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Enhanced Therapeutic Potential of Berberine via Zein-Polysaccharide Nanoparticle Encapsulation"

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ABSTRACT

Berberine, a natural compound found in *Berberis lycium*, exhibits diverse therapeutic properties. But its poor water solubility, limits its clinical applications. Main focus of this study was to enhance the solubility of berberine through encapsulation in zein-polysaccharide nanoparticles. Various formulations of berberine-loaded nanoparticles were synthesized by mixing sodium alginate and pectin in different ratio.

The nanoparticles characterized techniques, like SEM, TEM, FTIR, and XRD. The % drug loading, % encapsulation efficiency, bioavailability, antioxidant, antibacterial, and antifungal activities of the nanoparticles were comparatively determined against crude berberine.

Results indicated a time-dependent increase in drug loading and entrapment efficiency, suggesting improved encapsulation efficiency over time. Comparative studies between berberine-loaded nanoparticles and crude berberine demonstrated enhanced bioavailability, antioxidant, antibacterial, and antifungal activities of the nanoparticles. The resulting NPs possessed an excellent 55 %EE, 70 %DL, and 90%>Bioavailability, respectively. In addition, Berberine loaded zein polysaccharide NPs possessed better antibacterial potential against, *Salmonella typhi*, *Streptococcus aureus, Klebsiella pneumoniae Escherichia coli* and *Pseudomonas aeruginosa*, respectively. The NPs also possessed excellent antifungal activity against different fungal species such as *Aspergillus flavus*, *Candida albicans, Fusariumsolani,* and *Aspergillus Niger,* respectively.

The findings suggest that zein-polysaccharide nanoparticles provide an efficient platform for delivering berberine, addressing its solubility challenges and augmenting its therapeutic effects. The study emphasizes the potential translational applications of

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these nanoparticles in diverse medical contexts, including cancer treatment, anti-inflammatory interventions, and antimicrobial therapies. Further exploration through in vivo studies is essential to establish their safety, efficacy, and potential in practical medical settings. These findings cover the way for a development of novel drug delivery systems to overcome a limitations of poorly soluble therapeutic agents like berberine.

INTRODUCTION

The low solubility of many therapeutic drugs significantly limits their bioavailability and therapeutic effectiveness. Solubility plays a crucial role in achieving the required drug concentration in systemic circulation. Studies show that more than 90% of newly developed synthetic drugs suffer from poor oral bioavailability mainly due to inadequate aqueous solubility and slow dissolution rates (Das et al., 2022; Khan et al., 2022). Drugs with low solubility often require higher doses or more frequent administration to achieve therapeutic effects, which can increase the risk of adverse side effects. Therefore, improving drug solubility and dissolution rate has become an important focus in pharmaceutical research. One effective strategy to overcome this limitation is reducing drug particle size to the nanoscale. The reduction in particle size increases the surface area of the drug, which enhances solubility, dissolution rate, and overall bioavailability (Guo et al., 2023; Salunke et al., 2022).

Nanotechnology has emerged as a promising approach for improving drug delivery and therapeutic efficiency. It involves the manipulation and application of materials with dimensions generally below 100 nanometers. At this scale, materials exhibit unique physical and chemical properties that differ from their bulk counterparts (Talebian et al., 2021). In recent years, nanotechnology has been widely applied in medicine and pharmaceutical sciences to develop advanced drug delivery systems. Nanoparticles can serve as carriers that transport drugs to specific target sites, protect them from degradation, and enable controlled or sustained release. Pharmaceutical nanoparticles are typically biodegradable and biocompatible systems designed to enhance the stability and bioavailability of therapeutic compounds (Suyal et al., 2023; Zhao et al., 2022). This approach is particularly beneficial for delivering plant-derived bioactive compounds that often exhibit poor solubility and limited bioavailability (Ayala-Fuentes & Chavez-Santoscoy, 2021).

Medicinal plants have been used for centuries as natural remedies for the treatment of various diseases. Many modern drugs originate from plant sources or are derived from plant-based compounds (Mohanty et al., 2017). It is estimated that more than 25% of currently available pharmacological agents are obtained from natural products or their derivatives (Swamy & Sinniah, 2016). Plant-derived compounds possess diverse chemical structures and biological activities, which makes them valuable candidates for drug discovery. They often exhibit therapeutic effects with relatively fewer side effects compared to synthetic drugs. However, a major limitation of many plant-based bioactive compounds is their poor aqueous solubility, which restricts their absorption in the gastrointestinal tract and reduces their therapeutic potential (Mohanty et al., 2017; Patel et al., 2018).

To overcome the limitations associated with poor solubility and low bioavailability of many active pharmaceutical ingredients, innovative drug delivery systems have been

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developed. Conventional carrier systems such as liposomes and micelles have been used to improve drug solubility and stability. However, these systems have several disadvantages including poor physical stability, drug leakage during storage, and low encapsulation efficiency (Elzoghby et al., 2012). As a result, researchers have focused on developing more stable and efficient nanocarrier systems. Among these, protein-based nanoparticles have gained considerable attention due to their biodegradability, safety, and ability to effectively encapsulate bioactive compounds (Nunes et al., 2022; Tortorella et al., 2021).

Zein, a natural protein derived from maize, has emerged as a promising material for nanoparticle synthesis due to its biocompatibility, biodegradability, and low production cost (Li & Song, 2020). Zein possesses amphiphilic properties, allowing it to self-assemble into nanoparticles through techniques such as the antisolvent precipitation method. These nanoparticles are capable of encapsulating hydrophobic bioactive compounds and improving their stability and solubility (Yuan et al., 2022). However, zein nanoparticles alone may show limited stability in aqueous environments. To enhance their stability and functionality, they are often coated with polysaccharides such as gum arabic, pectin, or hyaluronic acid. The electrostatic interaction between positively charged zein nanoparticles and negatively charged polysaccharides results in the formation of a stable core–shell nanostructure (Kaushik et al., 2020). These zein–polysaccharide nanoparticles provide several advantages, including high encapsulation efficiency, improved stability, controlled release of active compounds, and enhanced bioavailability (Li et al., 2020; Yang et al., 2022).

