Review Article ISSN 2769-6294

International Journal of Biomedical Research & Practice

Zinc Nanoparticles as a Cancer Therapeutic

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Received: 03 Jun 2024; **Accepted:** 16 Jul 2024; **Published:** 24 Jul 2024

Citation: Amos Gelbard. Zinc Nanoparticles as a Cancer Therapeutic. Int J Biomed Res Prac. 2024; 4(3); 1-10.

ABSTRACT

In this essay, Zinc specific method of use as Nano particles will be examined for its role as an anti-cancerous agent. In a long list of referenced studies, presented one by one by the authors' own words, in a seeming endless line, this essay will show that Zinc Nanoparticles are efficient against Cancer in a way that reaches maximum inhibition capacity. Unfortunately, per the researches available on this study, that only some would be summarized here for not to overload, but these studies are often in vitro, sometimes in vivo and mostly haven't been tested almost at all on humans. Since Zinc in all its forms is anti-cancerous, more studying regarding Zinc Nano particles and plain Zinc in the treatment of human cancer patients, is urgently needed.

Keywords

Zinc, Nano particles, Cancer, Toxicity, Medicine.

Background

The Anti-Cancerous properties of Zinc, an abundant chemical element in nature and in food that is known to be essential to bodily functions especially of the immune system, have been thoroughly demonstrated, it has been proven in people [1], *in vivo* [2] and *in vitro* [3] (all 3 studies chosen, from just the past month before the writing of this essay) that Zinc is extremely toxic to cancer cells without showing any toxicity towards healthy cells. It's also been demonstrated in hundreds of studies that Zinc levels among Cancer patients are lower than normal and correlate with disease progression and mortality [4].

This review will examine specifically the efficiency of Zinc as a Nano medicine, in this area Zinc Nano particles, often in combination with different drugs/substances, has also been thoroughly demonstrated as Anti-Cancerous with specific toxicity towards cancer cells without harming normal cells. There are hundreds of studies specifically proving zinc Nano particles and Nano structures to be completely Anti-Cancerous. I'll bring studies, done mostly *in vitro* and *in vivo*, that show again and again Zinc's ability to combat cancer, possibly making it a candidate to be a therapeutic and perhaps the ultimate therapeutic to the disease of Cancer. I'll continue to review just some of the articles found on this subject as I tried not to make the paper too long, I'll quote the article headline and then the most telling quote, most of the times from the abstract, that will summarize the research findings.

Results

"Zinc oxide nanoparticles induce toxicity in CAL 27 oral cancer cell lines by activating PINK1/Parkin-mediated mitophagy." A study by Wang et al. they say "We analyzed the dose-dependent cytotoxic effects of ZnO NPs on CAL 27 cells. Cells were cultured in media containing 0, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 μg/mL ZnO NPs for 24h. We further examined the intracellular reactive oxygen species levels, monodansylcadaverine intensity and mitochondrial membrane potential following the administration of 25 μg/mL ZnO NPs for 4, 8, 12, or 24h and investigated the role of PINK1/Parkin-mediated mitophagy in ZnO NP-induced toxicity in CAL 27 cells."

Their Results: "The viability of CAL 27 cells decreased after treatment with increasing ZnO NP concentrations. The inhibitory concentration 50% (inhibitory concentration 50% or IC50 is also called "Half-maximal inhibitory concentration" It indicates how much drug is needed to inhibit a biological process by half – A.G.) of the ZnO NPs was calculated as 25 μg/mL. The ZnO NPs increased the intracellular reactive oxygen species levels and decreased the mitochondrial membrane potential in a time-dependent manner as well as activated the PINK1/Parkin-mediated mitophagy process

in CAL 27 cells"[5].

The next article: "Zn-doped CuO nanocomposites inhibit tumor growth by NF-κB pathway cross-linked autophagy and apoptosis." By Xu et al. they "Aimed to investigate the antitumor effects and action mechanism of Zn-doped CuO nanocomposites. Therapeutic effects and mechanisms of Zn-CuONPs were investigated both *in vitro* and *in vivo*."[6].

