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Research Article

Biogenic Copper Nanoparticles From Medicinal Plants As Novel Antidiabetic Nanomedicine

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ABSTRACT

In an attempt to design rapid, efficient and eco-friendly process to fabricate nanoparticles with potent biomedical applications, herein we report for the first time synthesis of copper nanoparticle (CuNPs) using three medicinal plants, B. prionitis leaf extract (BPLE), L. chinensis peel extract (LCPE) and P. orientalis leaf extract (POLE). The synthesis was completed within 5 h indicated by visible colour change and UV-visible spectroscopy. High resolution transmission electron microscopy revealed that the bioreduced CuNPs were very small. CuNPs synthesized by BPLE were between 11 to 15 nm while for POLE they were between 90 to 200 nm. LCPE synthesized CuNPs in a size range between 10 to 100 nm. Further the CuNPs were characterized using energy dispersive spectroscopy (EDS), dynamic light scattering (DLS) and fourier transform infrared spectroscopy (FTIR). Both α-amylase and α-glucosidase were found to be inhibited by the CuNPs providing the strong rationale for their further use in clinical studies as candidate nanomedicine against Type II Diabetes Mellitus.

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INTRODUCTION

Nanomedicine is one of the most emerging applications of material science and nanotechnology. One of the major challenges is biocompatibility as most of the synthesis processes involve hazardous and corrosive chemicals leading to toxicity.[1] Hereby, there is a growing need to design environmentally benign routes for synthesis of biocompatible nanoparticles with potent medicinal importance.[2] Among various metal nanoparticles like silver, gold, platinum, palladium, etc copper nanoparticles have gained considerable attention owing to its diverse applications as anticancer, antibacterial and antifungal agents addition to their catalytic, optical, and electrical properties.[3] Various nanomedicines are being explored and evaluated for their efficacy to treat diabetes mellitus which is considered to be a multifactorial metabolic disorder responsible for significant morbidity and mortality due to its pathophysiological implications that include retinopathy, neuropathy, nephropathy, heart attack, stroke and peripheral vascular diseases. Type II diabetes or noninsulin-dependent diabetes mellitus (T2DM or NIDDM), is the most prevalent form of the disease, which according to World Health Organization is likely to increase up to 300 million or more by the year 2025.[4-7] Although currently available therapies include sulfonylureas, biguanides and glinides, the associated severe adverse effects have encouraged exploration of more effective and safer hypoglycemic agents. Traditional complementary and alternative medicines from medicinal plants offer great potential for the discovery of such novel antidiabetic drugs. Targeting α-amylase and α-glucosidase is considered to be a powerful strategy for designing antidiabetic drugs.[8-13] The spectacular success of our earlier research on fabrication of various antidiabetic nanomaterials have enabled us to design more effective, rapid, environmentally friendly methods for synthesis of such nanodrugs.

Recently, we have also demonstrated that bioreduced copper nanoparticles exhibits potent antidiabetic activity.[14] Hereby, it is of utmost importance to explore novel reproducible methods for synthesis of CuNPs with specific size, well defined surface composition, isolable and redispersable properties which is a very challenging task in chemical synthesis. Very little work has been carried out on the biological synthesis of CuNPs. Although bacteria, fungi, algae and plants are widely used for synthesis of various metal nanoparticles, there are very few reports on synthesis of CuNPs using medicinal plants.[15-19] Owing to the spectrum of various bioactive principles, medicinal plants like Dioscorea bulbifera, Dioscorea oppositifolia, Gloriosa superba, Barleria prionitis, Gnidia glauca, Plumbago zeylanica, etc are considered to be a rich source of reducing and stabilizing agents towards nanoparticle synthesis.[20-28]

Medicinal plants like Barleria prionitis, Litchi chinensis and Platanus orientalis have immense significance in the traditional alternative and complementary medicine owing to their rich phytochemical composition. B. prionitis is known to possess antimicrobial, anthelmintic, antifertility, antioxidant, antidiabetic, anti-inflammatory, anti-arthritic, cytoprotective, hepatoprotective activity.[20] P. orientalis is known to be used for treatment of opthalmia, dysentery, toothache. It is also antiseptic, antimicrobial and anticancer.[29] Similarly, L. chinensis is reported to possess antioxidant, anticancer, antiinflammatory, antimicrobial, antiviral, antidiabetic, antiobesity, hepatoprotective and immunomodulatory activities.[30,31] However, there are no reports showing their potential to synthesize CuNPs.

