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Original article

# Biological synthesis of zinc oxide nanoparticles from the plant extract, *Wattakaka volubilis* showed anti-microbial and anti-hyperglycemic effects

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ABSTRACT

*Background:* In this study, a synthesis of zinc oxide nanoparticles (ZnONPs) was performed using *Wattakaka volubilis* leaf extract as a reducing and capping agent. The plant leaf extract contains various secondary metabolites, other nutritional and medicinal products.
*Methods:* The prepared ZnONPs were characterized using Ultra Violet-visible Spectroscopy, Fourier Transform Infrared Spectroscopy (FTIR), X-ray Diffraction (XRD) and Scanning Electron Microscopy (SEM) coupled with Energy Dispersive X-ray spectroscopy (EDX). The anti-bacterial study was done by the well diffusion method.
*Results:* The synthesized ZnONPs were spherical in shape, ranging from 100 to 200 nm. The FTIR bands were sharp with strong absorption peaks at 414.70 $cm^{-1}$, showing the Zn group's presence. The zinc oxide nanoparticles anti-bacterial effects were tested in gram-positive *Staphyllococcus epidermidis* (MTTC 9040) and gram-negative *Enterobacter aeurogens* (MTCC 8100). ZnONPs showed excellent anti hyperglycemic potential in zebrafish adults in the present work.
*Conclusion:* The zinc oxide nanoparticles have been effectively developed for antimicrobial in diabetic-based wound healing applications in biomedical fields. The findings of the current study have provided several interesting new avenues for future research exploration.
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## 1. Introduction

Diabetes mellitus is well known metabolic disorder causing more deaths and globally, the number of cases will double in the next 20 years (Lin et al., 1999). Zinc deficiency in beta cells is one of the reasons for the diabetic condition (Umrani and Paknikar, 2014). Zinc plays an influential role in activating more than 300 enzymes in the human body. The leading cause of diabetes is the higher level of oxidative stress (Haase et al., 2008) and the decreased levels of zinc in the pancreas are related to the highest chance of hyperglycemic conditions. In humans, there is a relationship between zinc levels and diabetes-associated complications. More importantly, zinc increases insulin's structural integrity and secretion (Sun et al., 2009; Chausmer, 1998). Some studies clearly showed that 70% of zinc is found in β-cells (Smidt et al., 2009). Zinc plays an essential role in activating NF-B in the diabetogenic pathway and protective effect on diabetes risk (Virtanen and Knip, 2003), homeostasis by activation of mitogen-activated protein kinases (MAPKs) (Hogstrand et al., 2009) and insulin-mimetic activity by activating

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insulin-signaling through Akt/PKB phosphorylation (Basuki et al., 2007).

In human cells, natural zinc oxide nanoparticles were available in the range of 1–100 nm (Bondarenko et al., 2013). The zinc oxide nanoparticles have been widely studied since 1935 and have gained significant attention in the scientific community as future material (Suresh et al., 2018). The zinc oxide nanoparticles were widely used in nanodiagnostics, nanomedicine and anti-bacterial applications (Bobo et al., 2016; Ahmed et al., 2016).

The beneficial effects of zinc oxide nanoparticles on antioxidant enzymes and oxidative stress levels were also studied in streptozotocin-induced rats (Umrani and Paknikar, 2015). Zinc is essential for the growth of the beta cells and insulin production in streptozotocin-induced diabetic rats (Bhattacharya and Gupta, 2005). Biological synthesis of nanoparticles have many advantages including cost and eco-friendly (Ezhilarasi et al., 2016; Ezhilarasi et al., 2020) and, alternative for physical and chemical methods (Ezhilarasi et al., 2020). The plant extracts mediated nanoparticle synthesis has been considered reliable and ecofriendly to nature (Singh et al., 2018). The plant crude extract contains many secondary metabolites responsible for reducing into nanoparticles formation (Aromal and and Philip, 2012; Agarwal, 1986). The various plant leaf extracts were used for nanoparticles synthesis such as silver (Thomas et al., 2019; Valsalam et al., 2019), nickel oxide (Ezhilarasi et al., 2018; Ramesh et al., 2021), zinc zirconate (Matinise et al., 2021), iron oxide (Radhakrishnan et al., 2020), titanium dioxide (Fall et al., 2021), cadmium selenide (Iyyappa rajan et al., 2018), zinc-iron oxide (Matinise et al., 2018), and zinc tin oxide (Mayedwa et al., 2018).

In this study, a hyperglycemic condition in adult zebrafish was induced by alloxan, followed by the administration of ZnONPs. The ant-microbial activity was studied in *S. epidermidis* and *E. aeurogens* (Pullaiah, 2002; Nakamoto, 2009).