Their findings: "Zn-CuONPs could inhibit tumor growth both *in vitro* and *in vivo* significantly. Zn-CuONPs treatment resulted in cytotoxicity, reactive oxygen species (ROS) production, DNA damage, apoptosis and autophagy"[6].

The next study is one of many to research the green synthesis of Zinc nanoparticles from leaf extracts and their anti-cancerous ability. It's titled "Biosynthesis of zinc oxide nanoparticles using Albizia lebbeck stem bark, and evaluation of its antimicrobial, antioxidant, and cytotoxic activities on human breast cancer cell lines." By Umar et al.

Their findings are as follows "The biosynthesized ZnO NPs showed significant cytotoxic effects on MDA-MB 231 and MCF-7 breast cancer cell lines ($P< 0.001$, $n\geq3$) in a concentration-dependent manner. All the concentrations of ZnO NPs used in our study showed significant activity against MCF-7 cells when compared with control" [7].

The next study by Baskar et al. Studied once again Zinc particles in combination with another substance, it's titled "Anticancer activity of fungal L-asparaginase conjugated with zinc oxide nanoparticles". Their findings: "Nanobiocomposite of zinc oxide nanoparticles conjugated with L-asparaginase was produced by Aspergillus terreus and was confirmed using maximum UV-Vis absorption at 340 nm in the present work. The anti-cancerous nature of the synthesized zinc oxide conjugated L-asparaginase nanobiocomposite on MCF-7 cell line was studied using MTT assay. The viability of the MCF-7 cells was decreased to 35.02 % when it was treated with L-asparaginase conjugated zinc oxide nanobiocomposite"[8].

Another study by Dumontel et al. is called "ZnO Nanocrystals Shuttled by Extracellular Vesicles as Effective Trojan nano-horses Against Cancer Cells". Their findings: "*In vitro* studies showed a high internalization of TNHs (Trojan Nano Horses) into cancer cells and efficient cytotoxic activity thanks to ZnO intracellular release"[9]. Another study: "Zinc oxide-decorated polypyrrole/chitosan bionanocomposites with enhanced photocatalytic, antibacterial and anticancer performance." By Ahmad et al.

Their findings: "Moreover, the Ppy/C/Z bio-nanocomposite shows potential application with anti-bacterial and anti-cancer activity against Gram-positive and Gram-negative bacterial pathogens and human cancer cell lines (HeLa and MCF-7). The experimental data confirm that the bio-nanocomposite of Ppy/C/Z showed excellent anti-bacterial and anti-cancer activity as compared to a pristine polypyrrole and chitosan formulation (Ppy/C). The apoptosis data with varying concentrations of Ppy/C/Z reveal the remarkable activity against these cancer cell lines"[10].

The next study is "The Self-Adaptation Ability of Zinc Oxide Nanoparticles Enables Reliable Cancer Treatments" by Taylor and Marucho. "Our results show that non-functionalized spherical zinc oxide nanoparticles with surface density N = 5.89 × 10-6 mol/m2, protonation and deprotonation rates pKa = 10.9 and pKb = -5.5, and NP size in the range of 20-50 nm are the most effective, smart anti-cancer agents for biomedical treatments"[11].

This study by Subramaniam et al. found not only Zinc nanoparticles but also Aluminum NP's to be excessively anti-cancerous. Their study is called "Comparative study on anti-proliferative potentials of zinc oxide and aluminium oxide nanoparticles in colon cancer cells" and their findings are that both "ZnO-NPs and ANPs (aluminium nano particles) inhibit HT29, colon cancer cell proliferation in a dose dependent manner, and affect the membrane potentials and also prevent the colony formation"[12].

The next study, published in Nature Magazine is "Green Synthesis of Zinc Oxide Nanoparticles Using Aqueous Extract of Deverra tortuosa and their Cytotoxic Activities" by Selim et al. Their findings: "The potential anticancer activity was in vitro investigated against two cancer cell lines (human colon adenocarcinoma “Caco-2” and human lung adenocarcinoma “A549”) compared to their activities on the human lung fibroblast cell line (WI38) using the MTT assay. Both the aqueous extract and ZnO.NPs showed a remarkable selective cytotoxicity against the two examined cancer cell lines"[13].