The medicinal plant Berberis lycium Royle, belonging to the Berberidaceae family, is widely distributed in the Himalayan region and has long been used in traditional medicine. The plant contains a wide range of bioactive compounds including alkaloids, flavonoids, tannins, saponins, vitamins, and minerals (Nazir et al., 2021). One of the most important alkaloids present in this plant is berberine, which has been reported to exhibit various pharmacological activities such as antimicrobial, antioxidant, antidiabetic, hepatoprotective, and anti-inflammatory effects (Mustafa et al., 2020; Mughal et al., 2022). Extracts from different parts of the plant have been traditionally used for the treatment of several diseases including liver disorders, gastrointestinal problems, diabetes, and infections. Despite its significant therapeutic potential, the bioactive compounds present in Berberis lycium often exhibit limited solubility and poor bioavailability, which restricts their clinical application.

Therefore, the development of advanced nanocarrier systems such as zein–polysaccharide nanoparticles provides a promising strategy for improving the stability, solubility, and therapeutic efficiency of plant-derived bioactive compounds. Encapsulation of Berberis lycium extract into such nanoparticle systems may enhance the protection of active compounds from environmental degradation, improve their bioavailability, and enable controlled release, thereby increasing their overall therapeutic effectiveness.

Methodology

Identification of *Berberis lycium*

*Berberis lycium Royle*plants were collected from District Shangla Khyber Pakhtunkhwa. The plants were identified by a well-known taxonomist Dr.Asif

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Mehmood, Department of Botany, Sarhad University of Science and Technology, Peshawar. For the purpose of the experiment the whole roots and seeds of the plant were washed about 250 gm with distilled water they were dried under shade and later on they were converting in to the powder form. In addition, it was macerated for fourteen days in 80% methanol. After maceration the mixture was filtered using muslin fiber cloth and Whattman filter paper After that 100ml of 5%Hcl was added to the methanol extract in order to cause berberine to precipitate out of the solution. The precipitate and the supernatant were filtered after the whole night's refrigeration. Cooling the solution in the refrigerator helps to further promote the precipitation of berberine. Secondly, refrigeration helps in the separation of the solid precipitate from the liquid supernatant. The precipitate (crude berberine) was dried at room temperature (Sabir *et al.*, 2013).

Oil extraction from plant parts

Powdered parts of*BerberisLycium*plant (250gm) was soaked in 140 ml of analytical-grade n-hexane in blue-capped bottles for 48 hrs at room temperature i.e. (25^{o}C). The extracts were the filtered through Whattman filter paper 4 (Sabir et al., 2021).

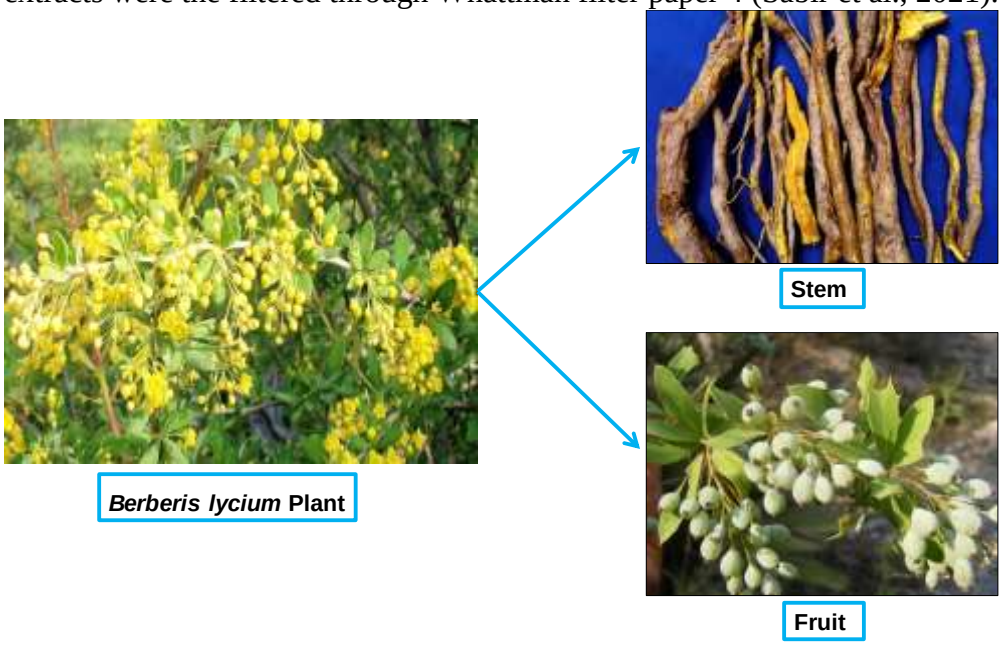


Figure 1. Berberis lycium plant, stem and fruit picture

Separation of berberine from the extracted oil

A liquid-liquid extraction process was used to extract berberine from the oil produced from *Berberis lycium* plants (Llano et al., 2015). In a separating funnel, the extractswere mixed with 80% methanoland then allowed to settle, resulting in the separation of two different layers: the oil-containing lower layer and the solvent-containing upper layer with berberine. The upper layer which was enriched with berberine, was collected and cleaned with water to get rid of impurities. The solvent was then evaporated, leaving a concentrated berberine solution.

