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Synthesis and Cytotoxicity Assessment of Curcumin-Derived Nickel Chloride Nanoparticles for ID8 mouse ovarian epithelial cancer cells

Namir Ibrahim Mohammed

Faculty of Veterinary Medicine, University of Kerbala, Karbala, Iraq
ORCD: 0000-0003-0732-6700
Corresponding Author Email: namer.i@uokerbala.edu.iq

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Abstract:

Background: In 2020, the US had approximately 1.8 million new cancer cases and over 606,000 cancer-related deaths. Between 1991 and 2017, overall cancer death rates decreased by 29%. This represents 2.9 million fewer cancer deaths than projected at high prevalence. Traditional tumor treatments like chemotherapy, radiation, and surgery are popular. Chemotherapy fights cancer but has major negative effects. Surgically excised tumors may reappear and resist radiotherapy. ***Aims:*** The objective of the current work was to evaluate the possible anticancer properties of nickel chloride nanoparticles synthesized from curcumin. ***Methods:*** 250 grams of curcumin powder and 500 ml of ethanol were combined. After mixing for an hour, we refrigerated the mixture at 4°C for 24 hours. The mixture was centrifuged for 10 minutes at 8,000 rpm. The supernatant was quickly collected and refrigerated for the next step. Next, we cooked 200 ML of the previous preparation on a 60 °C hotplate with 20 g of nickel chloride for 1 hour. Nano precipitates with NaOH. Next, we quickly centrifuged the mixture to extract nanoparticles. After two rinses with 5 ml of deionized water. ***Results:*** The image presents an X-ray Diffraction (XRD) spectrum utilized for identifying the crystalline structure and phase of a material—the pronounced and well-defined peaks in the spectrum, especially the most powerful peak at 2θ=43.310°. The NiO nanoparticles demonstrated the highest cytotoxic effects at 24 hours. ***Discussion:*** Elevated intracellular [Ni] levels result in decreased activity of Cu-dependent enzymes and transcription factors. ***Conclusions:*** Curcumin powder can be used to synthesize NiO nanospheres ecologically. Synthesized NiO nanoparticles are monoclinic and spherical, having a particle size of 20 nanometers. The synthesized nanoparticles are anticancer and have few adverse effects.

Keywords:
Nickel chloride; Curcumin; MTT; Anticancer

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Introduction:

In 2020, in the United States, there were about 1,806,590 newly diagnosed cancer cases and 606,520 cancer-related deaths. Cancer death rates had been rising until 1991, and subsequently declined consistently until 2017, culminating in a 29% reduction in total deaths. This indicates a reduction of 2.9 million cancer fatalities compared to the projected figures, which had the high prevalence persisted [1]. Conventional clinical methods for treating or excising tumors, including chemotherapy, radiation, and surgical resection, are widely employed [2]. Chemotherapy, while an effective approach in combating cancer, is often accompanied by significant disadvantages and adverse consequences. Consequently, there exists the potential for surgically exhibited tumors to recur and exhibit resistance to radiation therapy [3]. Marine and terrestrial natural materials significantly enhance treatment outcomes in disorders characterized by complex pathological behavior. Natural chemicals, due to their molecular properties, can interact with multiple biological targets, including genes and proteins [4,5].

Herbal formulations and associated natural items play a crucial role in cancer treatment and chemoprevention. Selected medicinal plants have been created to target various malignancies, as they are harmless and can reduce adverse effects on healthy cells [6,7]. The advancement of innovative therapeutic strategies is essential for effectively treating tumors and inhibiting the progression of cancer to the metastatic stage. Researchers are examining herbal remedies, Classical therapies, and nutrition to tackle the prevalent challenges in conventional cancer treatment [8,9]. Curcumin is the principal polyphenol extracted from the rhizomes of Curcuma longa L. (family: Leguminosae), which has a historical heritage of use in East Asian countries as a curry powder (turmeric) [10]. Curcumin offers a wide range of therapeutic benefits, revealed anti-inflammatory, antioxidant, antifungal, antibacterial, antidiabetic, antiproliferative, anticancer, and liver-protective effects [11]. It has demonstrated unique and strong cancer-inhibiting activity in both laboratory and animal studies, effectively targeting several tumor types across all stages of development—initiation, promotion, and progression. [12-14]. Curcumin's hydrophobic nature hinders its ability to traverse cellular membranes, as it interacts with membrane lipid fatty acyl chains through hydrophobic interactions and hydrogen bonding. Consequently, curcumin concentrations within the cytoplasm remain exceedingly low. Curcumin nano systems enhance the therapeutic properties of curcumin by addressing existing problems and augmenting bioavailability.