## 2. Materials and methods

### 2.1. Zinc oxide nanoparticles synthesis

The fresh leaves of *Wattakaka volubilis* were purchased from the vegetable market in Tiruchirappalli, India. The fresh green leaves were air-dried in shadow and made into fine powder. The 1 g of fine powder was mixed with 25 ml of deionized water and 50 mM of zinc acetate (Himedia Laboratory, India). The reaction mixture was kept at 120 °C for 30 min. After centrifugation at 15,000 rpm for 15 min, the supernatant was discarded. The washing step was continued at least four times and sonication was done for 1 min.

### 2.2. Characterization of ZnONPs

#### 2.2.1. FTIR analysis

In the present study, the functional groups of zinc oxide nanoparticles were evaluated in Fourier Transformer Infrared spectrophotometer (Shimadzu-8400, Japan) by KBr pellet method (Jeyabharathi et al., 2015).

#### 2.2.2. X-ray diffraction study

The synthesized zinc oxide nanoparticles were studied by using X-ray diffraction (D8 Advance ECO XRD Systems with SSD1601 D Detector, Bruker, USA) with CuKa radiation. The XRD patterns of the zinc oxide nanoparticles were calculated as per the following Scherer's equation.

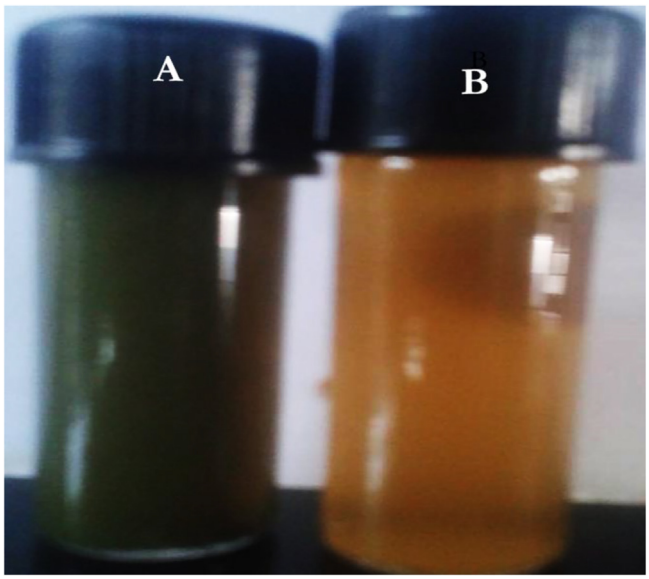


**Fig. 1.** Precipitation of the ZnONPs from *Wattakaka volubilis.*

$$D = \frac{K\lambda}{\beta\cos\theta}$$

**D -** Crystalline size of nanoparticle
**K -** Scherer, s constant (0.94)
**λ -** Wavelength ($1.546 \times 10^{-10}$)
**β -** Full width half maximum of the diffraction peak
**cosθ -** Bragg angle

#### 2.2.3. The SEM-EDX mapping of ZnONPs

The shape of the ZnONPs was studied by Scanning Electron Microscope (Carl Zeiss Evo 18, Germany). For study purposes, one drop of the sample was taken for SEM analysis and further, the elemental composition was analyzed by an Energy Dispersive X-ray spectroscopy (Bruker, USA) coupled with SEM.

#### 2.2.4. Experimental setup for alloxan administration

The healthy zebrafishes were maintained in good laboratory conditions (14 h light: 10 h dark photoperiod, 28 ± 1 °C).