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Preparation of Berberine-zein stock solution

Preparation of zein stock solution: The following previously described method by Yao et al., 2018 was used. Copolymer of Berberine-zein solution was prepared by dissolving 2.0 g zein in 100 ml ethanol (85% v/v) using mechanical stirrer at 1h. Afterwards 70g of dried berberine powder was dissolved in the above solution and the mixture was stirred for 30 minutes without exposure to light. Precipitated solid impurities were then removed by centrifugation at 1006 x g for 15 min.

Preparation of Pectin /sodium alginate solution

The pectin alginate solutions were prepared in distilled water at 0.2% (w/v) concentration with varying ratio as shown in Table 3.1.From the above table, it can be seen that pectin sodium alginate ratios have been prepared by completely dissolving pectin in sodium alginate solution by stirring at 700 rpm on a magnetic stirrer for 30 minutes at 70°C. A solutions were allowed to cool under the tap water and stirring for one more hour. The Insoluble particles were then separated from the solutions using Whatman filter paper 4, then the pH was brought to 4.0 using 0.1 mol HCL.

Table1 Pectin and Sodium alginate ratio used for preparation of pectin-alginate solution

S/No.	Percentage (%) of Pectin +Alginate	
	Pectin	Alginate
1	100	0
2	70	30
3	50	50
4	30	70
5	0	100

Preparation of Berberine loaded zein-pectin/alginate core shell nanoparticles

Berberine loaded zein-pectin/alginate core shell nanoparticles were synthesized according to method described by (Shangguan et al., 2015) with a little modification. From the Berberine-zein stock solution, 20.0 ml was taken through a sterile syringe and added to 80.0 mL of acidified water (pH 4.0) with continuous stirring at 900 rpm for 3 minutes under darkat 25-30°C.Ethanol was evaporated from the dispersion solution using rotary evaporator (RE 2000A, Yarong, China). From the solution, 20 ml was mix with 25 ml of each pectin-alginate solutions (Table 3.1) and continuously stirred at 700 rpm for 30 minutes for synthesis of Berberine loaded zein-pectin/alginate core shell nanoparticles.

Characterization of the prepared nanoparticles

The prepared berberine loaded zein-pectin/alginate core shell nanoparticles were characterized.

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Determination of size and morphology of the nanoparticles

SEM (Hitachi-s 3400 N, Japan) and TEM (Techni-G2-300 kV) were used to study size and shape of zein-pectin/alginate core shell nanoparticles containing berberine. In preparing the sample, a tiny layer of test solution was first put on a carbon-coated copper grid and after that, was irradiated with a mercuric vapour lamp for five minutes. Finally the particle size distribution of the obtained NPs was determined by measuring the two dimensional micrograph of the sample. Furthermore, using a copper grid, a sample of core shell nanoparticles made from zein-pectin/alginate materials containing berberine was made and left to dry. After drying, the SEM was run at a high voltage of 100 KV. Zein-pectin/alginate core shell nanoparticles loaded with berberine, produced using different ratios of pectin and sodium alginate solution, are shown in cross sectional transmission SEM images.

Determination of structural nature of nanoparticles

The Nature of the nanoparticles was characterised by XRD. The structure determination was carried out the help of a JDX-3532 diffractometer which utilizes a Ni filter and Cu-Kα which is a source of monochromatic light with a wavelength of 1.5418 Åo. The machine was run at 30mA of current, 40KV of voltage. Hence, the 2θ/θ range was chosen for broad spectrum scanning while coarse and fine movements for sample scanning were done at a rate of 10 min -1.

Identification of functional groups attached to the nanoparticles

Fourier Transform Infrared Spectroscopy (FTIR) was used to examine the presence of functional groups in these zein-pectin/alginate nanoparticles that have Berberine integrated into their core shell. This was done with the help of a Prestige Fourier transform infrared spectrophotometer produced in Japan, by Shimadzo company. The region of wavelengths used for analysis was established to be 4000-600 cm-1.

Particle size and charge measurements

In this experiment, based on the commercial instrument name of the instruments (Nano-ZS, Malvern Instruments, UK), Using dynamic light scattering (DLS), the zeta potential of the colloidal dispersions' particle size distribution was determined. The study was conducted at the University of Peshawar's Department of Pharmacy in Khyber Pakhtunkhwa, Pakistan. From the obtained light scattering data, Z-average diameter as well as Polydispersity Index (PDI) could be derived. Before being used, the colloidal dispersions were diluted with 5 mM phosphate-citric acid buffer at pH 4 in order to determine the electrical characteristics, the particle Zeta potential of the particle in the colloidal dispersions for each sample, and the result analyzed using micro electrophoretic equipment (Nano-ZS Malvern, Instruments UK). Every sample was examined three times.

Thermal stability

A DTA/TGA (differential thermal analysis. thermogravimetric analysis)instrument was used to perform thermal analysis to assess the thermal stability of prepared NPs (Gharanjig et al., 2020). A TGA instrument (Pyris Diamond TG/DTA, PerkinElmer, USA) was used to test the thermal stability in the temperature

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ranging from 0 °C to 800 °C with a heating rate of 5 °C/min and flow of nitrogen with rate of 30 mL/min.

