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Antimicrobial Properties of Zinc Oxide Nanoparticles

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ABSTRACT

Researchers from all around the world are interested in nanoparticles of zinc oxide (ZnO-NPs) because of their extensive biological functions. In addition to be less toxic and biodegradable, they can dramatically increase pharmacophore biological activity. ZnO-NPs are the most commonly utilized metallic nanoparticle in electronics and optics due to their distinct visual and chemical characteristics, which may be easily altered by modifying the structure and broad bandgap. Repetition their affordability, biocompatibility, and biodegradability, ZnO-NPs are a viable option as a nanocarrier for conventional medications. ZnO NPs' tiny particle size and large surface area can improve surface reactivity by enhancing antibacterial activity. Additionally, as the surface characteristics of nanomaterials modify their interactions with cells, this may prevent ZnO NPs from having their intended antimicrobial effect. Surface modifications covering ZnO NPs can therefore play a role in moderating antimicrobial activity. ZnO NPs' antibacterial activity may be increased by adding surface modifiers containing groups harmful to microorganisms. This article discusses in detail the biopotency of ZnO-NPs in antibacterial, anti-inflammatory, antifungal, antidiabetic, anticancer, antioxidant, and antiviral applications.

Conclusion : It has been demonstrated that ZnO-NPs perform a wide variety of biological functions.

Keywords: zinc oxide nanoparticles, anti-bacterial activity, cytotoxicity.

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INTRODUCTION

As nanoparticles have a larger surface area and distinct physiological, biological, and chemical capabilities than their non-nanomaterial counterparts, the various applications of nanoparticles-based technologies have made up novel avenues in materials studies [1]. Nanoparticles' improved electrochemical interaction, heat transfer, and nonlinear optical characteristics provide novel uses in nanotechnology [2]. Researchers have determined that zinc nanoparticles are equally biocompatible and less harmful to humans than zinc ion, a liquid form of the trace element zinc oxide (ZnO), which is present in the human biological system. Biodegradability of ZnO-containing compositions in both normal (non-nano) [3]. Zinc ions are also important regulators of internal bacterial toxicity, resulting in cell membrane breakdown [4]. Zinc ions are also important mediators of intracellular bacterial toxicity, resulting in cell membrane breakdown [5],[6]. In human tumor cells, ZnO nanoparticles shows cytotoxicity, which led to cell death through the apoptosis mechanism [7], It is additionally demonstrated to promote cellular damage in epithelium cells (A549) and tumor cells [8],[9], as well as to enhance the antiproliferative activity of cells from breast cancer [10], and induce mortality in cancer cells of the human lung with epidermal growth factor receptor mutations, also known as EGFR [11]. It has been shown that ZnO nanoparticles affect horizontal gene transfer as they affect transduction efficiency of *Bacillus subtilis* [12], It also reduces parameters responsible for cirrhosis and nephrotoxicity [13]. At sub-minimum inhibitory concentrations, (ZnO-Ag NPs) reduces the extent of the creation of a biofilm as well as the activity of genes in *Staphylococcus aureus* [14]. Because of its antioxidant and antiproliferative qualities, it also lessens the gonadal toxicity brought on by the immunosuppressant and anticancer medication cyclophosphamide [15]. By stimulating autophagy, which encourages the dissolution of ions of zinc and the production of (ROS), cancer cells are killed [16]. Zinc ions and zinc oxide nanoparticles showes cytotoxic effects in the digestive tract of earthworms, affecting the intestinal epithelium and chlorogenic tissues [17]. It is found that zinc oxide nanoparticles dissolved slowly in physiological human fluids (pH 6–8). According to the USFDA, zinc oxide is a chemical that is safe and won't dissolve human blood cells [18].

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1. ZnO nanoparticles have antimicrobial properties.