Another study by Zhang et al. is titled "Anticancer Effects of Zinc Oxide Nanoparticles through Altering the Methylation Status of Histone on Bladder Cancer Cells." Their findings in their own words: "In this study, we investigated the potential anticancer effects and mechanisms of nZnO on histone modifications in bladder cancer T24 cells upon low-dose exposure. Our findings showed that low concentrations of nZnO resulted in cell cycle arrest at S phase, facilitated cellular late apoptosis, repressed cell invasion and migration after 48 hrs exposure"[14].

The next study, by Khalida K Abbas Al-Kelaby in Iraq is titled "Anticancer Impact and FOXM1 Regulation of Zinc Oxide Nanoparticles on HCT116 Colorectal Carcinoma Cell Line", her findings: "Results showed that ZnO NPs were effectively and significantly inhibited the cell proliferation ($p<0.0005$) by decreasing the viability of the HCT116 cells at different concentrations involved 1, 10, 100, 500 and 1000 µg/ml, with 27.327 µg/ml half-maximal inhibitory concentration (IC50)"[15].
Another study studying the synthesis of Zinc nano particles from leaf extracts is "Green synthesis of zinc oxide nanoflowers using Hypericum triquetrifolium extract: characterization, antibacterial activity and cytotoxicity against lung cancer A549 cells" by Al Sharie et al. Their results: "MTT assay had revealed that HT-ZnO nanoflowers caused a dose-dependent decline in the viability of

A549 adenocarcinomic human alveolar basal epithelial cells with an IC50 value of 20.45 µg/mL. The effect of HT-ZnO nanoflowers on the migration and colony formation abilities against the same cells was evaluated as well"[16].

The next study by Chen et al. is called "Biodegradable zinc-containing mesoporous silica nanoparticles for cancer therapy". They report their findings: "A significant reduction in the viability of triple negative MDA-MB-231 and MCF-7 (ER+) breast cancer cells was seen following 24h exposure to MSNPs-Zn. The more aggressive MDA-MB-231 cells, with higher metastatic potential, were more sensitive to MSNPs-Zn than the MCF-7 cells. MSNPs-Zn underwent biodegradation inside the cells, becoming hollow structures, as imaged by high-resolution transmission electron microscopy"[17].

Luisa Racca et al. suggested a synergistic therapy made of Zinc nano crystals and high energy shock waves. Their findings are as follows: "The cytotoxicity and internalization of ZnO NCs were evaluated in cervical adenocarcinoma KB cells, as well as the safety of the SW treatment alone. Then, the remarkably high cytotoxic combination of ZnO NCs and SW was demonstrated, comparing the effect of multiple (3 times/day) SW treatments toward a single one, highlighting that multiple treatments are necessary to achieve efficient cell death"[18].

Another leaf extract synthesis study is "Dendropanax Morbifera Extract-Mediated ZnO Nanoparticles Loaded with Indole-3-Carbinol for Enhancement of Anticancer Efficacy in the A549 Human Lung Carcinoma Cell Line" by Rupa et al. Their findings: "*In vitro* analysis revealed the cytotoxicity of DM-ZnO-I3C-NE against a human lung cancer cell line (A549) at 12.5 µg/mL as well as reactive oxygen species (ROS) production. The DM-ZnO-I3C-NE-induced ROS generation level was higher than that of DM-ZnO NPs and free indole-3-carbinol. The synergistic effect of DM-ZnO and indole-3-carbinol indicates DM-ZnO-I3C-NE as a potential candidate for future lung cancer drug" [19].

Another area thoroughly studied is Zinc as a photosensitizer in photodynamic therapy to Cancer which proves specifically anti cancerous across many studies, one of them is "A photosensitizer-loaded zinc oxide-polydopamine core-shell nanotherapeutic agent for photodynamic and photothermal synergistic therapy of cancer cells", by Wu et al. Their findings: "Experiment results demonstrated that the designed nanotherapeutic agent had outstanding phototoxicity upon the combination of laser irradiation at 660 and 780 nm. Thus, our work proves that the ZnO@Ce6-PDA is a promising photodynamic/photothermal dual-modal nanotherapeutic agent for enhanced cancer therapy"[20].