3.6 % Drug loading and % Encapsulation efficiency

The % Drug loading and % Encapsulation efficiency of the prepared nanoparticles was determined through already established methodology of(Bao et al., 2006). The % drug loading and % entrapment efficiency for berberine NPs were measuredafter 10-, 20- and 30-minutes time points.The Berberine nanoparticles underwent freeze-drying by a process that involved freezing the nanoparticle suspension at -80°C, followed by primary drying under vacuum at temperatures ranging from -40°C to -20°C in a freeze dryer. This was afterwards followed by secondary drying at ambient temperature to eliminate any remaining moisture. The dried nanoparticles were thereafter stored in hermetically sealed containers.Amount of Berberine in the nanoparticles were evaluated by dissolving 10 mg of freeze-dried nanoparticles in 10 mL dimethyl sulfoxide **(**DMSO), which is a highly polar organic solvent, by stirring overnight in dark. The solutions were then centrifuged at 16,099 × g for 30 mints(Golfakhrabadi et al., 2023). Then 10-fold dilution of the supernatant was done using DMSO. Absorbance of the solutions was measured at a 435 nm wavelength using UV-visible spectrophotometer (TU-1901, Persee, China). From the absorbance values, concentration of berberine in each sample was calculated using the calibration curve. The calibration curve was obtained from the absorbance values of 0 –10 mg pure berberine / DMSO mL.
Equations (1) and (2) were used to determine the drug loading and encapsulation efficiency, respectively.

Equation 1:
% drug loading is equal to (drug content in nanoparticles (mg) / (nanoparticle content (mg)) x 100.

The second equation is:
% Entrapment Efficiency = (drug content in nanoparticles (mg)) / (drug initial content (mg)) x 100

Antioxidant potential

Antioxidant activity of berberine nanoparticles were evaluated using two methods i.e. DPPH- scavenging activity and ABTS- scavenging activity.

DPPH· scavenging activity

DPPH radical scavenging activity of developed Berberine loaded zein-pectin/alginate core shell nanoparticles was determined by the method of Ayad et al., (2019). To this end, differently concentrated ethanolic solutions of encapsulated Berberine nanoparticles and crude berberine were synthesized. Then stabilised solutions of 100 µM DPPH in ethanol were prepared. Two millilitres of the DPPH-ethanol solution were then combined with equal volume of each of the ethanolic solutions of berberine loaded zein pectin/ alginate nanoparticles and crude Berberine. The obtained solutions were, therefore, later incubated for 30 minutes in the dark at temperature

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25°C. After 30 minutes, the solutions were filtered and analyzed for its absorbance using spectrophotometer with reference to wavelength of 517 nm.
The free radical scavenging activity from the sample was calculated using the following equation:

$$DPPH \cdot scavenging\ (\%) = Ac - As/Ac)\ x\ 100\%$$

Where the absorbance of sample and control (ethanol) solution are denoted by AS and AC, respectively. The free radical scavenging activity of in different concentration werecompared using the scavenging activity (SC50), which was defined as the sample concentration needed to inhibit scavenging by 50%.

ABTS·+ scavenging capacity

By using the previous method by (van der Werf et al., 2014), the scavenging activity of the prepared nanoparticles towards the $ABTS^{\bullet+}$ radical was evaluated. For the first time, ABTS•+ radicals were obtained by adding 2.45 mM potassium persulfate to 7 mM ABTS solution in the dark at 20 ± 2°C. The absorbance of the radical ABTS•+ solution was then brought to 0.700 ± 0.002 AU measured at 30 °C at the wavelength 734 nm by diluting it with buffer solution of 5mM, pH 7.4. The mixes in the 96-well microplate included the following reagents: This investigation investigated the radical scavenging capacity of Berberis lycium extract at a concentration of 0.014 to 0.0014 µg/mL diluted in 50% aqueous ethanol against a 45-minute ABTS•+ radical solution at 100 µL for 45 minutes at ambient temperature without exposure to light. The absorbance at 734 nm was measured using an automated plate reader. Trolox served as the reference point for comparison. The ABTS•+ inhibition percentage from Berberis lycium extracts was calculated using the following formula:

$$\%inhibition = AABTS\ control - (A\ sample - A\ sample\ blank)AABTS\ control \times 100$$

where "ABTS control" is the absorbance of the ABTS•+ radical in buffer at t = 0 min; "A sample blank" is a sample devoid of ABTS•+; and "A sample" is a solution of ABTS•+ combined with Berberis lycium extract. The IC50 value was used to compare extracts and specify the concentration.

Antimicrobial studies

Antibacterial Assay

For assessing the antibacterial activity of the berberine loaded zein-pectin/alginate core shell nanoparticles the Apaer well diffusion method was employed(Chavez Esquivel et al. 2020). Nutrient agar was prepared and solidify through sterilization and poured into petri plates. Circular holes of 6- 8 mm diameter were placed in each Petri plate by using cork borer. A single colony was picked from each bacterial strain of the two bacterial species which was sub cultured from the sub cultured plate using a sterile cotton swab stick and spread in distilled (injection) water. For the colony mix water is stirred around the whole plate and the member wells In the case of the colony mixture. After this, 10 µL of working solution was pipette into each well of petri plates to determine the antibacterial efficiency of the apricot seeds and so the petri plates were incubate at 37°C for 24 hours. The petriplats were then investigated for zone of inhibition after incubation for 24 hours. Cefixime (3^{rd} generation

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Cephalosporin), a typical antibacterial drug, was used as the positive control. A zone of inhibition forms around each well, and diameter of each zone was measured. The zone of inhibition's percentage was calculated by using the following formula:

$$\% \text{ Inhibition} = \frac{\text{Zone of Inhibition of test Sample(mm)}}{\text{Zone of Inhibiton of Standard(mm)}} \times 100$$