The global proliferation of bacterial infections and antibiotic resistance, human existence is seriously threatened by microorganisms. because their exceptional photo-oxidative and photocatalytic characteristics as well as their antibacterial qualities, zinc oxide nanoparticles are being considered as potent agents against bacteria that have developed multidrug resistance [19]. In aqueous ZnO suspensions, hydrogen peroxide and proteins from cell membranes may interact chemically. The different chemical species that are created as a result explain the various antibacterial activity [20]. The following are the suggested mechanisms: the release of Zn2+ ions [21],[22]. ROS generation [20]. the loss of cellular integrity brought on by ZnO NP interaction with the cell wall, and the internalized oppression of ZnO NPs [23]. One of the most frequently reported mechanisms for antimicrobial activity in the literature is the production of ROS by metal oxide NPs, as shown in figure (1). ROS include (O_2^-), (HO_2^-), and (H_2O_2) [24], all of which has the potential to harm biological elements like proteins, lipids, and DNA [25].

A conduction band (CB) and valence band (VB) make up the two bands that makeup ZnO's electrical structure. When a photon's energy exceeds the bandgap or 3.3 eV, it is quickly absorbed, and electrons leave the VB through the CB, starting a sequence of photoreactions [26]. ZnO NPs' antibacterial activity was enhanced by increased ROS production after UV light exposure [27]. However, some researchers demonstrate that ROS can be produced even in the absence of light [28]. ZnO NPs were effective at killing bacteria that were susceptible to hydrogen peroxide. With less sensitive bacteria, similar results are obtained. As a resultThe authors proposes that the main mechanism for ZnO NPs' antimicrobial activities could be peroxide hydrogen [29].

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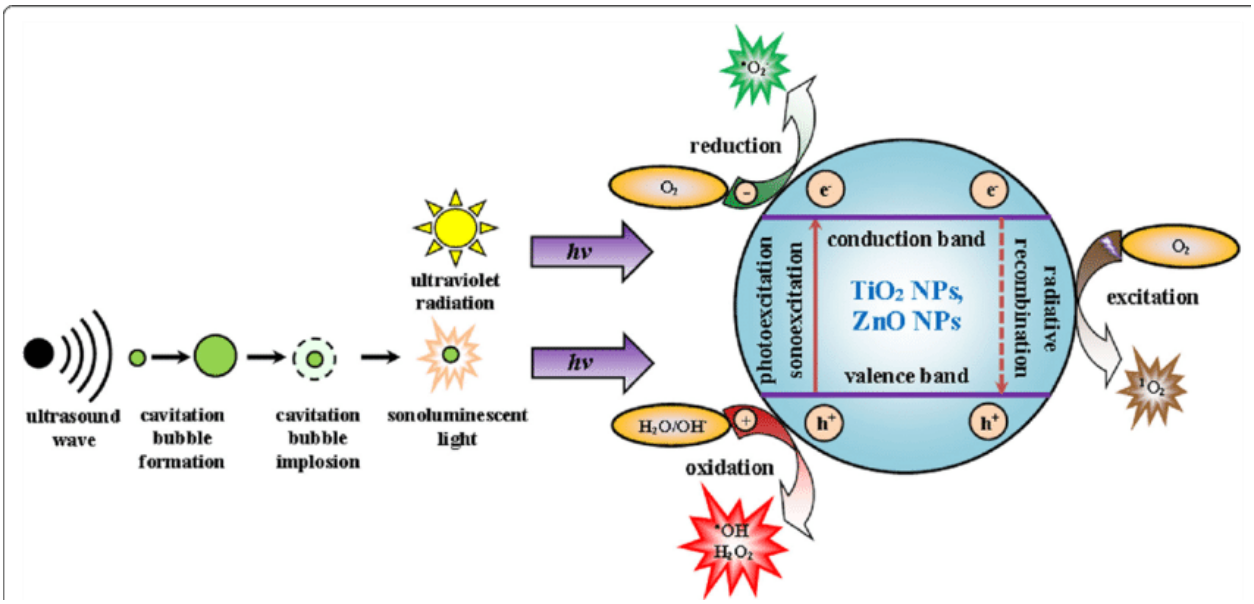