The success of entrapment and nanodrug loading is significantly dependent on the manufacturing method and the structure of the carrier utilized for the nano medicines. Both are essential in drug distribution and substantially influence the amount and extent of the release profile from the transporter. As a result of the relationship between the drug-to-carrier system proportions and loading capacity, encapsulation efficiency is a measure of how well the drug is adsorbed or trapped inside the nanostructures [15,16]. Multiple studies have demonstrated that nanotherapeutic approaches can significantly improve the efficacy of curcumin when delivered by various nanostructures, conjugates, dendrimers, cyclodextrins, liposomes, and other polymers [17-19].

The bulk of curcumin nanoformulations have been studied and used in clinical trials since 2011 [20]. After concentrating on increasing curcumin's absorption rate constant (Ka), researchers began to focus on efficiently targeting the affected area with curcumin using antibodies, aptamers, or peptide-mediated assistance. A study was conducted to determine the oral bioavailability of curcumin encapsulated within poly (lactic-co-glycolic acid) nanomaterials. The results showed that nanocurcumin had nine times the therapeutic efficacy of free curcumin [21]. Researchers have demonstrated that nanocurcumin can effectively treat a range of diseases and conditions, including liver disorders [22], brain tumors [23], cardiovascular diseases [24], and cancer [25-27]. Nickel chloride Nanoparticles (Ni

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Cl_2 NPs) have shown promising bactericidal and antifungal properties by disrupting microbial membranes and generating reactive oxygen species (ROS) [34]. Other studies have shown $NiCl_2$ NPs can stimulate oxidative stress and apoptosis in cancer cells, offering potential in cancer therapeutics when used at controlled doses [35]. $NiCl_2$ NPs are investigated as potential drug delivery systems that may enhance drug bioavailability and targeting due to their small size and surface modifiability [36]. This study aimed to investigate the hypothesis that nickel chloride nanoparticles synthesized from curcumin exhibit anticancer effects.

Materials and methods:

preparation of Nickel chloride Nanoparticles

Nickel chloride (NiO) nanoparticles were synthesized utilizing a biological approach at the Department of Pathology/College of Veterinary Medicine/ University of Kerbala/ Iraq. Curcumin powder purchased from the grocer. 250 grammes of powder were mixed with 500 milliliters of ethanol. The mixture was then mixed for an hour and stored at 4°C for 24 hours. The mixture was then centrifuged at 8,000 rpm for 10 minutes. The supernatant was quickly collected and stored in the refrigerator for subsequent processing. Then, 200 mL of the earlier preparation was combined with 2 g of Nickel chloride and heated on a hotplate (60 °C) for 1 hour. NaOH is used to precipitate the Nano. Next, the mixture was briefly centrifuged to extract the nanoparticles. The product was rinsed twice with 5 mL of deionized water. The precipitated nanoparticles were then centrifuged at 8,000 rpm for 5 minutes, recovered, transferred to a sterile Petri dish, and dried at 37°C for 24 hours. The grey perspiration was placed in the oven (400C^o). Figure 1: The steps for NiCl2 nanoparticles from Curcumin powder.