The zebrafishes were categorized into five sets followed by,

**Set I:** Control group - Untreated zebrafish

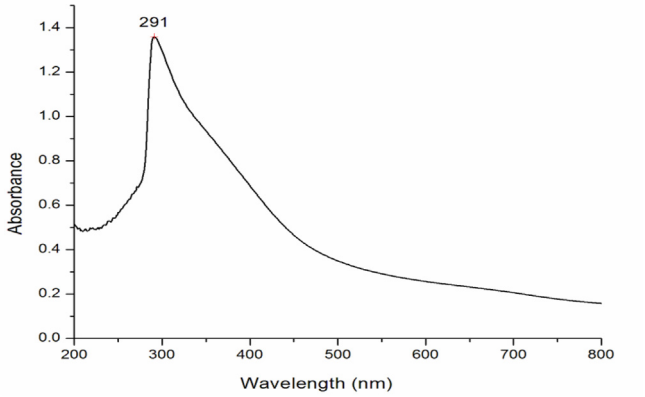


**Fig. 2.** The UV spectroscopic analysis of ZnONPs.

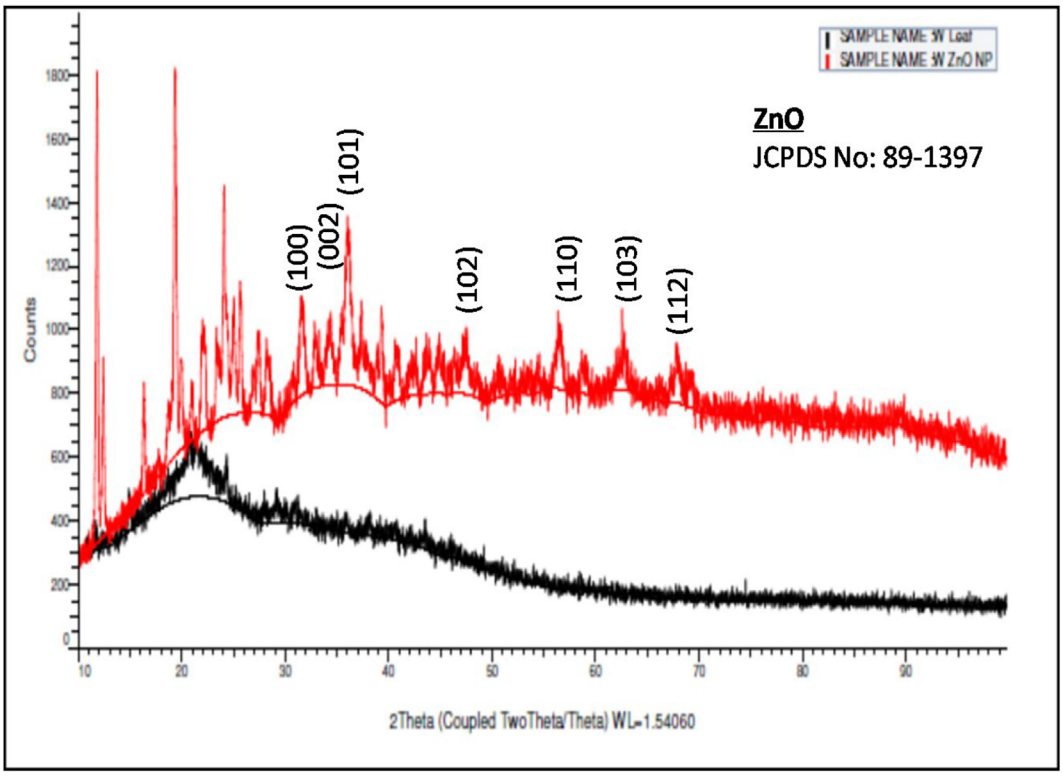


**Fig. 3.** XRD patterns of the zinc oxide nanoparticles.

**Set II:** Zebrafish induced with alloxan for diabetics (5, 25, 50, 100, 200, 300 & 400 mg/ml)

**Set III:** Diabetics induced with alloxan and treated with ZnONPs (1 mg/ml)

**Set IV:** Diabetics induced with alloxan and treated with crude extracts of *W. volubilis* (1 mg/ml)

**Set V:** Diabetics induced with alloxan and treated with standard drug Metformin (1 mg/ml)

*2.2.5. Measurement of glucose level in zebrafish blood*

The present study measured blood glucose levels in control and alloxan-treated zebrafish using a commercially available glucometer.

*2.2.6. Anti-bacterial study*

The anti-bacterial study was done by the well diffusion method. The bacterial inoculum was streak uniformly using a sterile cotton