Another substance studied more than once in combination with Zinc is Iron, here in the essay titled "Enhancing Chemotherapy of p53-Mutated Cancer through Ubiquitination-Dependent Proteasomal Degradation of Mutant p53 Proteins by Engineered ZnFe-4 Nanoparticles" by Qian et al. "Degradation of mutp53 by ZnFe-4, abrogated mutp53-manifested GOF, leading to increased p21 expression, cell cycle arrest, reduced cell proliferation and cell migration, and cell demise. ZnFe-4 also sensitized to cisplatin-elicited killing in p53 S241F ES-2 ovarian cancer cells, and dramatically improved the therapeutic efficacy of cisplatin in a subcutaneous ES-2 tumor model. The potential clinical utility of ZnFe-4 is further demonstrated in an orthotopically-implanted p53 Y220C patient-derived xenograft (PDX) breast cancer model"[21]. Next study, by Boksabadi et al. is called "The green-synthesized zinc oxide nanoparticle as a novel natural apoptosis inducer in human breast (MCF7 and MDA-MB231) and colon (HT-29) cancer cells". From their results: "Their cytotoxic impacts were studied on cancer (MCF7, MDA-MB231, and HT-29) and normal (Huvec) cell lines. Also, the apoptotic and antioxidant activities of the nanoparticles were detected and verified. The □40-nm ZnONPs significantly induce the cell-selective cytotoxic and apoptotic (BAX overexpression, Sub G1 peaks enhancement, and fluorescent stained apoptotic cells) impacts. The findings suggest the novel biocompatible ZnONPs can be useful as a safe natural apoptosis inducer in human breast and colon cancer cells"[22].

Another study on the green synthesis of Zinc and its anti-cancer properties is "Mentha mozaffarianii mediated biogenic zinc nanoparticles target selected cancer cell lines and microbial pathogens" by Ranjbar et al. and their results: "ZnO-NPs exerted distinct effects on cancer cell lines while posing no impact on normal fibroblast cells. ZnO-NPs were primarily effective against HeLa (IC50: 50.1 µg/ml) cells, followed by MDA-MD231 (IC50: 54.9 µg/ml), and LS180 (63.4 µg/ml) cell lines"[23].

The next study is "Zinc Oxide Nanoparticles Induces Apoptosis in Human Breast Cancer Cells via Caspase-8 and P53 Pathway" by Haitham Ali et al. Their findings in their own words: "Zinc oxide nanoparticles were determined to exert cell growth arrest against MCF-7 cell lines. The anti-proliferative efficiency of ZnO nanoparticles was due to cell dying and inducing apoptosis that were confirmed by the usage of acridine orange/ethidium bromide dual staining, DAPI staining and genotoxicity assay"[24].

"Zinc Oxide nanoparticles induce oxidative and proteotoxic stress in ovarian cancer cells and trigger apoptosis Independent of p53-mutation status" by Padmanabhan et al. Their findings: "Our results demonstrate that the ZnO-NPs induce acute oxidative and proteotoxic stress in ovarian cancer cells leading to their death via apoptosis. The cytotoxic effect of the ZnO-NPs was found to increase slightly with a decrease in nanoparticle size. While ZnO-NPs caused depletion of both wild-type and gain-of-function (GOF) mutant p53 protein in ovarian cancer cells, their ability to induce apoptosis was found to be independent of the p53-mutation status in these cells"[25].

Another study checking for Zinc's anti-cancerous ability as well as its anti-bacterial is "Selective toxicity of ZnO nanoparticles toward Gram-positive bacteria and cancer cells by apoptosis through lipid peroxidation". Their results regarding cancer: "ZnO nanoparticles exhibited a preferential ability to kill cancerous HL60 cells as compared with normal PBMCs (normal peripheral

blood mononuclear cells)"[26].

This next study was done *in vivo*, on lab animals, unlike most studies here done *in vitro* but its results are among the same lines, the article is titled "Bioenergetic signature as a target of zinc oxide nanoparticles in Ehrlich ascitic carcinoma-bearing mice" by Morsy et al.