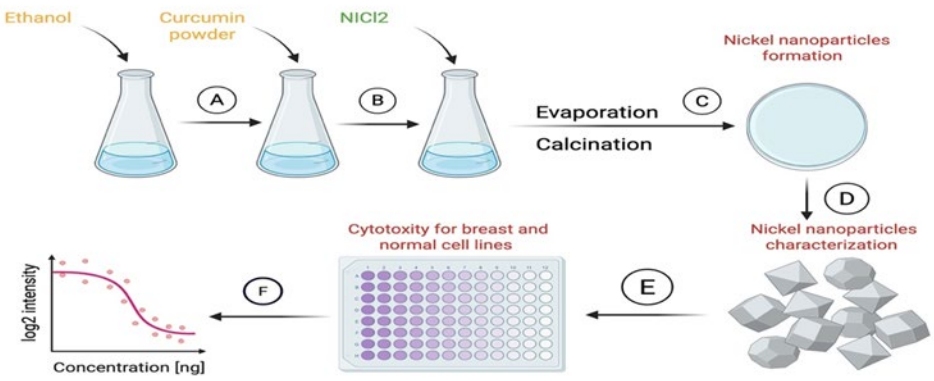

Fig. 1 Schematic diagram of Nickel oxide NP preparation and biological activity.

Results:

XRD analysis:

The image presents an X-ray Diffraction (XRD) spectrum utilized for identifying the crystalline structure and phase of a material. The pronounced and well-defined peaks in the spectrum, particularly the most

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intense peak at 2θ = 43.310 °, indicate that the material is crystalline and has a regular structure. The identification of the substance as "NiO nanoparticles" (nickel oxide nanoparticles) aligns with this XRD data: Characteristic Peaks: Each peak in the XRD spectrum corresponds to a distinct set of diffraction planes within the material's crystal lattice. The existence of distinct peaks at particular 2θ angles signifies the emergence of a crystalline nickel oxide (NiO) phase. The most prominent peak at 2θ = 43.310 ° is indicative of NiO. Wider XRD peaks are generally indicative of smaller crystallite dimensions (on the nanometer scale). The FWHM of the most prominent peak (0.461°) corroborates that the crystallite size is small, aligning with the characterization of the material as nanoparticles. The determined crystal size of around 18.53 nanometers further substantiates this. The strength of a peak corresponds to the abundance or quantity of the crystalline phase. The primary peak for NiO is the most powerful peak. The XRD spectrum reveals that the sample comprises crystalline NiO nanoparticles with nanometer-scale crystallite dimensions, and the peaks correspond to the established pattern for NiO (Fig. 1).

