kg bw)$^{-1}$ throughout the testing period (DG).

The morphological changes, the toxicity of GNPs and plant extract were analysed through histopathological studies after the treatment of 28 days were performed by examining the changes in the organs such as liver, kidney, and pancreas. The organs were collected and stored in 10% formalin neutral buffer solution, embedded in paraffin, and cut into 5-μm-thick sections. The fixed sections were stained using hematoxylin and eosin (H and E). The sections obtained were examined under a light microscope (400x).

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