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Quercetin loaded zinc nanoparticles: Recent applications and developments

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Abstract

A member of the flavonoid class, Quercetin, can be found universally in vegetables, fruits and other plant sources. Quercetin is the focus of interest due to its diverse biological activities *viz*. antioxidant, anti-inflammatory, anticancer and antimicrobial properties. But Quercetin faces limitations, including poor water solubility, low bioavailability and rapid metabolism and demands novel delivery systems development. Delivery and efficacy of Quercetin can be improved by means of nanotechnology. Zinc has such unique properties as biocompatibility, biodegradability and the potential for synergistic effects with Quercetin that make it an attractive material for the formulation of nanoparticles. In the current study, recent applications and developments of Quercetin loaded zinc nanoparticles are reviewed, including their synthesis techniques, characterization techniques, and diverse applications in drug delivery, wound healing, food preservation, cancer therapy and antimicrobial action. We also outline possible future direction in this emerging area, with a reflection of the current literature to fill the gaps.

Keywords- Quercetin; Nanotechnology; Zinc; Nanoparticles; Applications

1. Introduction

Quercetin, a member of the flavonoid class, is universally distributed in a variety of vegetables, fruits, and other plant sources [1,2,3]. Due to its diverse and potential biological activities, Quercetin has been the subject of interest. Its inherent antioxidant, anti-inflammatory and antimicrobial properties constitute a multifaceted therapeutic potential, thereby making it an important subject of research and development for use in various biomedical applications [2,4,5]. However, Quercetin possesses limitations, including poor water solubility, low bioavailability and rapid metabolism and these limitations restrict it from being therapeutically effective in its native form [4,5,6]. As a result, it requires the development of novel delivery systems to overcome these challenges and unlock its full therapeutic potential.

These limitations are being overcome using nanotechnology, as a promising means. Delivery and efficacy of Quercetin can be improved by means of nanotechnology. Recent advances have focused on improving confines of Quercetin through innovative nanoparticle formulations as Quercetin can be encapsulated in nanocarriers, namely nanoparticles, nanoliposomes or nanomicelles, which increase its solubility, stability and bioavailability. These nanocarriers enhance the Quercetin absorption by protecting it from degradation while its passage through the gastrointestinal tract, and thus promote delivery of the compound to the target tissues. Additionally, Quercetin nanocarriers can give targeted delivery of Quercetin to distinct places inside the body, boosting treatment effectiveness whilst lowering negative effects. One of the additional ways that Quercetin can be used therapeutically is its controlled release from nanocarriers, that will prolong its therapeutic effects and maximize the impact while minimizing the frequency of administration [2,3].

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Zinc has unique properties, such as biocompatibility, biodegradability that renders it functionally biodegradable within biological and medical frameworks and potential synergistic effects with Quercetin. These properties make it an attractive material for nanoparticle formulation. The solubility of Quercetin is increased by zinc nanoparticles which otherwise is low in aqueous environments. It is important for its bioavailability in biological systems [7]. Incorporating zinc nanoparticles into formulations show ability to shield Quercetin from degradation [4].

The objective and scope of the review is to provide a comprehensive understanding of the advancements in Quercetin-loaded zinc nanoparticles, their applications, and the future perspectives necessary for their effective therapeutic use. In the current study, recent applications and developments of Quercetin loaded zinc nanoparticles are reviewed, including their synthesis techniques, characterization techniques, and diverse applications in drug delivery, antioxidant and anti-inflammatory properties, food preservation, cancer therapy and antimicrobial action. We will also have a look of the current literature to identify the gaps and future directions in this emerging area of research.

2. Methodology

To find every study that examined Quercetin-loaded zinc-based nanomaterials, their applications, and advancements during the previous ten years, a search technique was developed. Using a variety of search terms, we searched the Scopus, ScienceDirect, Pub-Med, and Google Scholar databases to find and gather the pertinent study literature. The search was carried out using several different strings like “quercetin and zinc nanoparticles” , “applications of quercetin-zinc nanomaterials” , “quercetin and zinc nanoparticles as antimicrobial” , “quercetin based zinc nanomaterial use”,“ zinc with quercetin nanoparticles synthesis methods” ,“zinc and quercetin in nanotechnology” , “quercetin zinc nanomaterial recent technology” , “zinc and quercetin in cancer therapy”,“ quercetin and zinc for food industry” , “quercetin and zinc nanoparticles in drug delivery” etc. The searched papers were further studied to select specific studies connected to “applications of quercetin loaded zinc nanoparticles” and other non-relevant studies were removed. The final selected papers were those for which the full text was available and which fitted the objectives of the review. Fig 1 shows screening process of methodology.