In view of the background, herein we have attempted the synthesis of CuNPs using three medicinal plants namely, B. prionitis, L. chinensis and P. orientalis. In this paper, we have characterized the bioreduced nanoparticles followed by evaluation of antidiabetic potential by inhibition of α-amylase and α-glucosidase.

MATERIALS AND METHODS

Plant material and preparation of extract

B. prionitis leaf, P. orientalis leaf and L. chinensis peel were collected and dried in shade at room temperature for 2-3 days. The dried plant materials were pounded into fine powder in an electric blender. B. prionitis leaf extract (BPLE), P. orientalis leaf extract (POLE) and L. chinensis peel extract (LCPE) were prepared by boiling 5g of corresponding powder in 100 mL distilled water for 5 min. Supernatant was filtered through Whatman No.1 filter paper after centrifugation at 3000 rpm for 10 min. The filtrate was collected and stored at 4 ℃ for further use.[20]

Synthesis and characterization of copper nanoparticles

5 mL of BPLE, POLE and LCPE were added separately to 95 mL of 1 mM aqueous $CuSO_4.5H_2O$ solution and kept under shaking condition at 150 rpm in the dark at 40℃. Visible colour change along with UV-visible spectroscopy at regular intervals on a spectrophotometer (SpectraMax M5, Molecular Devices Corporation, Sunnyvale, CA) operated at resolution of 1 nm were used to monitor the reduction of Cu^{2+} ions to CuNPs. Bioreduced CuNPs were characterized employing high resolution transmission electron microscopy (HRTEM), energy dispersive spectroscopy (EDS), dynamic light scattering, X- ray diffraction (XRD) and fourier transform infrared spectroscopy (FTIR) as per our earlier reports.[18]

Glycosidase inhibitory activity

Porcine pancreatic amylase inhibition assay

Chromogenic 3,5-dinitrosalicylic acid (DNSA) method was used as per our earlier report to evaluate α-amylase activity.[5] Bioreduced CuNPs (10 µg/ml) were incubated with 50µg mL-1 of porcine pancreatic α-amylase at 37˚C for 10 min followed by addition of 1% starch solution which was used as substrate. Appropriate controls were kept. Reducing sugar was estimated using DNSA assay at A 540 nm and the inhibitory activity was calculated by using the formula.

% Inhibition = (A540 Control – A540 Test) / A540 Control × 100

α-glucosidase inhibitory assays

CuNPs were checked for α-glucosidase inhibitory activity as reported earlier.[4] 100 µL of α- glucosidase (0.1 unit / mL) was mixed with 200 µL of CuNPs (100µg/mL) and incubated for

1 h at 37℃. Addition of 10 mM p-nitrophenyl-α-D-glucopyranoside in 100 mM phosphate buffer of pH 6.8 marked the initiation of enzyme activity which was stopped by addition of 2 ml Na_2CO_3 (0.1 M) after an incubation of 10 min at 37˚C. α-Glucosidase activity was determined by measuring absorbance of the p-nitrophenol released from pNPG at 420 nm. One unit of glucosidase activity is defined as the amount of enzyme that hydrolyzed 1 µM of p-nitrophenyl pyranoside per minute under assay condition.