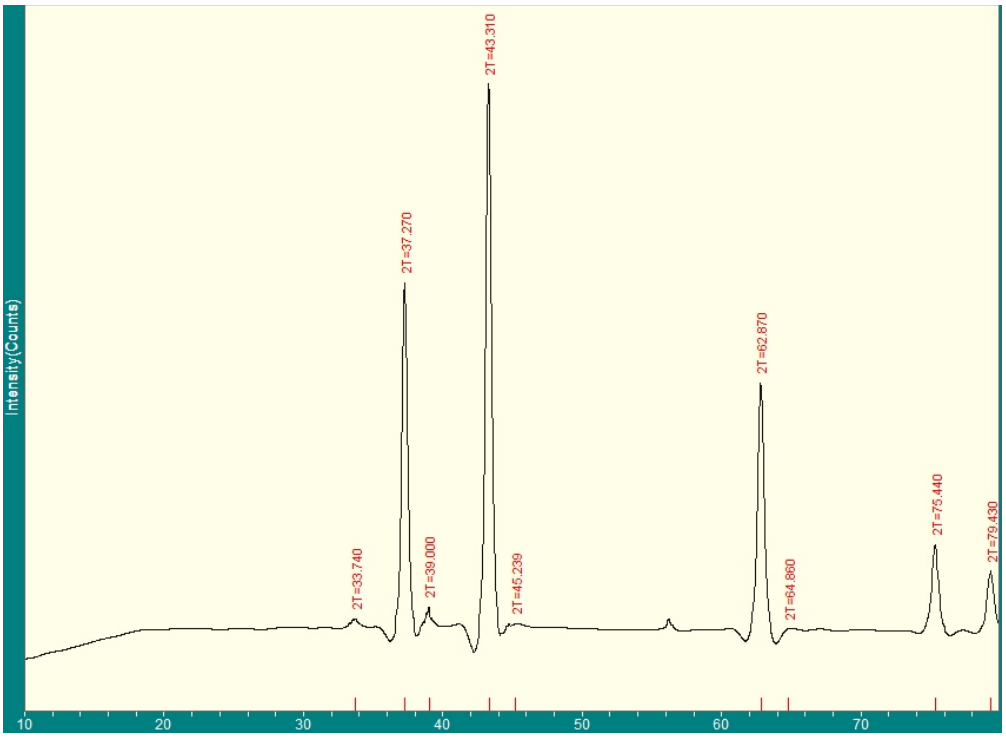

Figure (2): XRD for Nickel nanoparticles for Curcumin powder extract with ethanol.

(FESEM) and (EDS) analysis:

The structure and shape of the synthesized nanoparticles are validated using FESEM analysis. It is undeniable that particles are the fundamental building blocks of the sphere. The overall photos depicting the obtained particles show structural nanoparticles with structures resembling flowers or a sponge-like appearance. The subsequent photographs depict particles with unusual shapes, such as ovals and flowers. The size of NiO nanoparticles (GFM) typically falls between 21 and 46 nanometers. We can gain a more precise understanding of the particle size through morphological analysis if the particles are distributed evenly. It was noted that the use of natural particles as reducing agents led to the formation of particle agglomeration, similar to what was observed in NiO nanoparticles produced through biological synthesis [34]. This provides considerable support for the hypothesis that nanoparticles of pure NiO might be created. The results of this study demonstrate that either method can be used to obtain

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NiO nanoparticles. Nickel is confirmed to be present through the use of EDS, which demonstrates the presence of an elemental NiO signal.

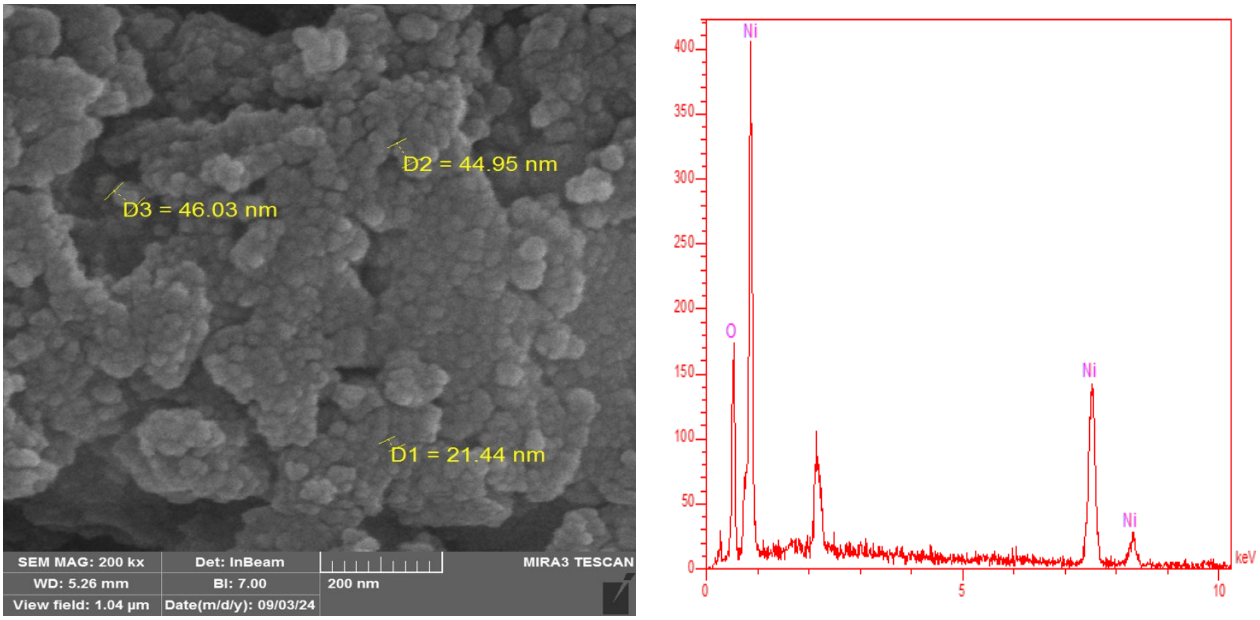

Figure (3): FESEM (200 micrometers) for NiO nanoparticles for Curcumin powder extract with ethanol.