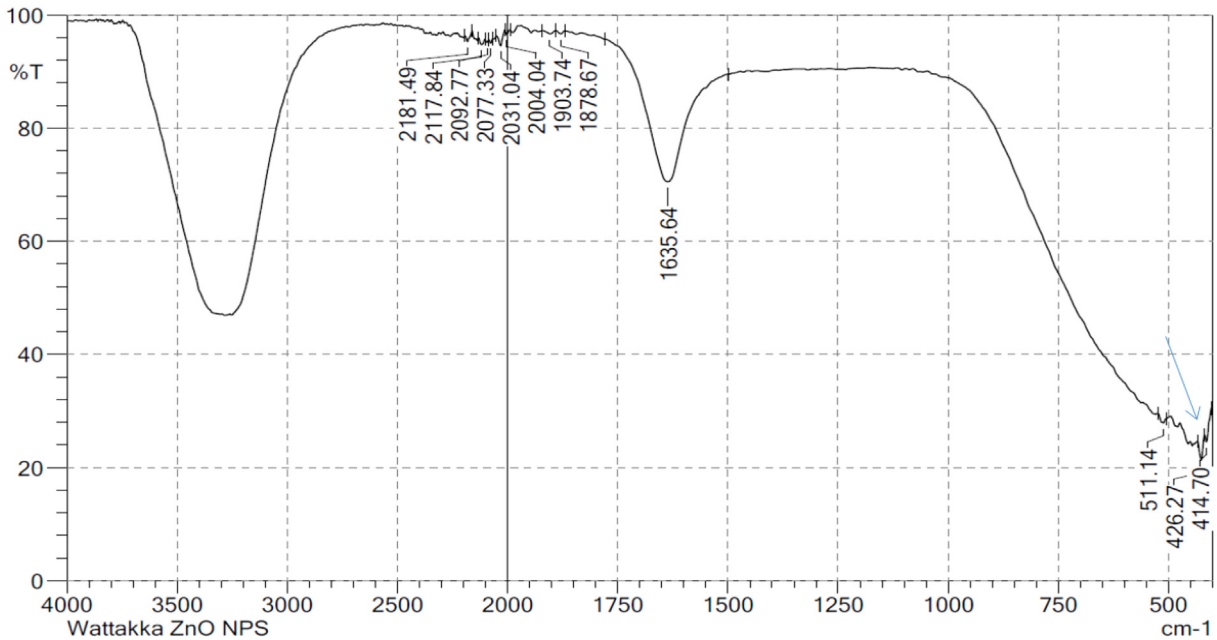


**Fig. 4.** The FTIR analysis of zinc oxide nanoparticles.

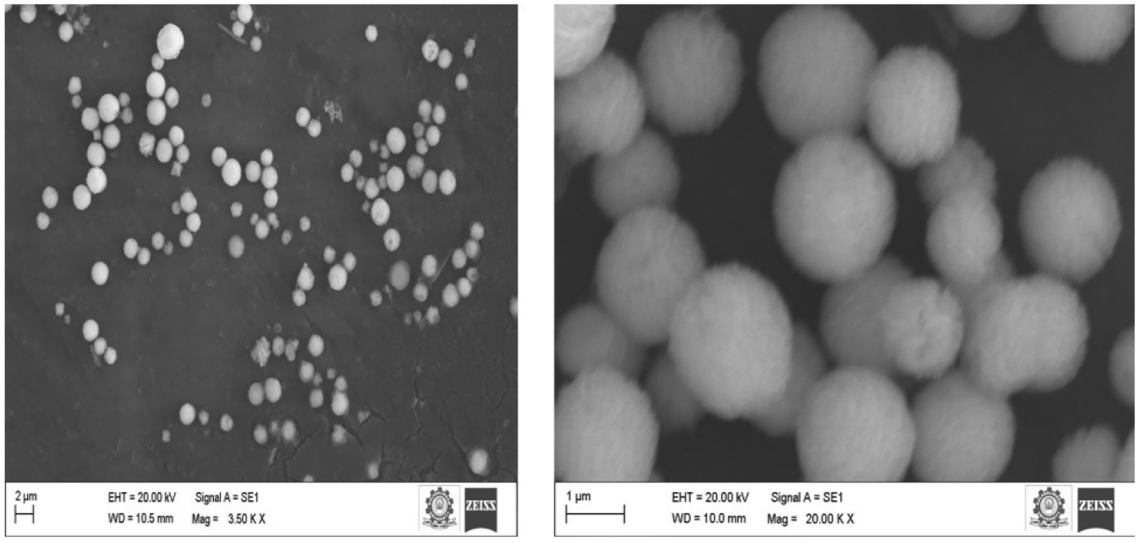


**Fig. 5.** Scanning Electron Microscopy analysis of zinc oxide nanoparticles.

swab on a sterile petri plate with nutrient agar. The petri dishes were incubated for 24 h at 36 ± 1 °C. After incubation, the bacterial growth was measured (dm in mm).