% Inhibition = (A420 Control – A420 Test) / A420 Control × 100

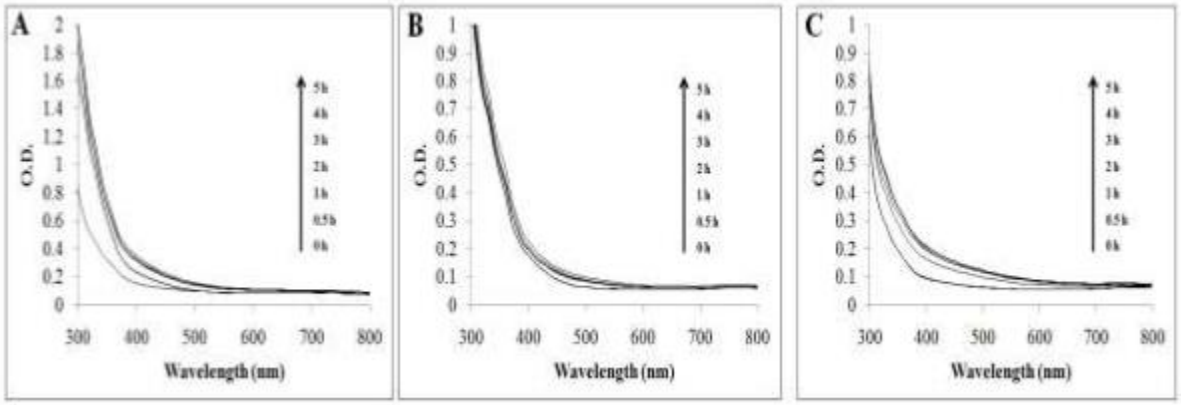
RESULTS

UV-visible spectroscopy

Synthesis of CuNPs was confirmed by gradual colour change on addition of plant extracts. Initially the light blue colour changed to faint yellow which later developed into intense brown colour. Simultaneous monitoring using UV-visible spectroscopy showed the increase in the intensity of the spectra with time at 40℃. In case of BPLE the synthesis was completed almost at 1 h as no significant increase in the intensity was observed between 1 to 5 h (Fig. 1A). Rate of synthesis with POLE was found to be comparatively faster as maximum synthesis was completed within 0.5 h (Fig. 1B). A significant increase in the synthesis of CuNPs was observed till 2 h with LCPE as evident from the spectra while

beyond 2 h no more increase in the spectral intensity was noticed (Fig. 1C).

Figure 1: UV-vis spectra recorded as a function of reaction time for CuNPs formation at 40°C using (A) BPLE, (B) POLE and (C) LCPE.



HRTEM, EDS, DLS analysis

CuNPs synthesized by BPLE were found to be monodispersed and spherical in shape. The size varied between 11 to 15 nm (Fig. 2A). The particles were found to be very small and free from any agglomeration. POLE mediated bioreduced CuNPs were found in small clusters of irregular morphology ranging between 90 to 200 nm (Fig. 2B). LCPE synthesized CuNPs were found to vary from 10 to 100 nm in size as long dispersed stretches of spherical nanoparticles (Fig. 2C). EDS analysis confirmed the presence of elemental copper in the biogenic nanoparticles synthesized using BPLE, POLE and LCPE (Fig. 3). Particle size distribution indicated in DLS was found to be in well agreement with the HRTEM analysis (Fig. 4). Widely distributed particle dimensions show the initial synthesis of smaller CuNPs which with time might grew bigger by deposition of more copper on its surface. Later, such larger aggregates were formed due to surface attraction and agglomeration of numerous smaller CuNPs.

Figure 2: High-resolution transmission electron micrographs of CuNPs synthesized. (A) CuNPs bioreduced by BPLE, inset bar representing 100 nm; (B) CuNPs bioreduced by POLE, inset bar representing 200 nm; (C) CuNPs bioreduced by LCPE, inset bar representing 50 nm.

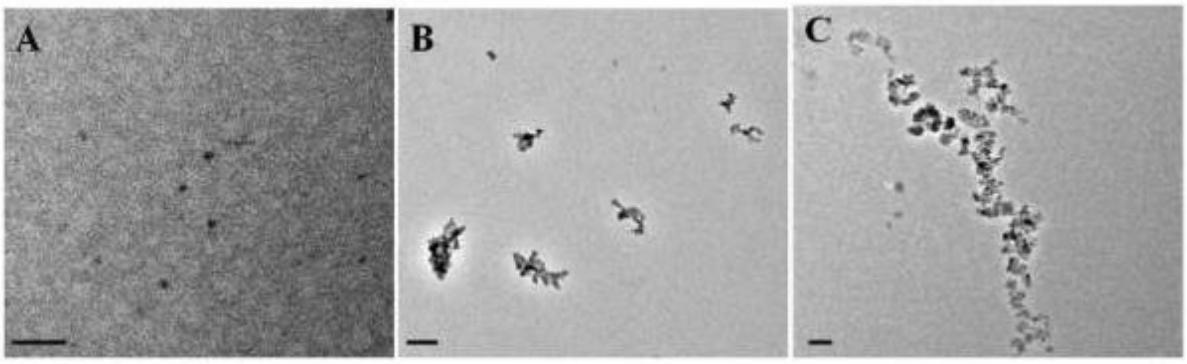


Figure 3: Representative spot EDS profile of CuNPs synthesized by (A) BPLE, (B) POLE and (C) LCPE.