Cytotoxicity of Nickel nanoparticles prepared with an Autoclave:

To assess the cytotoxic effects of the synthesized NiCl2 nanoparticles, the ID8 and HFF cell lines were exposed to varying concentrations (15.6, 31.25, 62.5, 125, 250, and 80 µg/ml) of the NiCl2 nanoparticles. The NiCl2 nanoparticles demonstrated the highest cytotoxic effects at 24 hours; hence, this duration was selected for calculating the IC50 values. Upon analyzing the MTT results, the IC50 values for the nanoparticles were determined to be 2.8%V/V for ID8. The NiO nanoparticles exhibited a suitable anticancer effect due to their reduced cytotoxicity on the normal cell line; therefore, they were selected for future investigation. Figure [4] demonstrated that the cytotoxic effects of all NiO nanoparticles and NiO bulk were dependent on both time and dosage. [28] have revealed that biogenic NiO nanoparticles generated from Erythrina variegate exhibit cytotoxicity against the HeLa cell line (IC50 = 48 µg/ml), while demonstrating reduced toxicity towards the HEK293 cell line. The NiO nanoparticles synthesized using Annona muricata extract inhibited the multiplication of Mouse ovarian epithelial cancer cells in another study. Furthermore, in a separate study, the NiO nanoparticles obtained from Houttuynia cordata exhibited lethal effects on cervical cancer cells. Furthermore, [29] observed that NiO nanoparticles synthesized from Ficus religiosa extract diminished A549 cell survival in a dose-dependent manner. NiO nanoparticles have demonstrated a dose-dependent lethal effect on the PANC-1 cancer cell line. Consequently, the outcomes of this study were analogous to those of prior research. Furthermore, our findings indicated that the anticancer efficacy of the NiO nanoparticles is associated with their size. The NiO-900 nanoparticles demonstrated reduced cytotoxicity on the HFF cell line compared to other NiO nanoparticles.

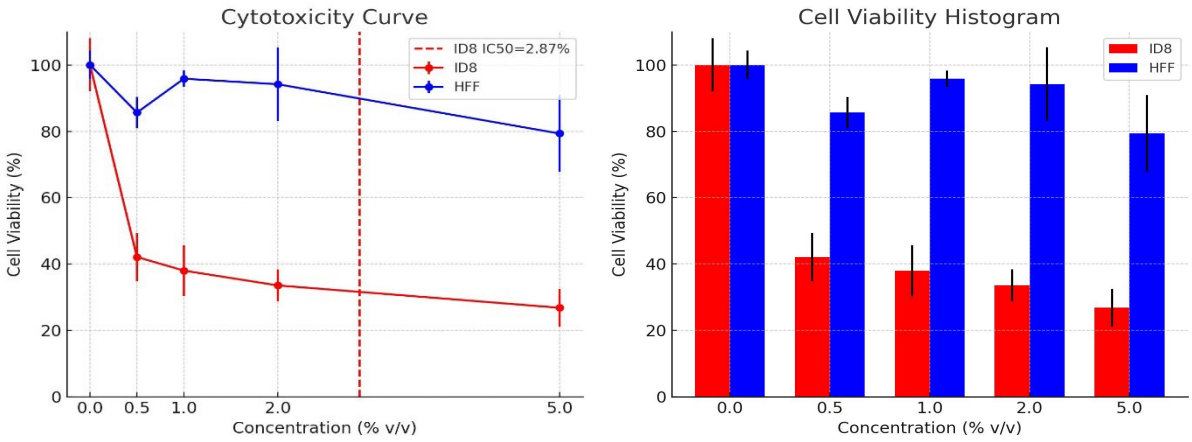

Figure (4): MTT NiO nanoparticles for HFF in red, and cells and ID8 mouse ovarian epithelial cancer cell in blue color.