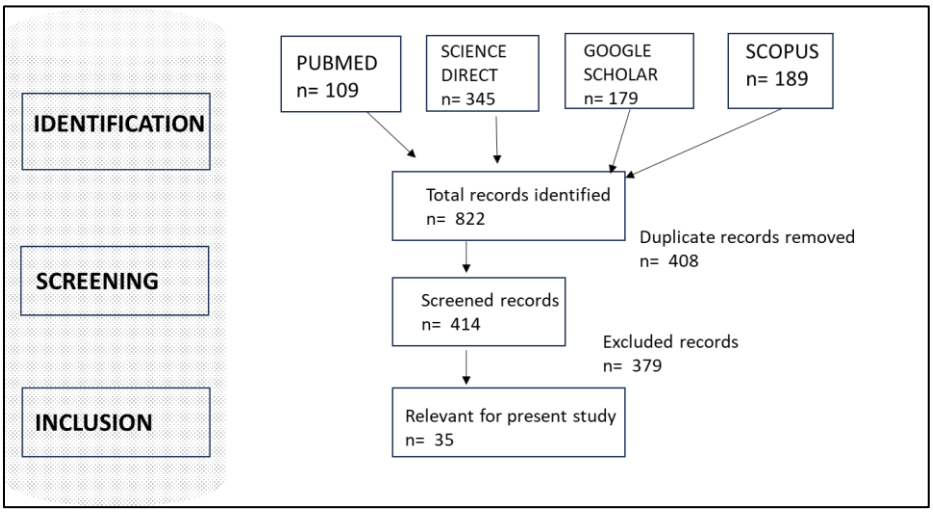

Figure 1 Screening process of methodology

3. Synthesis Methods of Quercetin-Loaded Zinc Nanoparticles

Quercetin loaded zinc nanoparticles have been synthesized by several methods. The most common method is the homogenous precipitation method in which the Quercetin is added at the time of formation of ZnO nanoparticles. The method is to allow controlled precipitation of zinc ions with Quercetin resulting in the entrapment of Quercetin in the ZnO nanoparticle matrix. There are various specific conditions (pH, temperature, reactant concentrations) that govern the size, morphology and the Quercetin loading efficacy of the resulting nanoparticles [8].

Another method is the chemical synthesis of ZnO@Quercetin nanoparticles (quercetin functionalized wurtzite type zinc oxide nanoparticles) confirmed by DRS UV-vis spectroscopy. The ZnO@Quercetin nanoparticles were hexagonal, monocrystalline with an average size of 20–25 nm as confirmed by XRD and Raman spectroscopic analysis [9].

The Quercetin drug delivery matrix was developed by one study which used sonochemical methods to synthesize Zn/SBA-15 (silica based mesoporous material functionalized with zinc nanoparticles). The precursor for SBA-15 preparation was rice husk ash, a readily available and inexpensively source of silica. This, with a relatively simple and scalable sonochemical approach, enabled the controlled nanoparticle synthesis with precise size and morphology [10]. In another study by Trendafilova et al., the incipient wetness impregnation method was used to synthesise similar Zn-modified SBA-15. The pores of Zn modified SBA-15 were loaded with Quercetin. This method efficiently exploited the benefits of Zn modification and the high loading capacity of Quercetin, thus making the resulting delivery system a promising dermal application [11].

Quercetin functionalized bimetallic nanoparticles, in particular, iron and zinc oxide (zinc ferrite) nanoparticles were prepared using another synthesis method involving co precipitation. This method offers a convenient route for the production of bimetallic nanoparticles with predetermined properties, albeit with the need for careful optimization of reaction parameters to achieve consistent results [12].

A notable progress is reported in the synthesis of zeolitic imidazolate framework-8 (ZIF-8) nanoparticles using zinc ions. In this method, Quercetin is encapsulated using the properties of a metal organic framework, ZIF-8, to undergo controlled drug release [13].