## 3. Results

In this study, zinc acetate stock solution, when added to the *W. volubilis* extracts, leads to the synthesis of zinc oxide nanoparticles denoted by the change in green to golden yellow color (Fig. 1.) The UV–visible spectroscopic study has established the synthesis of ZnONPs. The peak found at 291 nm established the presence of zinc oxide nanoparticles in the mixture (Fig. 2) The XRD pattern of the study showed the amorphous nature of the ZnONPs with the calculated crystallite size was found to the 16.79 nm (Fig. 3). Meanwhile, FTIR peak at 414.70 $cm^{-1}$ reveals the presence of ZnONPs (Fig. 4). The band observation of (NH) C=O stretching band at 1635.64 $cm^{-1}$ and C–H strong stretching band at 2181.49 $cm^{-1}$ were sharper and broader for zinc oxide nanoparticles in the reaction. Indeed the ZnONPs were further confirmed by spherical shaped morphology (Fig. 5) similar to a recent study (Jeyabharathi et al., 2017). The mapping of ZnONPs revealed a

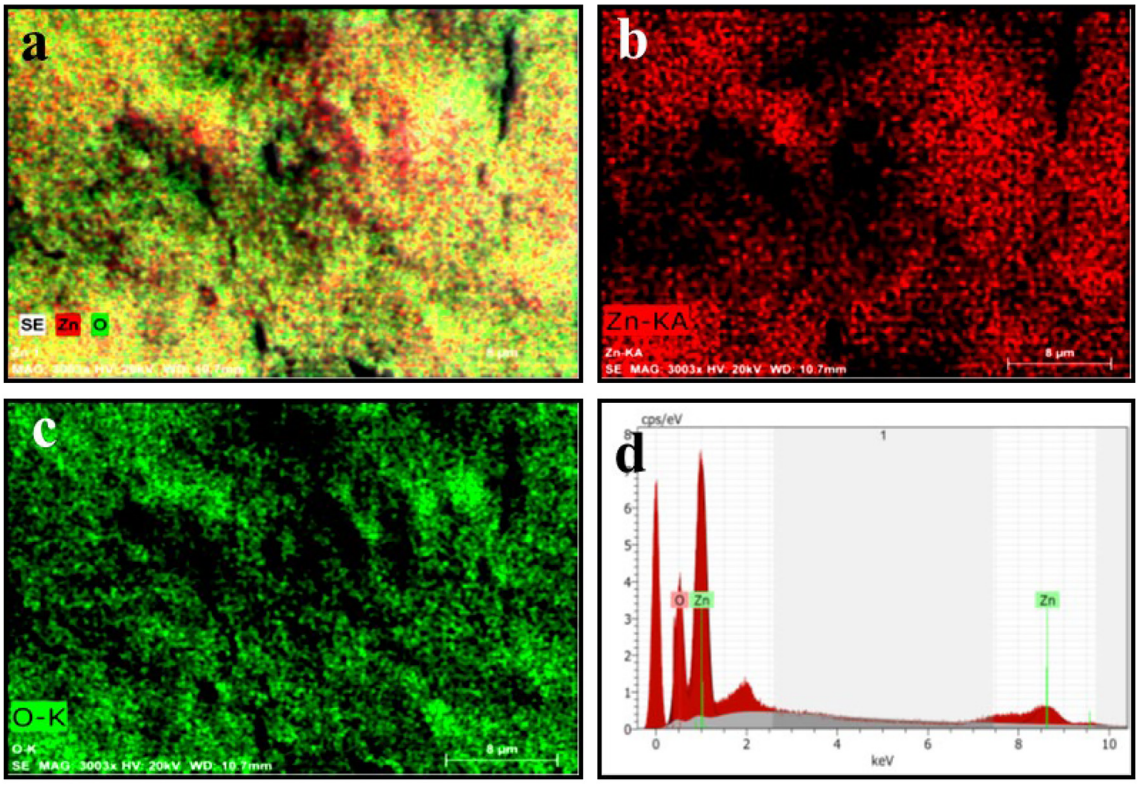


**Fig. 6.** The SEM-EDX mapping (a-SEM analysis; b- Red colour indicates (Zn); C-Green colour indicates (O); d. EDX analysis of zinc oxide nanoparticles.