Discussion

NiO nanoparticles cell line toxicity:

NiO nanoparticles can produce toxicity in three different ways due to their unique mechanism of action, which allows them to interact with various types of cells [21]. Because of the breakdown of extracellular NiO nanoparticles, Figure 3 illustrates an increase in the quantities of nickel found within the biological cells [22]. A decrease in the activity of Cu-dependent enzymes and transcription factors occurs if there is an increase in the quantity of nickel found inside individual cells. It is possible that this mechanism will influence BeAS-2B and C2C12 cells [23]. The activity of enzymes and transcription factors that are dependent on NiO nanoparticles is inhibited whenever these nanoparticles dissolve inside cells [24]. Some cell types, including RKO and 3T3-L1, may undergo this process. The pH of the lysosomes is lowered as a result of the dissolution of NiO nanoparticles. Lysosomal instability arises from a decrease in pH, adversely affecting protein-digesting lysosomal enzymes, and from elevated intra-lysosomal nickel levels [25].

This study sought to investigate the cytotoxic effects of nickel chloride (NiO) in conjunction with curcumin-derived organ chemical nanoparticles on mouse ovarian epithelial cancer cells relative to normal Mouse ovarian epithelial cells. The combination therapy approach was assessed for its physicochemical properties and anticancer efficacy utilizing XRD, FESEM, and MTT assays. The X-ray diffraction (XRD) patterns validated the successful synthesis of curcumin-based nanoparticles, exhibiting distinctive crystalline peaks, while the presence of NiO was established through its unique diffraction characteristics. The crystallite size, determined via the Scherrer equation, indicated that the particles were on the nanometre scale, which is crucial for effective cellular uptake and molecular interaction.

Field Emission Scanning Electron Microscopy (FESEM) revealed that the nanoparticles exhibited relatively homogeneous and spherical morphology, with an average particle size suitable for cellular internalization. The morphological study corroborated the incorporation of $NiCl_2$ into the nanoparticle system, demonstrating structural uniformity throughout the formulation [30]. The cytotoxicity evaluation using the MTT test indicated that the concomitant administration of NiO and curcumin nanoparticles markedly diminished cell viability in Mouse ovarian epithelial cancer cell lines relative to controls and to cells treated with either drug independently. Normalsely, the impact on

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normal Mouse ovarian epithelial cells was much diminished, suggesting a level of selective toxicity. This targeted approach suggests a potential therapeutic benefit by minimizing harm to healthy tissue [31]. The enhanced anticancer efficacy of the combination formulation may be ascribed to the synergistic interaction between NiO-induced oxidative stress and the apoptotic and anti-inflammatory properties of curcumin [32]. Curcumin nanoparticles may enhance cellular absorption and bioavailability, addressing the solubility challenges of native curcumin; however, NiO could amplify reactive oxygen species (ROS) generation and mitochondrial impairment in cancerous cells [33].

Conclusion:
The findings substantiate the concept that NiO-curcumin nanoparticle formulations demonstrate preferential cytotoxicity towards Mouse ovarian epithelial cancer cells, providing a solid foundation for subsequent in vivo validation and mechanistic investigation. Subsequent investigations should incorporate gene expression profiling and apoptotic marker assays to further our understanding of the molecular processes implicated.

Declarations

Study Limitations:

A limitation of this study is the use of green nanoparticles on different cancer cell lines.

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Competing Interest:
The authors declare that they have no competing interests related to the content of this study.

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Human And Animal-Related Studies:

Author Contributions:
The study design and the experiments were performed by Namir Ibrahim Mohammed. In addition, Namir Ibrahim Mohammed analyzed the data and wrote the manuscript.

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