In another approach, a cellulose nanofiber–Quercetin complex was made incorporating zinc ions, forming a Quercetin loaded cellulose nanofiber composite (CNF–Zn–QT) with improved properties and high loading capacity for use in various applications [14]. Additionally, a study made use of a novel complex of metal ions (including zinc) with quercetin which increased its antioxidant properties. Then, polycaprolactone based nanoparticles were synthesised, vitamin E was loaded onto them and an enhanced antioxidant profile was achieved [15].

ZnO nanoparticle synthesis was explored using green synthesis techniques using plant extracts. These methods provide an environmentally friendly route for the preparation of nanoparticles with improved biocompatibility and stability, as compared to the conventional chemical methods. However, the yield and control over nanoparticle characteristics may differ with plant extract as well as with specific synthesis conditions [16, 17]. The various approaches show versatility of zinc in forming Quercetin-loaded nanoparticles with varying and customized properties. Table 1 summarizes the comparison, advantages and disadvantages of different synthesis methods of Quercetin loaded zinc nanoparticles.

Table 1 Comparison of different synthesis methods for Quercetin-loaded zinc nanoparticles

Technique	Process	Advantage	Disadvantage	Quercetin Loading	Reference
Homogeneous Precipitation	This method involves the gradual development of ZnNPs in a uniform solution by managing factors like pH, temperature, and the concentration of precursors.	It yields consistent nanoparticles with precise morphological control.	It necessitates exact conditions to prevent issues related to agglomeration and precipitation.	Quercetin can be added during or after the precipitation process, influencing its dispersion and bioavailability.	[8]
Chemical Synthesis	This approach employs chemical precursors (such as zinc salts) that are reduced by agents like sodium borohydride to create ZnNPs.	It is simple, scalable, and capable of producing small nanoparticles.	It involves the use of hazardous reducing agents and stabilizers, raising potential environmental concerns.	Frequently involves post-synthesis functionalization through ligand exchange or direct integration during the synthesis phase.	[9]
Sonochemical Method	This technique utilizes ultrasonic waves to create cavitation, leading to localized high temperatures and	The process is quick, energy-efficient, and results in well-dispersed nanoparticles.	It requires specialized equipment and may produce inconsistent particle sizes.	Quercetin can either be co-synthesized with ZnNPs or added after synthesis.	[10,11]

	pressures that facilitate nanoparticle generation.				
Co-precipitation	This involves the simultaneous precipitation of ZnNPs and quercetin in a carefully controlled environment (considering pH and ionic strength).	It is simple, cost-effective, and permits greater encapsulation of quercetin.	There is a risk of particle aggregation and variations between batches.	Direct incorporation during the synthesis improves the efficiency of drug loading.	[12]
Green Synthesis	This method employs plant extracts, bacteria, or fungi as reducing and stabilizing agents to create ZnNPs in an environmentally friendly way.	It is biocompatible, avoids toxic substances, and enhances bioactivity.	Controlling particle size and morphology can be more challenging	Quercetin can be integrated into biosynthesized ZnNPs using plant-derived polyphenols, boosting antioxidant properties.	[16,17]

3.1. Characterization Techniques for Quercetin- Loaded Zinc nanoparticles

Physicochemical properties of Quercetin loaded zinc nanoparticles are studied using various characterization techniques.

The presence and concentration of zinc nanoparticles within the matrix is confirmed using X-ray fluorescence (XRF) and X-ray diffraction (XRD). XRF and XRD are used to assess the purity and crystalline structure of the ZnO-NPs. The results of a study [18] indicated that high-purity ZnO-NPs were successfully fabricated. The results show that the crystalline structure is essential for determining the stability and reactivity of the nanoparticles, which can impact their performance in biomedical applications.

Detailed information on nanoparticle size, morphology and distribution is obtained using transmission electron microscopy (TEM) [10,18]. In the study conducted by Azizah et al. [10], it was observed that zinc nanoparticles ranging from 4-14 nm and were located on the surface of the mesoporous channels of SBA-15. In another study [18], the average size of the ZnO-NPs was determined to be 45.924 ± 27.910 nm, with hexagonal and rod-like shapes observed. The results show that the size and distribution of nanoparticles are crucial for their effectiveness in drug delivery. Smaller nanoparticles can enhance the surface area and improve interaction with the drug, which is essential for achieving higher encapsulation efficiency. Smaller particles also enhance bioavailability and improve the solubility of compounds like diosgenin [18].

Scanning electron microscopy (SEM) provides understanding of surface morphology and particle aggregation [12]. It corroborates the findings from TEM, confirming the nanoscale dimensions and shapes of the particles. The surface characteristics observed through SEM can influence the interaction of ZnO-NPs with biological systems, affecting their efficacy as drug delivery vehicles.