In their own words: "90 female albino mice were included in this study and were divided into six equal groups (n =15 per group): saline-treated group, ZnO NP-treated, EACs-bearing mice, and three groups of EACs-bearing mice treated with ZnO NPs at a dose of 20 mg/kg every other day, 10 mg/kg every other day, 10 mg/kg every day, respectively, for 14 days. The tissues from treated groups and control groups were homogenized and used for the assay of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and F1 beta subunit of adenosine triphosphate (ATP) synthase levels, as well as the determination of lactate level. The survival time of mice was improved in all ZnO NP-treated groups, especially in EACs-bearing mice treated with ZnO NPs at a dose of 10 mg/kg every other day. This improvement was associated with an increased F1 beta subunit of ATP synthase level and a decreased GAPDH level. Also, the lactate level was significantly decreased in all treated groups when compared with the untreated group. The overall effect was the increased bioenergetic signature as compared with EC. These results implied that ZnO NPs have a significant efficacy against cancer cells and they significantly increased the bioenergetic signature"[27].

Yet another study on the green synthesis of Zinc from leaf extracts is "Crotalaria verrucosa Leaf Extract Mediated Synthesis of Zinc Oxide Nanoparticles: Assessment of Antimicrobial and Anticancer Activity" by Sana et al. regarding the anti-cancerous impact of zinc they say "In addition, NPs are also found to be effective against the studied cancer cell lines for which cytotoxicity was assessed using MTT assay and results demonstrate highest growth of inhibition at the concentration of 100 µg/mL with IC50 value at 7.07 µg/mL for HeLa and 6.30 µg/mL for DU145 cell lines" [28]. Another study is "Zinc-Phosphate Nanoparticles as a Novel Anticancer Agent: An I*n Vitro* Evaluation of Their Ability to Induce Apoptosis" by Vafaei et al.

"The measurements correspondingly showed that the cytotoxicity of MCF-7 cells depends on the concentration of NPs (IC50 = 80.112 µg/mL). MCF-7 cells were associated with initiation of apoptotic pathway in cells. Additionally, flow cytometry revealed cell cycle arrest in sub-G1 phase. ROS production was also obtained after treatment with IC50 concentration. According to annexin V-FITC/PI staining kit data, the percentage of early and late apoptotic cells was 78.2% in those treated with ZnPNPs"[29].
Another study, which studied zinc nano particles in combination and in comparison to known drugs is "Zinc oxide nanoparticles (ZnO NPs) combined with cisplatin and gemcitabine inhibits tumor activity of NSCLC cells" by Hu and Du. In their own words: "MTT, western blot and Annexin V-PI were used to assess the anti-tumor role of ZnO-NPs(Cp/Gem) in A549 cells. The viability for A549 cells showed a significant decrease in the ZnO NPs(Cp/Gem) group, Furthermore, ZnO-NPs(Cp/Gem) remarkably enhanced the apoptosis-promoting effect of Cp and Gem in A549 cells. The xenograft model showed that Zno-NPS (Cp/Gem) significantly enhanced the inhibition of Cp and Gem on tumor formation"[30].

"Targeted delivery of quercetin via pH-responsive zinc oxide nanoparticles for breast cancer therapy" is another study, by Sadhukhan et al. "Results suggested that PBA-ZnO-Q induced apoptotic cell death in human breast cancer cells (MCF-7) via enhanced oxidative stress and mitochondrial damage. In line with the *in vitro* results, PBA-ZnO-Q was found to be effective in reducing tumor growth in EAC tumor bearing mice. Most interestingly, PBA-ZnO-Q is found to reduce tumor associated toxicity in liver, kidney and spleen…"[31]. The next study I'll review is "Interaction of Ras Binding Domain (RBD) by chemotherapeutic zinc oxide nanoparticles: Progress towards RAS pathway protein interference" by Mathew et al. "The ability of ZnO NP to inhibit 3-D tumor spheroid was demonstrated in HeLa cell spheroids the ZnO NP breaking apart these structures revealing a significant (>50%) zone of killing as shown by light and fluorescence microscopy after intra-vital staining. ZnO 100 nm was superior to ZnO 14 nm in terms of anticancer activity. When bound to ZnO NP, the anticancer activity of RBD (Ras Binding Domain) was enhanced"[32].