Figure (1): Mechanisms of ROS generation brought on by ZnO NPs [30]**.**

A recent study [31] demonstrated the antibacterial activity of ZnO NPs toward methicillin-resistant *Staphylococcus aureus*. In contrast to earlier investigations, which showed that Zn ions or ROS are necessary for antimicrobial activity, ROS cytotoxicity is not the main mediating factor of antibacterial activity in this study. The mechanisms including sugar metabolism, pyrimidine synthesis, and amino acid biosynthesis made up the most pertinent characteristics to explain the action of ZnO NPs. Another potential mechanism for microbe harm is photoconductivity, a photo-induction process [26]. Due to its semiconductor features, ZnO has significant photocatalytic productivity, possibly related to its antimicrobial effect [32]. Due to this, whenever ZnO is exposed to ultraviolet (UV) rays, its antimicrobial effect improves because of an increase in conductivity, which turns on the contact between ZnO and cells of bacteria. Conductivity continues even when ultraviolet (UV) light is switched off [32]. Another method of killing bacteria is the production of Zn 2+ ions. The partial breakdown of ZnO NPs in solvent causes the release of antibacterial Zn 2+ ions. ZnO NPs dissolve, which reduces amino acid synthesis and destroys the enzymatic system, increasing their antibacterial action [33]. In acidic conditions, ZnO NPs dissolve and release Zn 2+ ions. At biological pH or a neutral pH, ZnO NPs are unaltered. But in lysosomes of microorganisms, which have an acidic pH of 4.5, they quickly disintegrate, causing death by attaching to biological components within the cell of

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the bacteria and limiting its growth [34]. The interaction of the ZnO nanoparticle with the cell's wall, resulting in bacterial integrity degradation [21], is another putative cytotoxic mechanism of NPs made of ZnO. ZnO NPs' toxicological effects on E. coli were examined by Brayner et al. [23] in their study. According to the results, the bacterium cells are killed, which caused membrane instability. As a result, the permeability of the membrane increased, which caused ZnO NPs to accumulate in the membrane of bacterial cells and also NP internalization. As has been previously shown, ZnO NP toxicity is not always reliant on bacterial cell internalization. By generating ROS or increasing ZnO NP solubility, which both have the potential to harm cells, ZnO NPs have the ability to change the surroundings around bacteria [34].

2. ZnO-NPs have antifungal properties.

The shape, size, and concentration of ZnO-NPs have a significant impact on their fungicidal action. Investigations into the antifungal efficacy of fabricated ZnO-NPs versus isolates of Candida albicans revealed that they were more effective against drug-resistant Candida albicans isolates, proving the fungicidal potency of ZnO-NPs. In addition, it has been demonstrated that prophylactic treatment of ZnO-NPs at lower concentrations shields G. mellonella from C. albicans disease [35],[36]. On clinical strains of Candida sp., a two percent ZnO-NP-based cold creme demonstrate more antifungal resistance than a two percent commercial antifungal lotion [37]. Even Aspergillus and Penicillium are susceptible to ZnO-NPs' antifungal effects, and Trichophyton mentagrophytes and Trichophyton verrucosum have been examined for their antidermatophytic effects [38]. The effectiveness of the ZnO-NP treatment increased as ZnO-NP concentrations increased from 3 to 12 mM, as demonstrated by the antifungal activity tested against two harmful fungi, Penicillium expansum and Botrytis cinerea [39].

3. ZnO-NPs' anti-inflammatory properties

The immune system is activated during the inflammatory response, and proinflammatory cytokines like TNF, interleukin (18, 12, 6, and 1), INF, and Macrophage Granulocyte Colony Stimulating Factor (GMS-CF) are released, according to figure (2). The activity of various genes, including iNOS and COX-2, which produce mediators that promote inflammation, is regulated by NF-, which in turn increases the production of PGE2 and nitric oxide [40]. ZnO-NPs blocks the NF path, myeloperoxidase, degranulation of mast cells, pro-inflammatory cytokines production, and iNOS expression [41]. In a dose-dependent manner, ZnO nanoparticles made

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from Polygala tenuifolia reduced the mRNA production of inflammatory cytokines [42]. Furthermore, when doped with aluminum , ZnO-NPs were found to reduce TSLP production and Activation of caspase-1 in mast cells, Consequently, the production of pro-inflammatory cytokines such as TNF, IL-6, and IL-1 is reduced [43]. When administered intraperitoneally, ZnO-NPs reduced edema in the paws caused by carrageenan as well as increased the anti-inflammatory activity of the nonsteroidal anti-inflammatory medicine ketoprofen [44] when compared to ZnO standard form. Both formulations, however, failed to shield the stomach mucosal from the ulcers brought on by the administration of ketoprofen when given per os (PO). ZnONPs have been shown to provide great capping of flavones like orientin, isoorientin, isovitexin, and vitexin, that induce an effective anti-inflammatory reaction in several methods, involving preventing the activity of an enzyme called phospholipase A2, as well as lipoxygenases (a type of enzyme that generates eicosanoids), leading to a decrease in steroid hormones and prostanoids [45].