Various techniques such as ultraviolet visible spectroscopy (UV-Vis), Fourier transform infrared spectroscopy (FTIR), and dynamic light scattering (DLS) are known to be used to ascertain zeta potential, particle size, and surface functionality [1,6,19]. These characterization methods are essential for ensuring the consistency and quality control of synthesized nanoparticles and for the understanding of their response to Quercetin. The measurement of the zeta potential, for example, reveals information on the colloidal stability of the nanoparticles, which is key for the long-term storage and effective delivery [10].

UV-Vis Spectroscopy technique measures the concentration of released Quercetin at specific time intervals. The percentage of drug release over time provides insights into the release kinetics, which is essential for evaluating the

effectiveness of the drug delivery system. A slower release rate can indicate better control over drug delivery, which is beneficial for therapeutic applications [10].

The FTIR analysis allows to identify the presence of the functional groups inside and their interactions between the nanoparticles; thereby, it gives information about the encapsulation and drug release mechanism. Understanding the interactions between Quercetin and Zn is vital for assessing how well the drug can be loaded and released from the carrier. The chelation suggests a strong bond between the drug and the carrier, which can influence the drug's release profile [6].

Therefore, the synthesized nanoparticles and their properties require multiple characterization techniques to make a complete understanding. Predicting their behaviour under biological systems and perhaps optimising their therapeutic efficacy require these techniques.

3.2. Applications of Quercetin-Loaded Zinc Nanoparticles

The exceptional blend of the bioactivity of Quercetin and delivery capability of zinc nanoparticles has unlocked a myriad of applications (Fig 2).

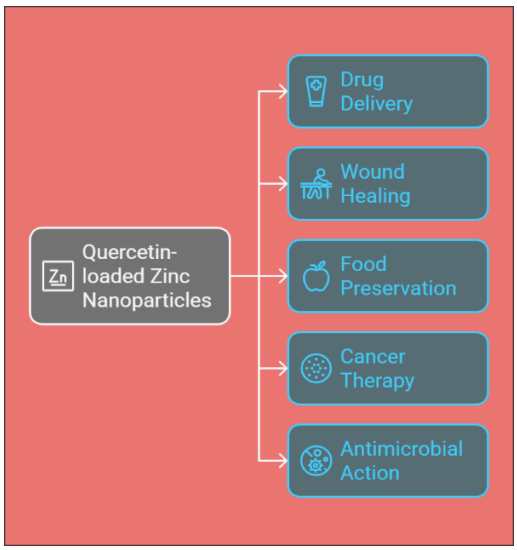

Figure 2 Applications of Quercetin-Loaded Zinc Nanoparticles

3.3. Drug Delivery

Enhanced drug delivery is the primary application. Quercetin is a low bioavailable compound which requires development of efficient delivery systems [4,5]. This problem is solved by zinc nanoparticles, which can enhance solubility and targeted delivery [10,13]. To illustrate, Azizah et al. showed Zn/SBA-15 to be a potential Quercetin delivery matrix, where Quercetin loading was 28.30mg/g and release was 33.64%, after 240 minutes. It was shown that Zn/SBA-15 was capable of sustaining Quercetin's therapeutic effect over an extended period with an improved efficacy. In this study, sonochemical route was used to synthesize SBA-15 using rice husk ash as a sustainable silica precursor and a well-ordered mesoporous material was obtained. Post-synthesis impregnation was used to incorporate zinc into the SBA—15 framework and XRD and FTIR analyses confirmed there was change in physicochemical characteristics of the material as affected by varying metal loadings. In addition to that, FTIR spectroscopy showed that quercetin and ZnSBA-15 interact via chelation of the carbonyl (C=O) and hydroxyl (C–OH) groups, suggesting strong host–guest interactions. It was shown that the diffusion rate of quercetin could be slowed by reducing pore diameters and by potential ZnO formation on SBA-15. The controlled release profile generated by ZnSBA-15 supports its ability to be used as an effective drug delivery platform for sustained topical delivery of quercetin with long photoprotective effect [10]. Additionally, in a separate study, ZIF-8 nanoparticles were also used in pH-responsive release of Quercetin to protect chondrocyte, both from inflammation and apoptosis in osteoarthritis and to enhance cartilage structural integrity [13].