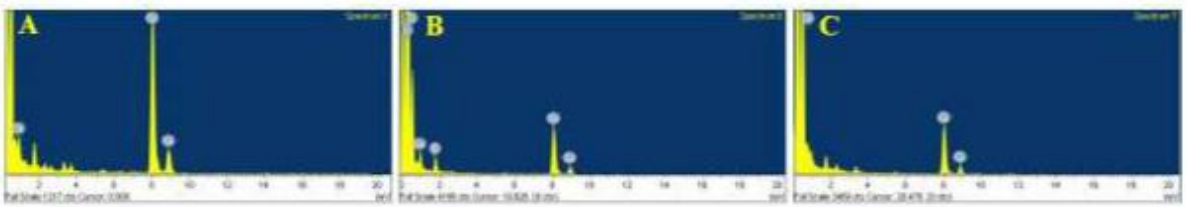
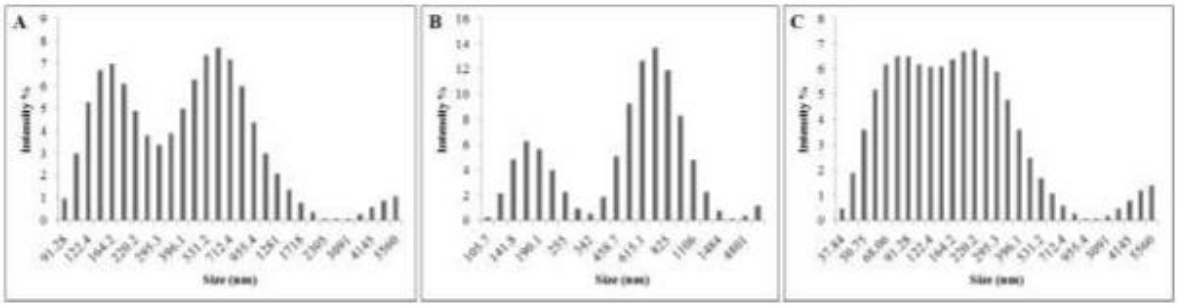


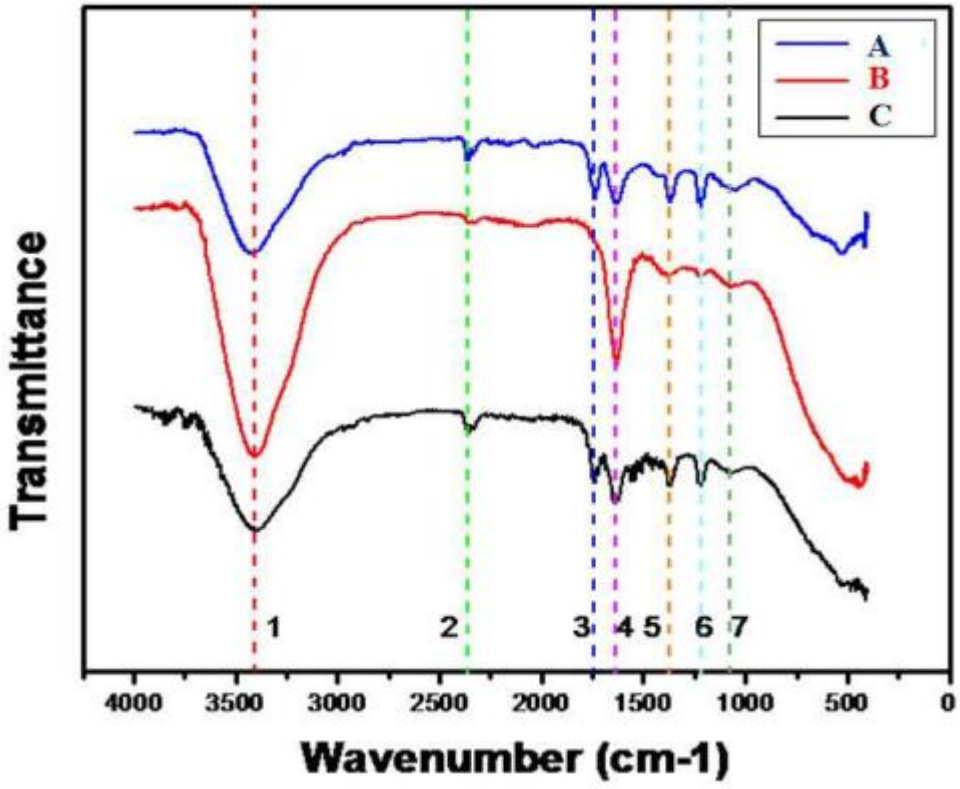
Figure 4: Histogram of size distribution of CuNPs synthesized by (A) BPLE, (B) POLE and (C) LCPE.