Yet another study regarding the green synthesis of Zinc Nano Particles is "Cyrtrandroemia nicobarica-Synthesized ZnO NRs: A New Tool in Cancer Treatment" by Sudha et al. Their results: "The toxic nature of the obtained ZnO NRs was analyzed using the Daniorerio model, and the results showed that it was nontoxic. The anticancer activity of ZnO NRs was also analyzed using a human lung cancer cell line (A549), and excellent results were observed about the cancer cell death pathway" [33].

The next study is "Apoptotic Signalling of Huh7 Cancer Cells by Biofabricated Zinc Oxide Nanoparticles" written by Ananthalakshmi et al. and their results are among the same lines: "The cytotoxic study of biofabricated ZnO nanoparticles by MTT assay against Huh7 liver cancer cell lines showed a dose-dependent effect and the lethal concentration (LC50) of ZnO nanoparticles was confirmed to be 40 µg/ml"[34].

Another i*n vivo* study is "Zinc Oxide Nanoparticle Synergizes Sorafenib Anticancer Efficacy with Minimizing Its Cytotoxicity" by Nabil et al. In their own words: "Sixty adult female Swiss-albino mice were divided equally into 6 groups as follows: control, SEC, MTX, ZnO-NPs, sorafenib, and ZnO-NPs+sorafenib; all treatments continued for 4 weeks. ZnO-NPs were characterized by TEM, zeta potential, and SEM mapping. Data showed that ZnO-NPs synergized with sorafenib as a combination therapy to execute more effective and safer anticancer activity compared to monotherapy as showed by a significant reduction in tumor weight, tumor cell viability, and cancer tissue glutathione amount as well as by significant increase in tumor growth inhibition rate, DNA fragmentation, Reactive oxygen species"[35].

Another study, by GAO Et Al. is titled "Synthesis, characterization and application of ZnO and Ag-doped ZnO nanostructures against human liver cells (HepG2). A suitable candidate for valproate "The performed experiments show that the prepared ZnO nanoparticles have a significant concentration (20 g/ml) and time-dependent cytotoxicity on the examined cell lines after 24h and proved damage of the cancer cells in this time interval"[36].

Yet another study about the green synthesis of Zinc Nano Particles is "Zinc oxide nanoparticles synthesized from Aspergillus terreus induces oxidative stress-mediated apoptosis through modulating apoptotic proteins in human cervical cancer HeLa cells" by Chen et al. "The ZnO NPs exhibited concentration-dependent cytotoxicity on HeLa cells and induced the apoptosis as evidenced by reduced superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) levels, and increased reactive oxygen species (ROS) and diminished mitochondrial membrane potential (MMP) was noticed in ZnO NPs treated HeLa cell."[37].

Another study on the green synthesis of Zinc NPs is "Unravelling the human triple negative breast cancer suppressive activity of biocompatible zinc oxide nanostructures influenced by Vateria indica (L.) Fruit phytochemicals" by Dsouza et al. Their results: "ZnOVI (Zinc Oxide Valeria Indica) nanostructures exhibited up to 91.18±1.98 % human triple negative breast cancer suppressive activity "[38].

Anoter is "Biosynthesis of Zinc Oxide Nanoparticles Using Hertia intermedia and Evaluation of its Cytotoxic and Antimicrobial Activities" by Soltanian et al, who examined Zinc's impact on multiple cancer cell lines and their findings: "MTT assay showed cytotoxicity of ZnO-NPs against Caco-2 (IC50 177 µg/mL), SH-SY5Y (IC50 184 µg/mL), MDA-MB-231 (IC50 168 µg/Ml, and HEK-293 (IC50 240 µg/mL) cell lines"[39]. Anohter study examining Zinc in a combination therapy (with asparatic acid) is "Extracellular Biocoordinated Zinc Nanofibers Inhibit Malignant Characteristics of Cancer Cell" by Xin et al. Their results: "The zinc-aspartic acid nanofibers have specific binding ability to eHSP90, which induces a decrease in the level of the tumor marker-gelatinases, consequently resulting in downregulation of the tumor-promoting inflammation nuclear factor-kappa B signaling, and finally inhibiting cancer cell proliferation, migration, and invasion; while they are harmless to normal cells"[40].