In another study, a co-biopolymer hydrogel containing zinc oxide nanoparticles improved Quercetin delivery to brain cancer cells by increasing penetration through the blood-brain barrier [20].

Sathishkumar et al. conducted a study by developing an advanced drug delivery system using zinc oxide-Quercetin (ZnO-Quercetin) nanocomposite. The ZnO nanoparticle successfully loaded a large amount of Quercetin (210 μg/mg) and release of Quercetin from ZnO nanoparticles is faster in acidic conditions like those found in cancer environments. Here, specific molecular interactions between Quercetin and its receptor were identified. Interactions at 5–OH in the A ring, 3–OH in the C ring of Quercetin were most important. Based on these results, this study provides a promising design concept for the development of smart drug delivery systems based on metal oxides and hydrophobic natural drugs for cancer therapy [21].

Another study concerned the manufacture of a new hydrogel formulation consisting of Quercetin extracted from onion peel waste via embedding green synthesized ZnO nanoparticles into a chitosan matrix. Electrostatic and hydrophobic interactions between QE and ZnO NPs increased the hydrogel's swelling and increased efficiency of drug loading and loading. Results showed that ratios of QE/chitosan and ZnO/chitosan, but not DAC/chitosan, had significant impact to loading efficiency. The drug release was Fickian diffusion showing that the drug release was diffusion controlled. Moreover, the hydrogel showed high biocompatibility to normal cells and selective cytotoxicity on cancer cells with potential use of topical therapies in infections and cancer. The research succeeded in demonstrating the ability of this green nanohybrid hydrogel formulation made from ZnO NPs and onion peel waste in controlled drug release, antimicrobial and anticancer applications. This formulation could be a promising alternative in biomedical field especially for topical applications [22]. These studies demonstrate the usefulness of zinc nanoparticles to deliver Quercetin to specific target sites and thereby, enable enhanced therapeutic effect and suppress its limitations.

3.4. Wound Healing

Quercetin has been proposed as a promising agent for wound healing due to its antioxidant and anti-inflammatory properties [2, 12]. Promising results for incorporating Quercetin loaded zinc nanoparticles into the wound dressings have been demonstrated [12]. In a rat model, Yadav et al., showed that Quercetin functionalized bimetallic (zinc ferrite) nanoparticles promoted wound healing. Molecular docking studies indicated strong binding affinity of quercetin with numerous wound healing protein targets, thus suggesting a molecular mechanism for its therapeutic effect. This synergy of the bioactivity of Quercetin with the nano delivery of zinc nanoparticles combines to offer a unique approach to enhancing wound healing when the tried-and-true treatments fail [12].

Further advancement of this application is the development of injectable hydrogels that comprise Quercetin modified zeolitic imidazolate framework-8 (ZIF-8@QCT) which enhances tissue regeneration and remediate challenges in alveolar bone restoration in periodontitis [23].

In mice, quercetin offered a means of mitigating testicular toxicity caused by zinc oxide nanoparticles. It lowered inflammation and oxidative stress markers, restored normal testosterone levels, suggesting its protection from nanoparticle induced reproductive toxicity [24]. Zinc ion containing cellulose nanofiber composite had superior antioxidant activity and sustained quercetin release. In addition, the composite demonstrated improved antibacterial properties, which would support its use in long term antioxidant and antimicrobial applications [14].

In a separate study, zinc oxide nanoparticles loaded with Quercetin (Quercetin@ZnO NPs) were created to deliver photoprotective effects from UVA induced damage to HaCaT cells. The research demonstrated that these nanoparticles played a dual role in the delivery of Quercetin and in reducing the toxic effects of free iron in skin cells. The findings suggest that Quercetin@ZnO NPs can markedly lower expression of inflammatory markers associated with photoaging and possibly make a potent therapeutic agent in skincare products. An approach of enhancing skin protection and tackling oxidative stress resulting from UV exposure was presented by the study [8]. While all of this show much promise for Quercetin-loaded zinc nanoparticles, a number of challenges about cytotoxicity and oxidative stress inherent with nanoparticles need to be overcome. Further research and development in nanotechnology is necessary in order to optimise these formulations for use in safe and efficient therapeutic applications [2].