FTIR analysis

As evident from the FTIR spectra, the peak at 3415 cm-1 corresponding to O-H stretch might be attributed by the polyphenols in BPLE, POLE and LCPE (Fig. 5). Upon reduction of the Cu2+ to CuNPs the –OH groups of polyphenols might be oxidizing itself, thereby showing the peak at 1740 cm-1 that represents C=O stretch. At the same time other functional groups were also observed to be present before and after bioreduction like C≡C (stretch) 2366 cm-1, C=C (stretch) or N-H (bending) 1646 cm-1, C-H (bending) 1365 cm-1, C-N (stretch) or C-O (stretch) 1223 cm-1, C=C (stretch) or C-H (bending) 1082 cm-1 which might play a significant role in capping or stabilization of the bioreduced nanoparticles.

Figure 5 Fourier transform infrared absorption spectra after complete bioreduction.

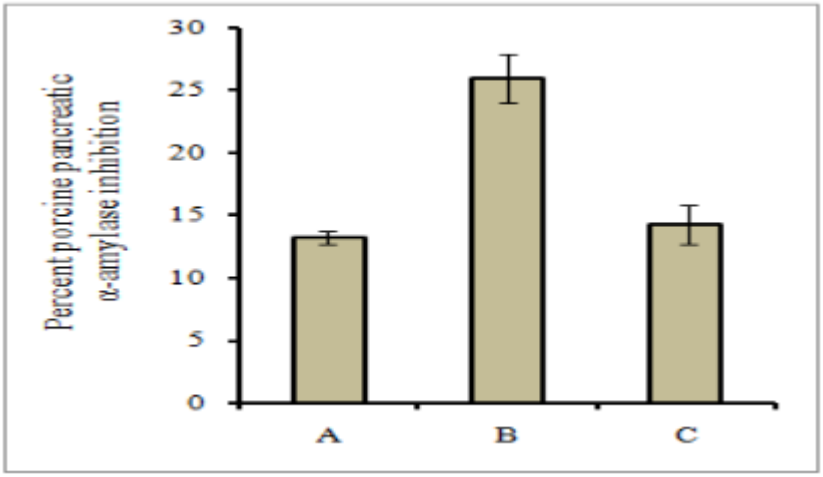


(A) LCPE, (B) BPLE and (C) POLE. The inset represents 1) O-H (stretch); 2) C≡C (stretch); 3) C=O (stretch); 4) C=C (stretch) or N-H (bending); 5) C-H (bending); 6) C-N (stretch) or C-O (stretch); 7) C=C (stretch) or C-H (bending).

Porcine pancreatic amylase inhibition assay

CuNPs synthesized by LCPE, BPLE and POLE showed variability in α-amylase inhibition. CuNPs synthesized by LCPE showed the highest inhibition upto 25.92±1.9 % followed by CuNPs synthesized by BPLE and POLE showing an inhibition of 14.28±1.58% and 13.22±0.52%, respectively (Fig. 6). Acarbose showed 77.24±0.52% inhibition.

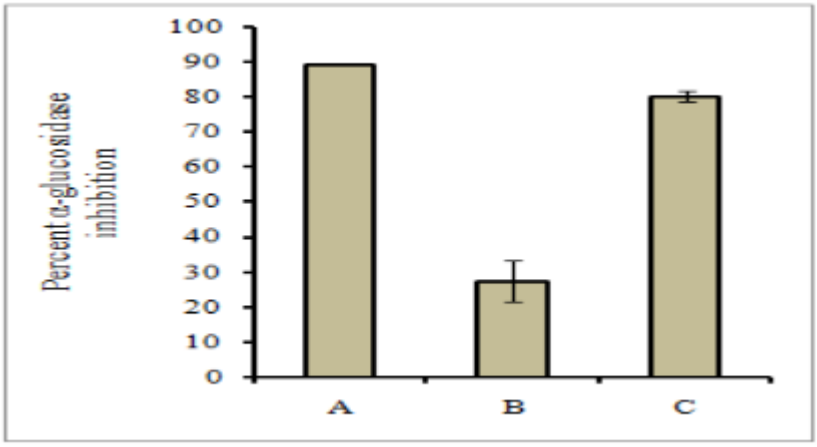
Figure 6: Percent porcine pancreatic α-amylase inhibition by CuNPs synthesized using (A) POLE, (B) LCPE and (C) BPLE.