Antifungal Assay

The antifungal potentials of crude aqueous seed extracts of *Berberis lycium* and berberine loaded zein polysaccharide core shell nanoparticles were analysed using the slant agar dilution technique (Ahmad *et al.*, 2017). Sterile Dimethyl sulfoxide (DMSO) was used to generate the test samples' first 24 mg/mL stock solution. Then, 70 µL working solution of berberine loaded zein polysaccharide core shell nanoparticles and crude aqueous extracts were added to the SDA medium. The test tube-containing media was allowed to solidify. The media treated with Sabouraud Agar or Sabouraud Dextrose Agar (SDA) was used to inoculate the pathogenic fungal species namely *Aspergillus flavus, Candida albicans, Fusarium solani, Aspergillus Niger, Penicillium spp. Trichophyton spp.* and *Trichdermaharzianum*,respectively. Thetest tube was sealed and kept in a fungal incubator for a week at 28 degrees Celsius. Amphotericin B, a typical broad spectrum antifungal drug, was used as a positive control. In contrast, crude berberine and berberine NPs formulation was tested for %inhibition assay against the mentioned fungal strains. The percent zone of inhibitions was calculated by using a following formula:

$$\%\text{Inhibition} = \frac{\text{Linear growth of fungi in test sample(mm)}}{\text{Linear growth of fungi in Standard(mm)}} \times 100$$

RESULTS

Extraction of oil and berberine from berberis lycium

*Berberis Lycium*plant was collected from different parts of District Shangla, Swat, Khyber Pakhtunkhwa, Pakistan. Form the plant extracts,55 ml oil was obtained. Upon further processing 10g of crude berberine was obtained from the oil. The crude berberine was then coated with zein- polysaccharide complex to form berberine nanoparticles.

Table No 2: 1 showed that from 1 kg of berberine lyceum plant root22.3 ml oil were extract

Berberine lyceum	**Quantity of roots**	**Oil extreted ml**
Berberine lyceum	1 kg	22 ml

Table No 3: Absorbed that from 1 kg of the roots 35.2 gram of berberbine were extracted.

Berberine lyceum	**Quantity of roots**	**Berberine in gram**
Berberine lyceum	1 kg	35.2 gram

The table no 2 showed that from 1 kg of berberine lyceum plant root22.3 ml oil were

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extract and similar from Table no 3 it was absorb that from 1 kg of the roots 35.2 gram of berberbine were extracted.

Characterization of the synthesized nanoparticles

Size and morphology determination

Using transmission electron microscopy (TEM) and scanning electron microscopy (SEM) the size and morphological aspects of synthesized zein-polysaccharide coated berberine nanoparticles was determined. TEM analysis results are presented in figure 2. All Berberine loaded zein polysaccharide nanoparticles such as 100% pectin ratio, 50% pectin and 50% alginate solution, 30% pectin 70% alginate solution and 100% alginate solution has an irregular shape and were non-uniform with sizes between 30-120 nm. However, displayed best results as it were all spherical, uniform in size and shape, with average diameter of 80-90nm. Zein polysaccharide nanoparticles were prepared using Berberine with a (70 % Pectin / 30 % Alginate solution).

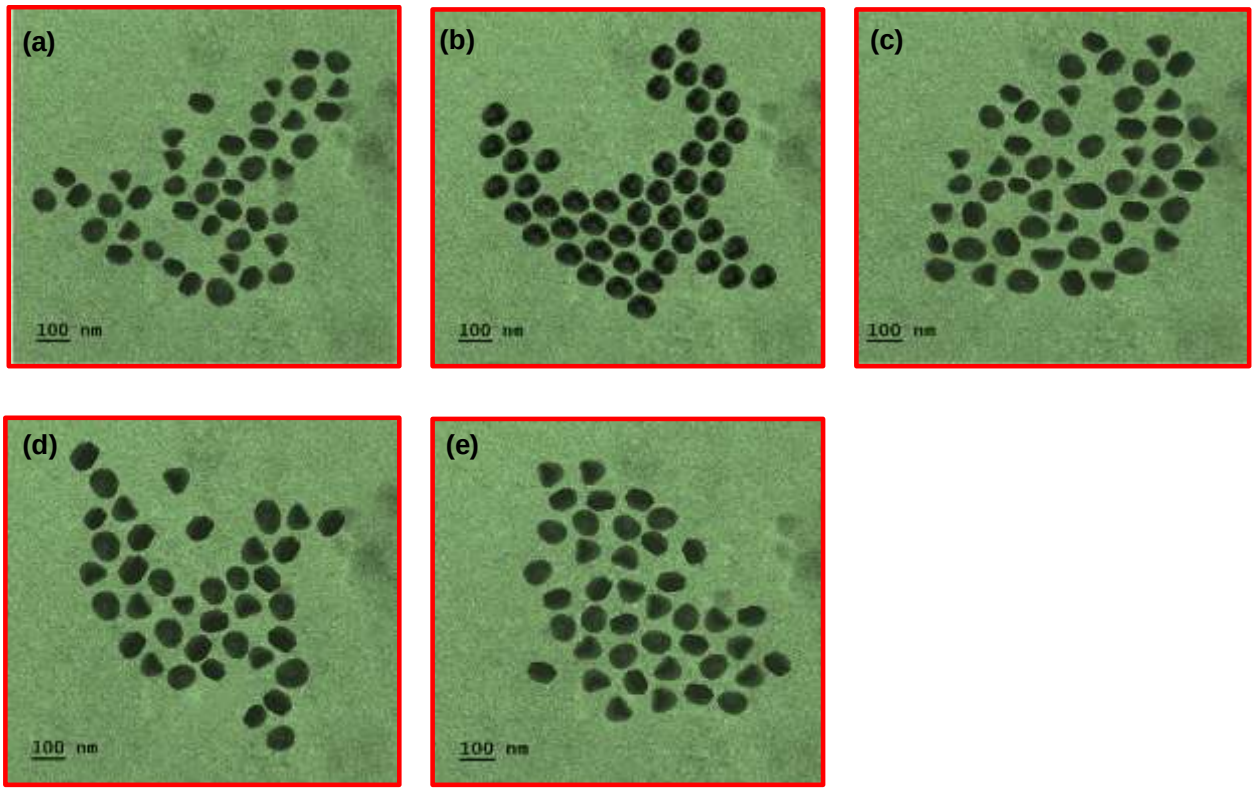


Figure 2: TEM images of berberine loaded zein alginate nanoparticles synthesized with different ratios of pectin and alginate.
(a) 70% pectin and 30% alginate solution,
(b) 50% pectin and 50% alginate solution,
(c) 100% alginate solution,
(d) 30% pectin and 70% alginate solution, and
(e) 100% pectin solution