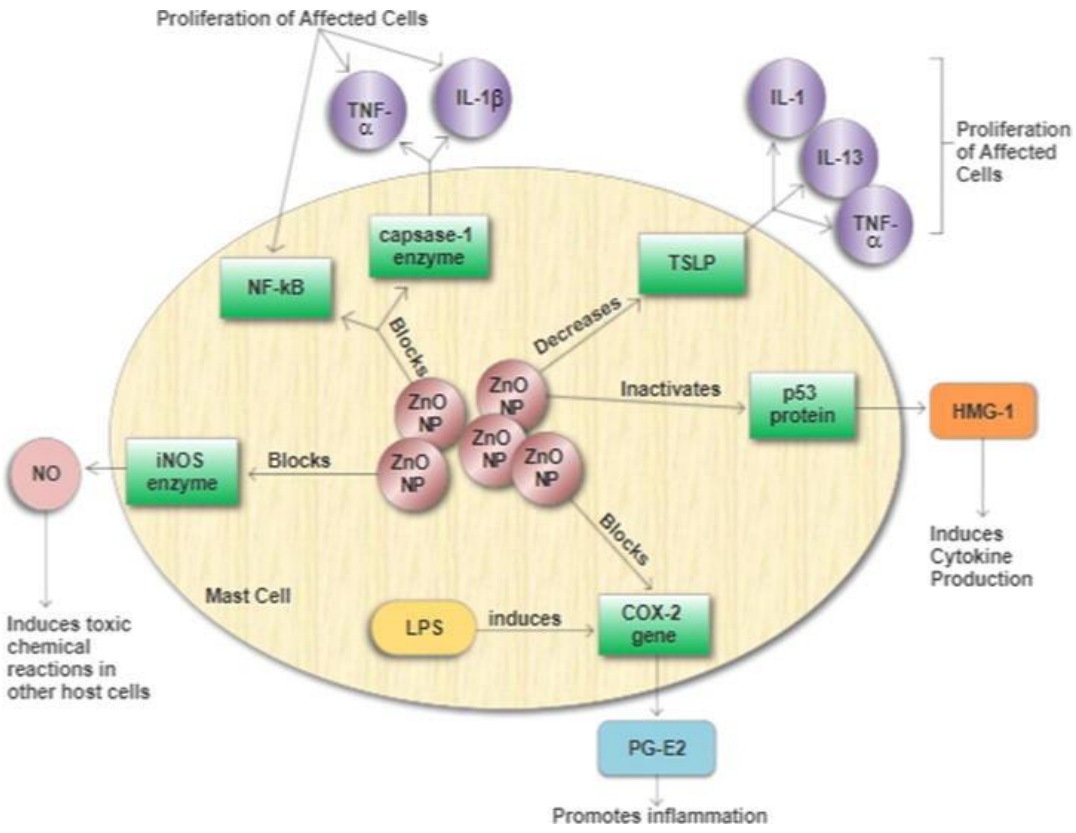

Figure (2): ZnO-NPs' anti-inflammatory properties [41].

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4. ZnO-NPs's anti-diabetic effects

The most common metabolic disruption disease, diabetes, is also one of the leading causes of death globally. The macrovascular consequences of diabetes include strokes, and cardiovascular disease, which are a result of atherosclerosis [46]. A metabolic condition called diabetes is characterized by chronic hyperglycemia. Zinc has been discovered to be essential for the growth, secretion, and storage of insulin [47]. Some mechanisms, such as insulin receptor tyrosine phosphorylation, PI3K activity, and inhibition of glycogen synthase kinase, increase insulin signaling [47]. Zinc's ability to imitate insulin has been associated with enhanced lipogenesis and decreased adipocyte production of nonesterified fatty acids [48]. Compared to other metal nanoparticles, ZnO-NPs are more frequently used for their anti-diabetic effects because they increase the expression of the INS and GLUT-4 genes because of a number of factors, including elevated cellular penetration of biosynthesized ZnO-NP glycolysis promotion by hepatic glycogenesis, which is and insulin elevation. Furthermore, it has an additive impact on the quantity of GLUT-2 and IRA expression, as well as the activity and expression of increased glucokinase [49]. One study found that the combination of zinc and insulin functions as autocrine molecules, causing GSIS to be released from rat-isolated islets of the pancreas and connecting with various insulin transduction system components to promote the metabolism of glucose and insulin mRNA levels in the hepatic tissue of diabetic rats [50]. According to this research, ZnO-NPs significantly reduce insulin and glucose levels, improve glucose tolerance, and reduce diabetic dyslipidemia.