Glucosidase inhibition assay

Glucosidase inhibition exhibited by the bioreduced CuNPs also showed variability (Fig.7). CuNPs synthesized by POLE exhibited maximum α-glucosidase inhibition of 89.31±0.17% followed by CuNPs synthesized using BPLE (80.09±1.41%). However, CuNPs synthesized by LCPE exhibited considerably low α-glucosidase inhibition (27.37±5.9%) which was comparable to its α-amylase inhibition. Acarbose showed 98.79±0.18% inhibition.

Figure 7: Percent α-glucosidase inhibition by CuNPs synthesized using (A) POLE, (B) LCPE and (C) BPLE.



DISCUSSION

Medicinal plants are considered to be treasures of diverse groups of phytochemicals that might lead to rapid synthesis of biogenic nanoparticles and thereafter their stabilization. Our earlier reports have demonstrated the potential of various medicinal plants to synthesize AuNPs, AgNPs, PtNPs and PdNPs. However, synthesis of CuNPs is less common owing to its difficulty for reduction and stabilization. In this report, we have shown the potential of POLE, LCPE and BPLE to synthesize and stabilize the bioreduced CuNPs.

The synthesis was rapid and completed within 5 h which is in agreement with our earlier reports.[17,18,20,22] P. orientalis leaf extract has shown similar potential to synthesize AgNPs which was considered to be faster and environmentally benign.[32] The biogenic AgNPs formed by P. orientalis were found to be between 15 to 500 nm which is in agreement with the size distribution observed in our study. L. chinensis is also reported to synthesize antimicrobial AgNPs which are with a size 20 to 50 nm.[33] Earlier, Calotropis procera L. is reported to synthesize CuNPs. Cysteine proteases present in the latex of C. procera L. played the key role in fabrication of CuNPs with average size of 15± 1.7 nm. It is already proved that phytogenic CuNPs are non-cytotoxic when checked against HeLa, A549 and BHK21 cell lines by MTT dye reduction assay.[34] P. orientalis leaf contains flavonoids, pentacyclic triterpenoids, tannins and caffeic acid in addition to various acylated flavonol glycosides and kaempferol derivatives.[35,29] Similarly, L. chinensis is also rich in flavonoids, isoflavone daidzein, cyanindin-3-glucoside and malvidin-3-glucoside, cyanidin-3-rutinoside, quercetin-3- rutinoside, and quercetin glucoside.[36,37] Similarly, B. prionitis is rich in various phytochemicals like balarenone, pipataline prionisides, barlerinoside, verbascoside, shanzhiside methyl ester, barlerin, acetylbarlerin, lupulinoside, scutellarein.[38] These phytochemical compositions rationalize the potential of the extracts to reduce metal ions to nanoparticles and its stabilization. The bioreduced CuNPs showed antidiabetic activity by inhibition of α-amylase and α-glucosidase which is supported by our earlier report on CuNPs synthesized by D. bulbifera.[14] Elevated concentrations of Cu^{2+} ions are reported to inhibit the digestive enzyme, amylase in giant freshwater prawn Macrobrachium rosenbergii.[40]

Likewise, Cu (II) ion and its complexes were reported to exhibit strong α-glucosidase inhibitory activity even greater than clinically used acarbose in in vitro studies.[41-45] This report provides the first hand evidence that CuNPs synthesized by medicinal plants demonstrate excellent inhibitory potential against α-amylase and α-glucosidase which are considered to be significant pharmacological targets for treatment of T2DM. This intensely rationalizes the promises of phytogenic CuNPs in emerging therapy and management of T2DM.

CONCLUSION

This is the first report on synthesis of CuNPs using Barleria prionitis, Litchi chinensis and Platanus orientalis. The bioreduction process was rapid and efficient yielding monodispersed, extremely small and stable CuNPs which is of utmost significance for a candidate nanomedicine. The CuNPs exhibited potent antidiabetic activity by inhibition of α-amylase and α-glucosidase. Hence phytogenic CuNPs can be considered as promising therapeutic nanomaterial for treatment of T2DM.

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