3.5. Food Preservation and Packaging

Quercetin has antioxidant capacity that can be used for food preservation. Quercetin-loaded zinc nanoparticles increase the antioxidant activity of polyvinyl chloride (PVC) films and can be used to prolong the shelf life of fatty foods [25]. Braga et al. have shown that PVC films containing zinc nanoparticles loaded with quercetin have enhanced structural, morphological, optical, and thermal properties, which are desired for food packaging applications. By this approach, a new strategy in food preservation is offered for active food packaging materials that prevent the food from undergoing oxidative processes, preserve the food quality, and mitigate food processing waste. With this application, quercetin loaded zinc nanoparticles are shown to have potential to be used as a shelf-life extension agent of food products, to reduce spoilage as well as to enhance food safety [25]. A further study was successful in developing a versatile packaging

material formed from methylcellulose (MC) and chitosan nanofibers (CNFs) combined with the addition of zinc oxide nanoparticles (ZNPs), quercetin (Qu), and natamycin (NAT). The purpose of this material is to be multifunctional, showing antibacterial, anti-fungal and antioxidant properties, which are essential for food preservation and safety. These green multifunctional packaging films are suitable as a promising alternative to traditional plastic packaging [26].

3.6. Cancer Therapy

The anticancer properties of quercetin and the targeted delivery potential of zinc nanoparticles provide the scope for novel cancer therapies [2,5]. Zinc oxide nanoparticles (ZnONPs) were incorporated into a hydrogel nanocomposite, which resulted in increased quercetin loading and improved controlled release, with cytotoxic effects on breast cancer cells. Targeted drug release was mediated due to the pH sensitivity of formulation. This facilitated an increase in number of apoptotic cancer cells [27]. Sadhukhan et al. studied phenylboronic acid (PBA) conjugated Zinc oxide nanoparticles (PBA-ZnO) with quercetin (PBA-ZnO-Q) for treating cancer. PBA-ZnO-Q significantly increased quercetin bioavailability and improved anticancer properties. Better tumor inhibition was seen using this formulation than PBA-ZnO or free quercetin alone. Targeted delivery to cancer cells inducing the apoptotic cell death via oxidative stress was achieved with the help of the PBA moieties. PBA-ZnO-Q acted selectively cytotoxic to cancer cells but was not cytotoxic to vital organs by impeding redox homeostasis. The chemotherapeutic potential with reduced tumor associated toxicity was significant for this nanoformulation and thus represents a promising candidate for clinical development [28]. In another study, wurtzite type zinc oxide (ZnO) nanoparticles were synthesized and functionalized with quercetin (ZnO@Quercetin) for ovarian cancer treatment. Excellent efficacy was demonstrated by ZnO@Quercetin nanoparticles for inducing intracellular oxidative stress and depolarizing mitochondrial membrane potential in human ovarian cancer cells. Dual staining assay further showed that the apoptosis triggered in PA-1 cells by ZnO@Quercetin was mediated by the intrinsic apoptosis signaling pathway. Overall, the results suggest that ZnO@Quercetin nanoparticles may represent a viable therapeutic for human metastatic ovarian cancer [9]. Majority of the studies explore quercetin nanoformulations for cancer treatment [1,2,5,29], whereas literature related to the quercetin loaded zinc nanoparticles in this context is still lacking. Nevertheless, the promising biocompatibility of such systems in drug delivery and the success of alternative zinc-based nanoparticle systems indicate a strong potential for future development [13,20].

3.7. Antimicrobial Therapy

Study done by Choi et al., successfully bio-conjugated zinc oxide nanoparticles (ZnO NPs) with quercetin (Q), to enhance its antibacterial efficacy. Formations of ZnO@Q nanocomposites were confirmed using advanced techniques. Overall, the resulting ZnO@Q NCs had greatly enhanced antibacterial activity against *Staphylococcus* species when compared to the Q and ZnO NPs alone. Bacterial membranes were disrupted and biofilm formation was also prevented by the nanocomposite. It showed that ZnO@Q NCs can act as an effective antibacterial agent in association with antibiotics with a low level of cytotoxicity, suggesting a strategy for combating antimicrobial resistant strains while improving bactericidal efficacy [30]. In another study, the researchers synthesized ZnO NPs using pure Quercetin extracted from *Ipomoea batatas* to study the organic dye reduction as well as antimicrobial and antioxidant evaluation [31].