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SEM Analysis

Upon SEM analysis, it was observed that the spherical nanoparticles were about 80 to 90 nm in diameter. The nanoparticles are round in shape with uniform size as shown in Figure 3.

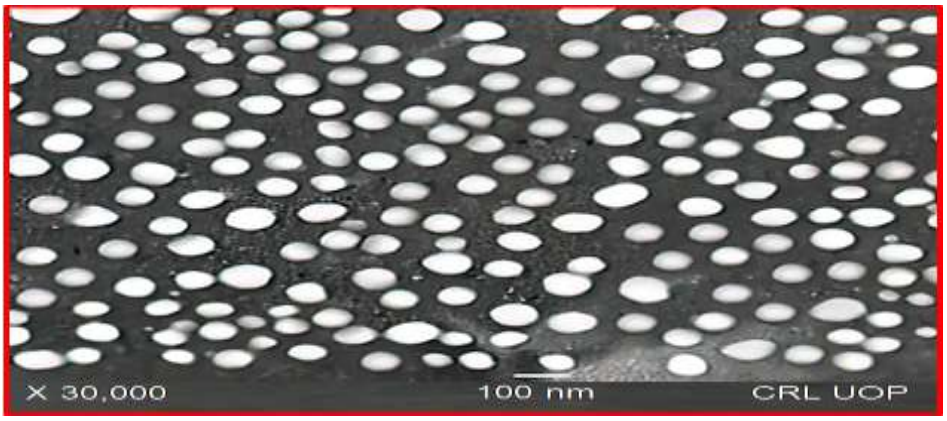
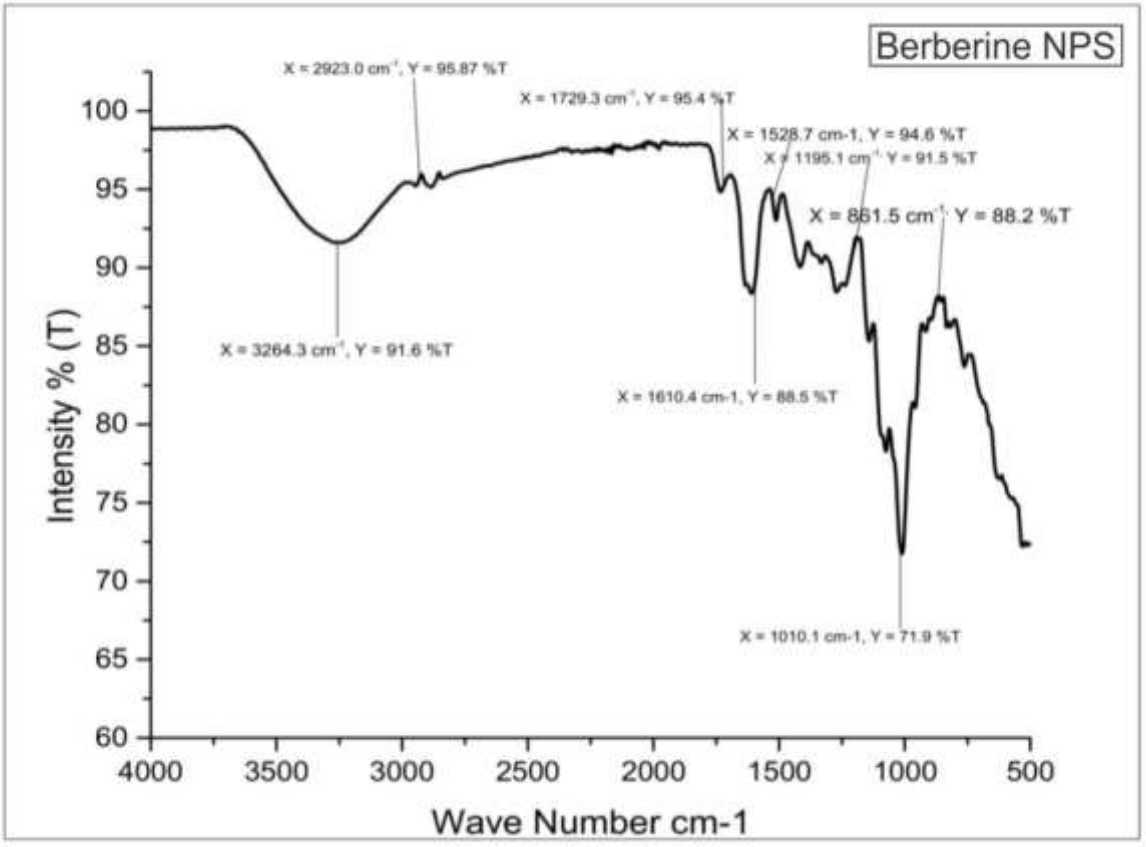


Figure 3: SEM image of Berberine loaded zein polysaccharide NPs (prepared in 70% pectin and 30% alginate solution)