5. ZnO-NPs' antioxidant activity

Consuming various oxidized foods has been related to a number of significant disorders in modern society, such as hepatomegaly and epithelium necrosis, due to their ability to produce peroxides of lipids as well as toxic-free radicals [51] **Figure (3)**. both synthetic and natural antioxidants are utilized to neutralize these detrimental free radicals; nevertheless, they have limitations like increased reactivity and cytotoxicity compared to the nanomaterials created today [52]. Some studies investigated the antioxidant properties of ZnO-NPs and discovered that the antioxidant properties of ZnO-NPs are caused by the shift of electrons from oxygen to the odd electron found on the atom of nitrogen in DPPH (2,2-diphenyl-1-picrylhydrazyl), leading to a

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decrease in the intensity of the change occurring at 517 nm wavelengths [53]. ZnONPs' promising antioxidant activity is explained by the previous study, which showed that the proportion of free radical reduction by ZnO-NP on DPPH increased with concentration [54]. Similar to the above, ZnO-NPs made from Aquilegia pubiflora extracts of leaves are subjected to four different assays to control their antioxidant activity. The results regarding the amount of ascorbic acid comparable per milligrams (g AAE/mg) were inversely proportional to the level of ZnO-NPs in every assay [55].

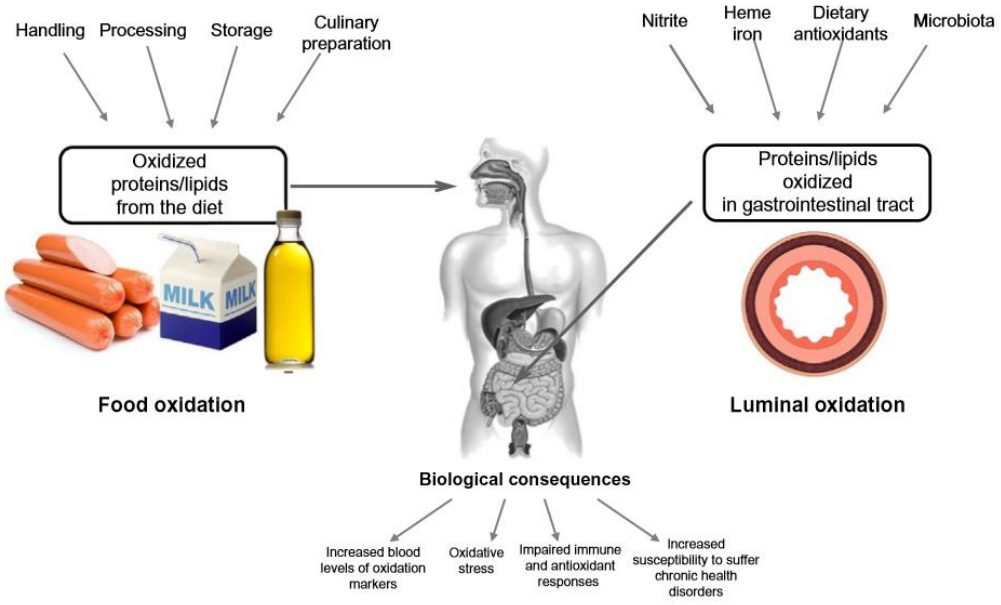

Figure (3): dietary protein and lipid oxidation products' biological effects [56].