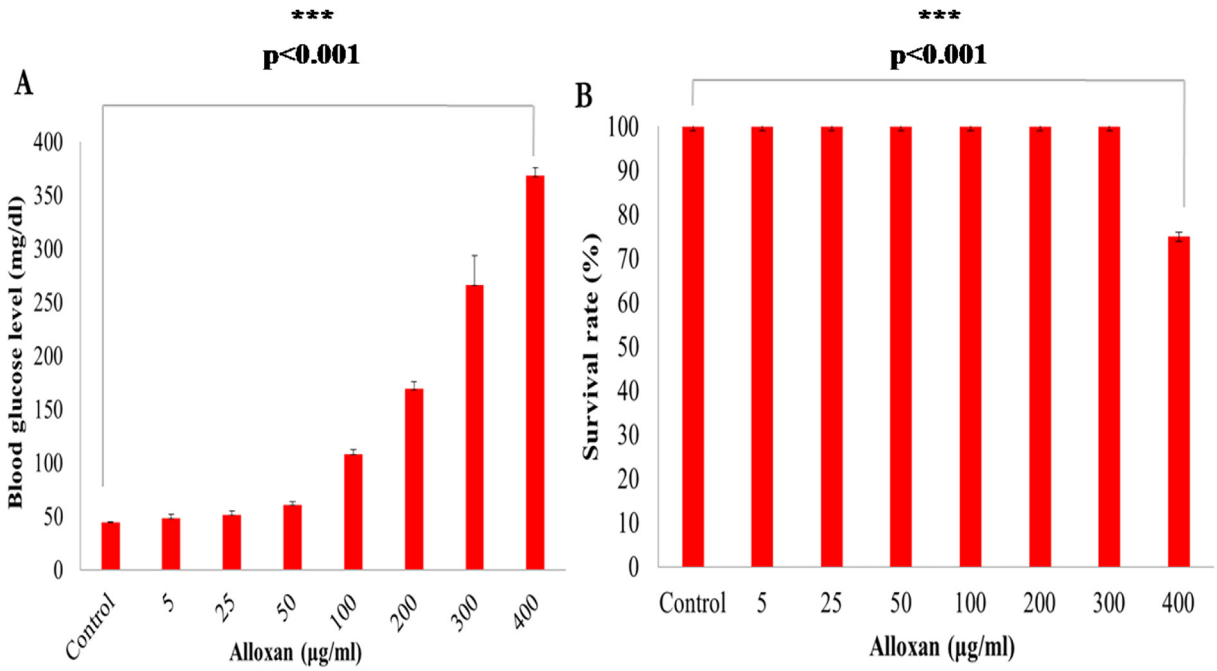


**Fig. 7.** A. Effects of different concentration of alloxan on blood glucose levels in zebrafish (24 h). B. Effects of different concentration of alloxan on survival of zebrafish (24 h).

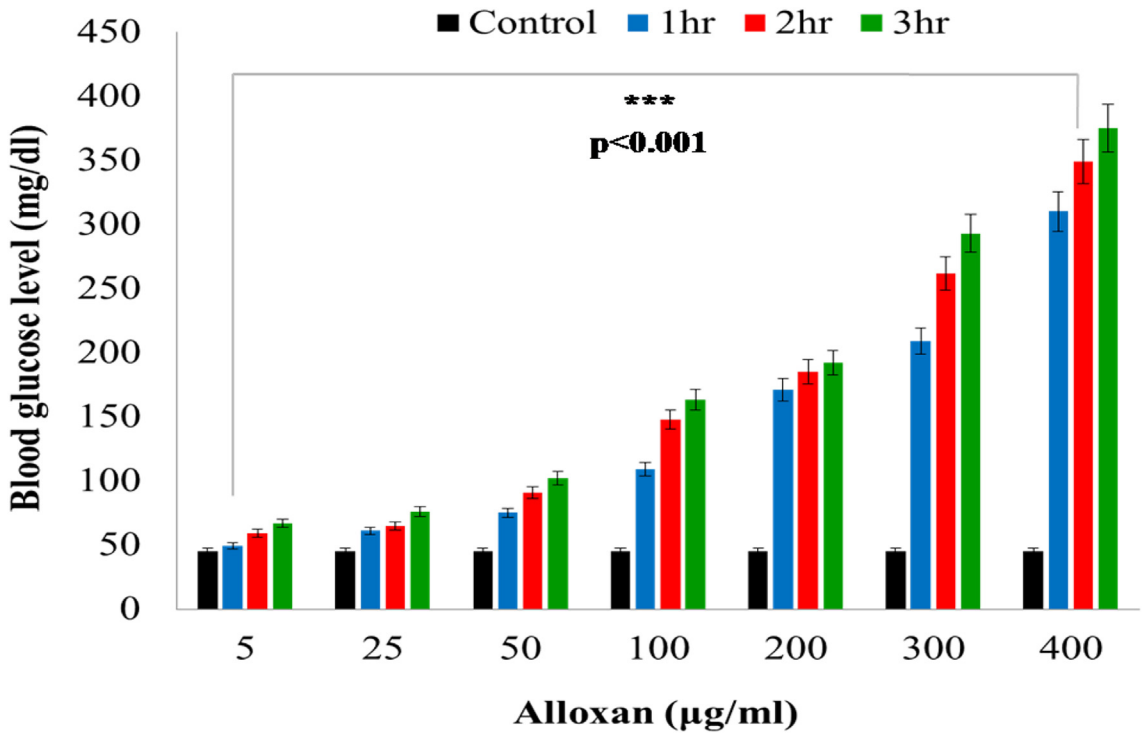


**Fig. 8.** Effect of alloxan on blood glucose level in zebrafish with different time intervals.

homogeneous distribution (Fig. 6A) of zinc (Red) and oxygen (Green) matrix, which was confirmed by small area element composition analysis (Fig. 6 B, C). The EDX spectrum confirmed the presence of zinc and oxygen in the sample (Fig. 6 D).