Liu et al. developed a hydrogel (QPQH) made of quercetin (QT), quaternary ammonium salt chitosan (QCS) and polydopamine coated zinc oxide nanoparticles (PDA@ZnO NP) in a matrix of Polyacrylamide-Poly(2-acrylamido 2 methyl 1 propanesulfonic acid (PAM-co-AMPS), which showed exceptional adhesion and mechanical properties, adhering thoroughly to lesions. It induced high efficiency sterilization of bacteria, *Staphylococcus aureus* and *Escherichia coli*, using its photothermal properties and Zn2+ release, combined with QCS. Antioxidant properties reducing oxidative stress and inflammation were also provided by Quercetin. This hydrogel was compatible with blood and cells, and therefore assisted in wound repair, angiogenesis and collagen deposition, making it a good candidate for treating bacteria infected wounds in clinical use [32].

Another developing area is antiviral potential of Quercetin loaded nanoparticles. Most research in this area relates to other types of nanoparticles [33], however the inherent antioxidant and anti-inflammatory properties of Quercetin, in conjunction with the enhanced delivery provided by zinc nanoparticles, make a strong case for antiviral applications [34]. Mechanisms of action and efficacy of Quercetin loaded zinc nanoparticles against different viruses need to be further investigated.

Additionally, a recent study investigated the combined therapeutic effects of a quercetin-zinc (Q/Zn) complex and mesenchymal stem cells (MSCs) in a diabetic rat model with pulmonary dysfunction. The findings revealed that this combination therapy significantly improved glycemic control, enhanced antioxidant defenses, and reduced oxidative stress and genotoxicity. Notably, the treatment also ameliorated structural alterations in pancreatic and lung tissues, suggesting potential benefits for diabetic patients with respiratory complications, including those associated with COVID-19 [35].

Future Directions and Limitations

Promising applications of this combination, however, are met with several research questions, limitations and challenges that warrant further investigation. Synthesis method and formulation parameters (such as Zn ion concentration, pH, nanoparticle mass, surfactant concentration) play an important role in encapsulation efficiency and kinetics of drug release from Quercetin loaded zinc nanoparticles [10,13]. Knowledge of these factors is essential for optimal nanoparticle design and the consistency of therapeutic outcome. Understanding how quercetin and zinc oxide molecules interact, will optimize their combined protective effects. A thorough evaluation of the lasting toxic effects on cells, along with environmental assessments of these nanoparticles, must be conducted to maintain their safety and sustainable nature.

In addition, some formulations require improved long-term stability [36]. The need is to carefully evaluate the potential toxicity of zinc nanoparticles especially under high concentrations or prolonged exposure [2, 37].

Rigorous toxicity studies of these nanoparticles are crucial to demonstrate that they are safe and biocompatible for clinical uses. In future research, synthesis methods should be optimized to improve efficiency of encapsulation and control release of the drug, to develop more stable formulations, and to provide comprehensive toxicity studies. Additionally, the synergistic effects when combining quercetin loaded zinc nanoparticles with other therapeutic agents should enhance the therapeutic efficacy [34].

The mechanisms of action of quercetin loaded zinc nanoparticles in various biological systems need to be investigated specifically to understand their therapeutic potential and to guide the formulation of more effective ones. Finally, more research is also needed to decode promising findings of these in vitro, and preclinical data into clinical trials, to assess whether these nanoparticles are effective and safe in humans. Although ZnO NPs hold promise for the enhancement of Quercetin's bioavailability and stability, long term safety issues concerning nanoparticles in biological systems, as well as the possible cytotoxicity of nanoparticles, deserves further study. Efficacy and safety, in balance, remains a major issue throughout the development of nanoparticle drug delivery systems.

4. Conclusion

Zinc nanoparticles loaded with Quercetin represent a major breakthrough achievement in nanomedicine and a potential solution for improving the bioavailability and therapeutic efficacy of Quercetin. The versatile applications in drug delivery, wound healing, food preservation, cancer therapy and antimicrobial therapy adds to the diversity of potential uses of this approach. Nevertheless, future work needs to be devoted to issues such as encapsulation efficiency, release kinetics, long term stability and toxicity. Future investigation of these mechanisms of action and development of suitable formulations will prepare this novel technology for broader clinical uses and the translation into effective therapeutics. Exciting future advancements in several fields derive from the synergy between Quercetin's bioactivity and zinc nanoparticles' delivery capabilities. To realize the full therapeutic potential of these innovative nanoparticles, complex new synthesis techniques need to be explored, more sophisticated characterization tools need to be developed, and the rigorous toxicity and efficacy studies need to be conducted.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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