Another study regarding the green synthesis of zinc NPS is "Eco-Friendly Formulated Zinc Oxide Nanoparticles: Induction of Cell Cycle Arrest and Apoptosis in the MCF-7 Cancer Cell Line" by Moghaddam et al. Their findings are extremely conclusive: "ZnO NPs were cytotoxic to the MCF-7 cells in a dose-dependent manner. The 50% growth inhibition concentration (IC50) of ZnO NPs at 24 h was 121 µg/mL. Cell cycle analysis revealed that ZnO NPs induced sub-G1 phase (apoptosis), with values of 1.87% at 0 µg/mL (control), 71.49% at IC25, 98.91% at IC50, and 99.44% at IC75"[41].

Another study done *In vitro* is "Zinc oxide nanoparticles promotes liver cancer cell apoptosis through inducing autophagy and promoting p53" by Yang et al. "Liver cancer cells Huh7 cells were transfected with GFP-LC3, and then, treated with DMSO, Sorafenib, and nano-ZnO respectively to set blank group, Sorafenib control group, and nano-ZnO group followed by the analysis of the expression of GFP-LC3, p53, and Caspase by Western blot and RT-qPCR, cell apoptosis and viability by flow cytometry and CCK-8 assay.

With a diameter of nano-ZnO 14.13±0.92 nm, the amount of GFP-LC3 protein was increased after treatment of nano-ZnO. Besides, the expressions of GFP-LC3, p53, and Caspase in Sorafenib group and nano-ZnO group were significantly higher than that of control group, while their levels were highest in nano-ZnO group ($p<0.05$). In nano-ZnO group, the values of D450nm at 24h, 48h, and 72h were 0.56±0.06, 0.39±0.05, and 0.22±0.04, respectively, and the apoptotic rate (83.11±2.79%) was significantly lower than that of blank group and control group"[42].

Anither study done *in vivo* is "*In Vivo* Anticancer Activity of Biosynthesized Zinc Oxide Nanoparticle using Turbinaria conoides on a Dalton's Lymphoma Ascites Mice Model" by Raajshree and Brindha.
Their results: "Nanoparticles were synthesized from the hydroethanolic extract of T. conoides (HETC)… Healthy Swiss albino mice were intraperitoneally induced with DLA cells and treated with ZnO-NPs and HETC at a dose of 50 µg/kg (p.o.). The effects of ZnO-NPs and HETC on body weight, tumor volume, hematological profile, and liver biochemical parameters were studied. The results of *in vivo* studies revealed that the treatment with ZnO-NPs and HETC decreased the tumor volume, thereby increasing the lifespan of DLA-bearing mice. The treatment also restored the alterations in hematological profile, antioxidant status, and activities of liver marker enzymes. These histopathological results provided the evidence for the protective effect of ZnO-NPs and HETC on DLA-induced mice. Thus, we conclude that ZnO-NPs possess more significant anticancer and antioxidant activities in DLA-bearing mice than HETC"[43].

Yet another study conducted both *in vitro* and *in vivo* is "Zinc oxide nanoparticles as a novel anticancer approach; *in vitro* and *in vivo* evidence" by Hassan et al. In their words:
" We aim to evaluate the possible antitumor activity of zinc oxide nanoparticles (ZnONPs) as a chemotherapeutic approach in *in vitro* and *in vivo* experimental models. An *in vitro* study was performed on three different cell lines, namely human hepatocellular carcinoma (HEPG2), human prostate cancer (PC3), and none-small cell lung cancer (A549) cell lines. An *in vivo* study using diethylnitrosamine (DENA)-induced HCC in adult male Wistar rats was conducted to investigate the potential antitumor activity of ZnONPs in HCC and the possible underlying mechanisms.