### 3.1. Induction of hyperglycaemic effect in zebrafish

In this study, alloxan-induced at the concentration of 400 µg/ml showed a high level of mortality in zebrafish and other concentrations did not change in the survival compared to control (Fig. 7A). The alloxan-induced zebrafish blood glucose levels were also studied (Figs. 7B, 8).

### 3.2. Effect of ZnONPs on hyperglycaemic zebrafish

Interestingly, zinc oxide nanoparticles lower the glucose level in alloxan-induced zebrafish compared to control (45–55 mg/dl). The hyperglycemic zebrafish were treated with ZnONPs, which decreased glucose levels (138 mg/dl) in a time and dose-dependent manner (Fig. 9).

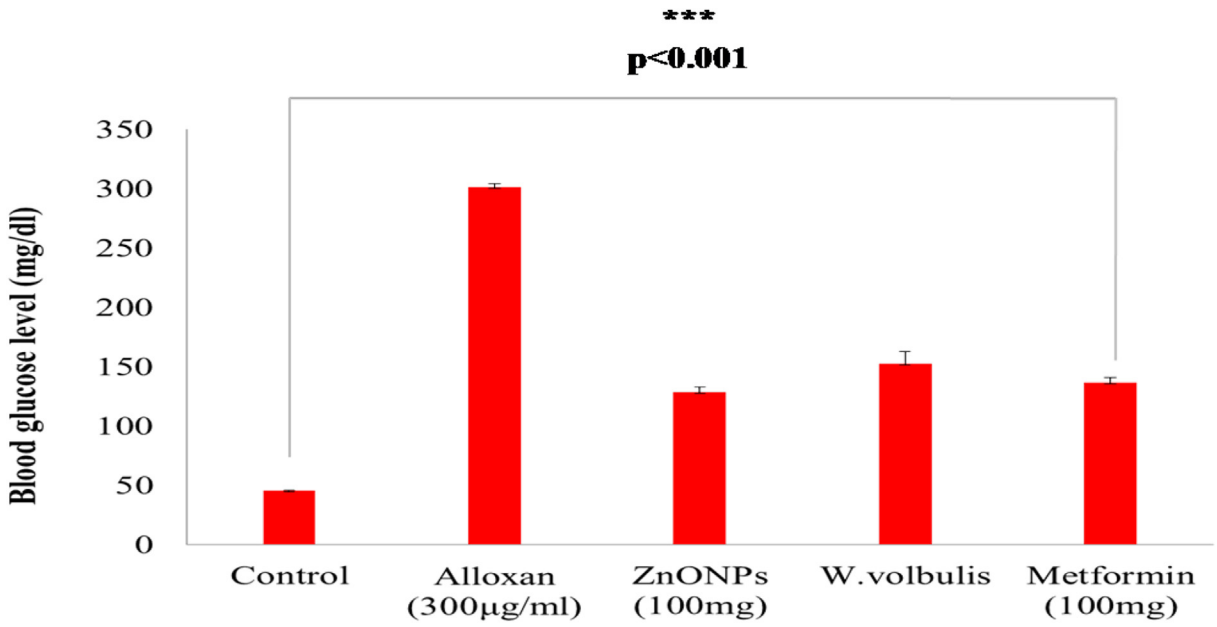


**Fig. 9.** Comparison of standard drug (metformin), ZnONPs and *W. volbulis.* on zebrafish.

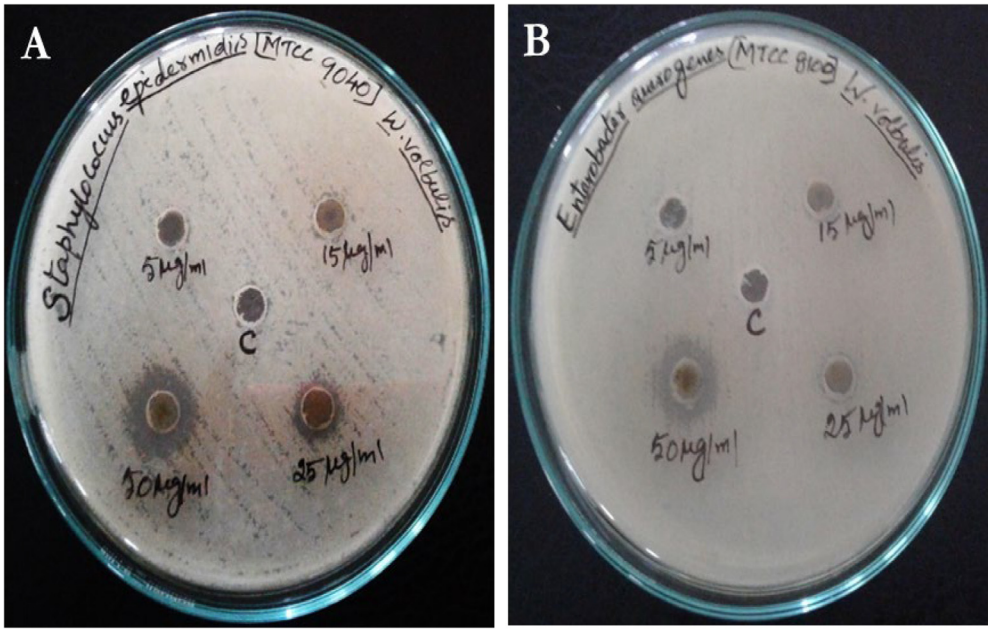


**Fig. 10.** Antibacterial effects of zinc oxide nanoparticles. A. *Staphyllococcus epidermidis* B. *Enterobacter aeurogens.*

### *3.3. Anti-Bacterial study of ZnONPs*

In control, there was no zone of inhibition (Fig. 10) was noted. The ZnONPs synthesized by *W. volbulis* plant extracts are found to possess good antimicrobial activity against *S. epidermidis* (16 mm) and *E. aerogenes* (10 mm). The present results showed that (Fig. 10) gram-positive bacteria are more susceptible towards ZnONPs from plants extracts (*W. volubilis*) when compared to gram-negative bacteria (Martin et al., 2004; Lin and Sun, 2010).

## 4. Discussion

In this study, the plant leaf extracts contain metabolites and other compounds as reducing and capping agents for zinc oxide nanoparticles synthesis. The present study's findings have collaborated with some studies with zinc oxide nanoparticles synthesis (Santhoshkumar et al., 2017). Furthermore, other studies were undertaken on streptozotocin-induced diabetes in rats (Bai et al., 2010; Barber, 2003; Aizu et al., 2002). The alloxan and streptozotocin were commonly used to induce diabetics in zebrafish, as well as present results were similar to the previous study (Stefani et al., 2018). From the study of Umrani and Paknikar, 2014, it was evident that zinc oxide nanoparticles can stimulate potent anti-diabetic activity in both types of (type 1 and type 2) diabetic rats. In the present study, zinc oxide nanoparticles were synthesized by the extracts of *W. volubilis* plant, which is promising in treating diabetes. In addition, these changes may be due to the cell wall in gram-positive bacteria being a single layer, whereas the gram-negative cell wall is many-layered (Bullani et al., 2011).

