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# *Spondias pinnata* (L.f.) Kurz Leaf Extract Derived Zinc Oxide Nanoparticles Induce Dual Modes of Apoptotic-Necrotic Death in HCT 116 and K562 Cells

Abdul Aziz Ahlam[1] · V. S. Shaniba[1] · P. R. Jayasree[2] · P. R. Manish Kumar[1]

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**Abstract**
This study evaluates the effects of phyto-derived zinc oxide nanoparticles (ZnONPs) on human cancer cells, colon carcinoma HCT 116, and chronic myelogenous leukemic K562, along with normal lymphocytes/erythrocytes. The commercial, chemically synthesized ZnONPs (cZnONPs) were also assessed in parallel. Using an eco-friendly approach devoid of harmful chemicals, biogenic nanoparticles were synthesized from aqueous leaf extract of *Spondias pinnata* (SpLZnONPs) by a sol-gel method. Optical, structural, and elemental characterization of both particle types were carried out deploying UV-Vis/photoluminescence spectroscopy, FTIR, XRD, FESEM, HRTEM, and EDX. Both SpLZnONPs and cZnONPs displayed hexagonal wurtzite structure with particle sizes averaging 30 and 48.5 nm, respectively. SpLZnONPs were found to be cytotoxic to both cancer cell types while cZnONPs exhibited toxicity only against HCT 116 cells. Interestingly, the cytomorphological changes and analysis of DNA laddering pattern observed in these treated cells were indicative of simultaneous induction of dual modes of death involving apoptosis and necrosis. Flow cytometric analysis of cell-cycle distribution, clonogenic, wound healing, and comet assays provided evidences of the antiproliferative potential of the tested nanoparticles. Apoptosis induction via oxidative stress-mediated $Ca^{2+}$ release, ROS generation, loss of mitochondrial membrane potential, and externalization of phosphatidylserine was also determined biochemically. Relative expression of apoptotic genes was quantified using RT-qPCR and Western blot analysis. Mitotic index analysis, MTT, and hemolytic assays on lymphocytes and erythrocytes clearly revealed the absence of any deleterious effect(s) of SpLZnONPs in these cells compared with the toxicity of the chemically derived cZnONPs, thereby attesting to the biocompatibility and selective action of the biogenic nanoparticles.

**Keywords** *Spondias pinnata* · Zinc oxide nanoparticles · HCT 116 · K562 · Apoptosis · Necrosis

## Introduction

The well-defined physico-chemical nature of inorganic metal oxide nanoparticles like zinc oxide (ZnONPs) confers enhanced interactive potential with biological components. This has evinced widespread interest due to implications in cancer therapy [1–3]. Rapidly dividing cancer cells have been shown to display high susceptibility to ZnONP-induced cytotoxicity while quiescent cells exhibit least sensitivity [4]. During phyto-mediated synthesis of ZnONPs, the bioreductive process which occurs in the presence of phytoconstituents, including those involved in capping and stabilization of the particles, underlies the observed variations in their cytotoxic potential. The capping agents are also reported to extend bioavailability of the nanoparticles [5]. Several recent studies attest to the anticancer potential of ZnONPs biosynthesized in the presence of various plant extracts. Interestingly, seaweed-derived ZnONPs have been reported with selective cancer cell killing ability without affecting normal cells, a highly desirous property sought in chemotherapeutic agents [6].

✉ P. R. Manish Kumar
manishramakrishnan@rediffmail.com; prmanishkumar@uoc.ac.in

Abdul Aziz Ahlam
ahlamabdulaziz@gmail.com

V. S. Shaniba
Shanibavsn@gmail.com

P. R. Jayasree
jayasreepr@uoc.ac.in

[1] Recombinant DNA Laboratory, Department of Biotechnology, University of Calicut, Kerala 673635, India

[2] School of Health Sciences, University of Calicut, Kerala 673635, India