Hepatocellular carcinoma (HCC) was induced by oral administration of DENA given in drinking water (100 mg/L) for 8 weeks. Rats were allocated into four groups, namely a control group, an HCC control group receiving DENA alone, a ZnONPs

(10 µg/kg per week, intravenous (i.v.) for 1 month) control group, and a ZnONPs treatment group (receiving ZnONPs + DENA). ZnONPs significantly reduced the elevated serum levels of HCC-related tumor markers alphafetoprotein and alpha-l-fucosidase and the apoptotic marker caspase-3 compared with the untreated HCC rats. In addition, treatment with ZnONPs significantly decreased the elevated levels of hepatocyte integrity and oxidative stress markers as compared with the untreated HCC control group. Furthermore, the histopathological study revealed anaplasia and fibrous degenerations which were significantly corrected by ZnONPs treatment. In conclusion, administration of ZnONPs exhibited a promising preclinical anticancer efficacy in HCC and could be considered as a novel strategy for the treatment HCC in clinical practices"[44].

Another study done mostly *in vitro* is by Tanino et al. "Anticancer Activity of ZnO Nanoparticles against Human Small-Cell Lung Cancer in an Orthotopic Mouse Model", their results: "Strikingly, ZnO nanoparticles were genotoxic against small-cell lung cancer cells, resulting in low viability, even in cells orthotopically grafted onto mouse models. However, the nanoparticles were less cytotoxic against normal lung–derived cells and did not elicit observable adverse effects after intravenous administration"[45].

Another *in vitro* study, on the green synthesis of Zinc NPS is "Genotoxic and Cytotoxic Properties of Zinc Oxide Nanoparticles Phyto-Fabricated from the Obscure Morning Glory Plant Ipomoea obscura (L.) Ker Gawl" by Murali et al. Their findings: "The cytotoxic studies on HT-29 cells showed that the phyto-fabricated ZnO-NPs could arrest the cell division as early as in the G0/G1 phase (with 92.14%) with 73.14% cells showing early apoptotic symptoms after 24 h of incubation"[46].

Another study done along the same lines is " Green synthesis of zinc oxide nanoparticles using the root hair extract of Phoenix dactylifera: antimicrobial and anticancer activity" by Naser et al. "ZnO NPs were observed to be around 45% more cytotoxic than doxorubicin (DOX) alone. Particularly, triple-negative breast cancer (TNBC) cells were observed to be more vulnerable to ZnO NPs than DOX alone which significantly reduced the viability of cancer cells to 9.01%. In addition, ZnO NPs were noticed to be 82.26% cytotoxic to lung cancer cells (A549)"[47].

We'll conclude with another *in vivo* study "Efficacy of zinc oxide nanoparticles on hepatocellular carcinoma-induced biochemical and trace element alterations in rats" by Bashandy et al. Their results: "The treatment of HCC (hepatocellular carcinoma) rats with ZnO-NPs alleviated the significant increase in cancer markers, alpha-fetoprotein (AFP), glypican-3 (GPC3), and Vascular Endothelial Growth Factor (VEGF). The treatment of HCC rats with ZnO-NPs relieved the increase in liver enzymes and histopathological changes. Also, ZnO-NPs lessened the increase in the inflammatory markers. Moreover, the treatment of HCC rats with ZnO-NPs led to a significant decline in hepatic malondialdehyde (MDA) and 8-hydroxy-2′-deoxyguanosine and a significant increase in reduced form of glutathione and DNA content of hepatic cells as compared to the HCC group. Additionally, ZnO-NPs prevented the significant increase in hepatic copper and manganese levels or the decrease in zinc level in rats with HCC. Furthermore, ZnO-NPs can modulate plasma glucose level and lipid profile associated with improved hepatic mucopolysacchrides and ATP that altered in the HCC group. In conclusion, the treatment of HCC rats with ZnO-NPs offered an anticancer remedy that may be considered as a new trend for control HCC"[48].

Conclusions

This was a short summary, not a complete one, as there are hundreds of studies not only studying Zinc nanoparticles for their anti-cancer properties but in fact proving it to be extremely anti-cancerous first of all *in vitro*, which is how most studies were obtained, but also *in vivo* that we can see results along the same lines of the *in vitro* studying. You can see that Zinc is anti-cancerous in almost every constellation and even a specific method of Nano Particles use has almost endless studying proving its worth. I therefore recommend intense and urgent studying of Zinc Nano Particles, as well as simple Zinc supplementation for perhaps an ideal candidate for Cancer Treatment.

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