6. ZnO-NPs's antiviral properties

human immunodeficiency virus (HIV), Human papillomavirus (HPV), herpes simplex virus (HSV), hepatitis E and C virus (HEV, HCV), and severe acute respiratory syndrome coronavirus (SARS-CoV) have all been demonstrated to be susceptible to ZnO-NPs' antiviral activity [57]. Synthesis of cytokines that are pro-inflammatory that block the virus arises from the stimulation of both adaptive and innate immune responses by toll-like receptor-mediated pathways of signaling and protein down streaming. Zn2+ ions have antiviral capabilities in that they inhibit

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virus reproduction, assembling, and releasing during the course of the virus's life cycle, as well as generating reactive oxygen species [58]. They also inhibit virus adsorption and entrance and block coating. Zinc has been demonstrated to modify the immune system of the host to prevent viral replication and reduce viral RNA polymerase that is RNA-dependent activities as well as viral polyprotein synthesis and entrance. It serves as an intermediary in the LPS-induced, TLR4-dependent MyD88 (myeloid differentiating primary reaction protein 88) signaling cascade that leads to nuclear factor kappa b in its early stages activation. TNF , IL-6, and IL-1 are examples of pro-inflammatory cytokines that are produced more as a result and are crucial for controlling viral pathogens [59]. Moreover, ZnO-NPs have the ability to absorb ultraviolet light, uncouple molecules of water, and release Zn2+ ions. This causes the generation of ROS like hydroxyl radicals, hydrogen peroxide, and superoxide, which damage the virus's lipids, proteins, carbohydrates, and DNA and finally cause the virus to perish [60]. Jana et al. achieved the survival of cells percentages of 93.6% and 92.4% at 400 g/mL, respectively. found that polysaccharide-encapsulated ZnO-NP has remarkable antiviral activity versus cytomegalovirus from humans [61]. Thus, both ZnO-NPs & PEGylated ZnO-NPs suppress the influenza H1N1 virus, while PEGylated ZnO-NPs display stronger anti-influenza effectiveness while having a lower impact on MDCK-SIAT1 cells versus ZnO-NPs [62].

Conflict of interests.

There are non-conflicts of interest.

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الخلاصة

يهتم الباحثون من جميع أنحاء العالم بالجسيمات النانوية لأوكسيد الزنك (ZnO–NPs) بسبب وظائفها البيولوجية الواسعة. بالإضافة إلى كونها أقل سمية وقابلة للتحلل الحيوي، فإنها يمكن أن تزيد بشكل كبير من النشاط البيولوجي للمستحضرات الصيدلانية. تعد ZnO–NPs من الجسيمات النانوية المعدنية الأكثر استخدامًا في الإلكترونيات والبصريات نظرًا لخصائصها البصرية والكيميائية المميزة، والتي يمكن تغييرها بسهولة عن طريق تعديل البنية وفجوة النطاق الواسعة. نظرًا لقلة تكلفتها، وتوافقها الحيوي، وقابليتها للتحلل الحيوي، تعد ZnO–NPs خيارًا قابلاً للتطبيق كحامل نانوي للأدوية التقليدية. يمكن لحجم الجسيمات الصغير لـ ZnO NPs ومساحة السطح الكبيرة أن يحسن تفاعل السطح من خلال تعزيز النشاط المضاد للبكتيريا. بالإضافة إلى ذلك، نظرًا لأن الخصائص السطحية للمواد النانوية تعمل على تعديل تفاعلاتها مع الخلايا، فقد يمنع ذلك ZnO–NPs من الحصول على تأثيرها المضاد للميكروبات. وبالتالي يمكن أن تلعب التعديلات السطحية التي تغطي ZnO NPs دورًا في تخفيف نشاط مضادات الميكروبات. يمكن زيادة النشاط المضاد للبكتيريا لـ ZnO NPs عن طريق إضافة معدلات سطحية تحتوي على مجموعات ضارة بالكائنات الحية الدقيقة. تتناول هذه المقالة بالتفصيل الخصائص المضادة للميكروبات لجسيمات أكسيد الزنك النانوية في التطبيقات المضادة للبكتيريا، والالتهابات، والفطريات، ومضادات السكر، والسرطان، ومضادات الأكسدة، ومضادات الفيروسات.

الاستنتاجات: لقد ثبت أن ZnO–NPs تؤدي مجموعة واسعة من الوظائف البيولوجية.

الكلمات المفتاحية: جزيئات أوكسيد الزنك النانوية، النشاط المضاد للبكتيريا، والسمية الخلوية

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