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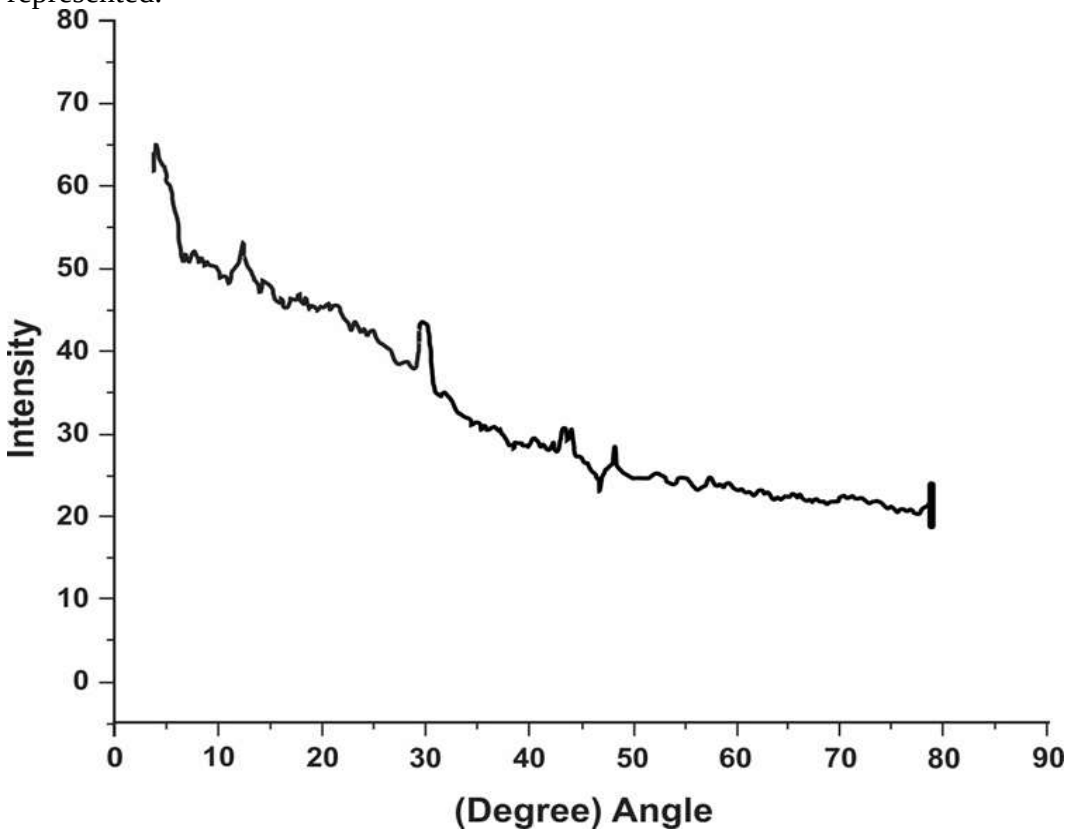
Figure 4: FTIR spectra of (a) crude berberine and (b) NPs.

Identification of functional groups attached to the Berberine nanoparticles

Several functional groups attached to the berberine nanoparticles have been identified through FTIR analysis (Figure 4) Results showed several peaks the peak at 8.615cm^{-1} indicate C-H bonding. The downward peak at 1010.5cm^{-1} shows C-O bonding, whereas the peaks formed at 1195.1cm^{-1} 1528.7cm^{-1} , 1729.3cm^{-1} and 2923.0cm^{-1} shows C=O, C=C, C=O and C-H stretching, respectively. On the other hand other 2 downward including 1610.4cm^{-1} and 264.3cm^{-1} C=C and o-h bonding.

Nature of synthesized nanoparticles

X-ray Powder Diffraction techniquewas employed to analyse the nature and chemical composition of the synthesized nanoparticles (figure 5). The peaks for Berberine loaded zein polysaccharide NPs (prepared in 70% pectin and 30% alginate solution) were recorded near 30.0^0, and 45.0^0 angles. Additional shorter range sharp peaks are visible between 10-20^{0}angles. The material's crystal lattice spacing is reflected in the angles at which these peaks appear. The results showed no sharp peaks so it indicates that the produced nanoparticles have an amorphous structure. The angles at which the peaks are noticed are particular indicators of the distances between atoms in the crystal lattice, which helps determine which crystalline or amorphous phases are represented.



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Figure 5: Shows XRD spectra of berberine loaded zein polysaccharide nanoparticles

Analysis of surface charges and size of the nanoparticles

Figure 6: Shows zeta potential of berberine loaded zein polysaccharide Nanoparticles. The highest zeta potential values were observed in the particle size range below 90 nm. The % intensity associated with these zeta potential values is greater than 15%. The observed zeta potential shows a suitable surface charge for stability.