On the other hand, the passing of the compounds through the gram-negative cell wall may be inhibited. The cell wall of gram-negative bacteria has Lipopolysaccharide (LPS) and outer membrane not present in gram-positive bacteria. Some of the common problems associated with diabetic patients are foot infections and Urinary Tract Infections (UTIs) (Diene et al., 2013). The infections were caused by some pathogens of aerobic gram-positive cocci, like *Staphylococci*. This organism was also a vital etiological agent in wound infections; in particular, *S. epidermidis* has been isolated from around 60% of all the infected feet of diabetic patients. *Enterobacter* spp. was one of the bacteria involved in UTI in diabetic patients (Nicolau and Stein, 2010). The silver and silver oxide nanoparticles were used to induce antibacterial against *S. aureus* and present results were similar to the previous study (Mani et al., 2021c, 2021b, 2021a).

## 5. Conclusion

We have successfully synthesized green ZnONPs via plant-based green synthesis, exhibiting an excellent anti-diabetic property with high compatibility and good anti-bacterial activity. The reduction of zinc ions and their capping was achieved by organic molecules present in the leaf extract of *W. volubilis* and the safety evaluation of ZnONPs. The advantages of this study are not limited to the synthesis of an anti-diabetic element but also revealed the nontoxic nature of the synthesized ZnONPs, extended to the reliable and facile formulation of the nano-drug and the possibility to be scaled up. The development of drug design may be traced back to the origins of the primary chemicals. In the future, it will be necessary to identify and isolate the active molecule responsible for the antidiabetic effect, as well as to elucidate the molecular structure of the active compound.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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