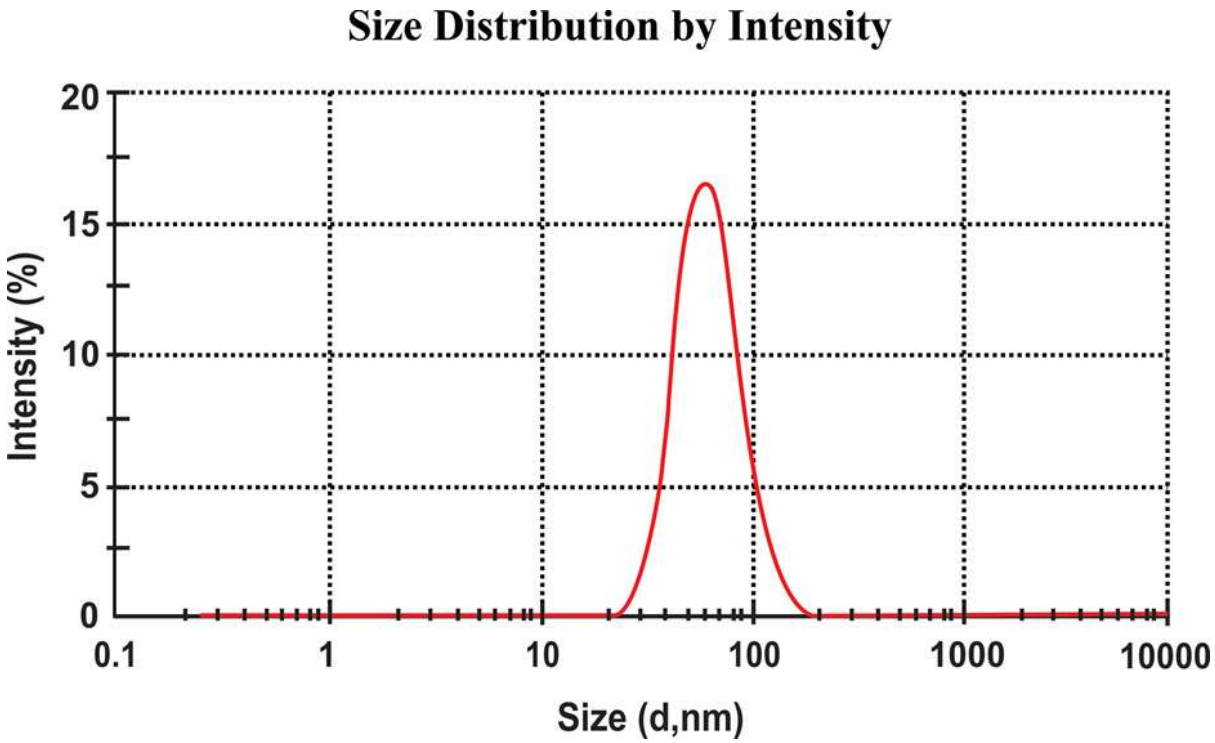


Figure 6: zeta potential of berberine loaded zein polysaccharide Nanoparticle

Thermal stability of the Nanoparticles

The thermal stability as well as mass loss of berberine loaded zein polysaccharide nanoparticle were analyzed using TG-DTA at 0°–800°C (Figure 7). The prepared NPs from selected plants were thermally stable up to 250 0C, a decrease in particle aptitude and mass was observed as the temperature increased between 200 – 800 oC, thus declared a thermally sensitive compound. The berberine NPs keeps stability and thermal decomposition temperature at a favourable balance.

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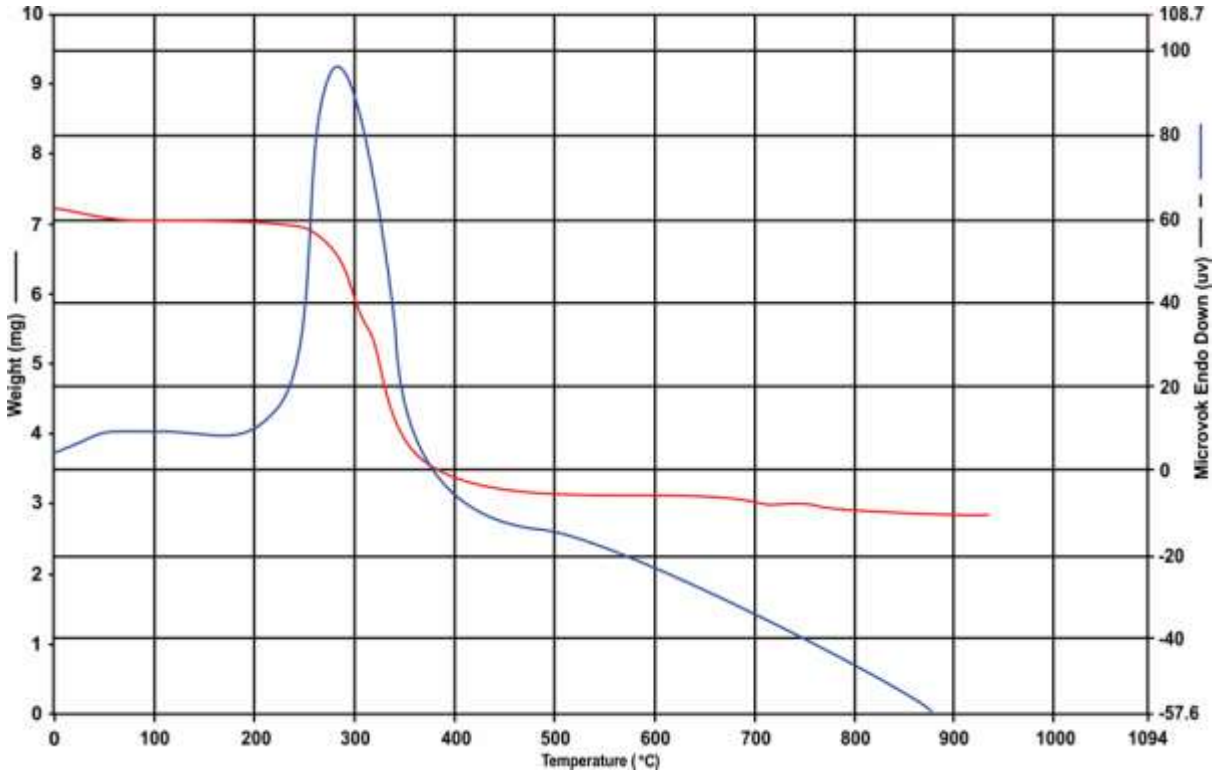


Figure 7: image of TG/DTA of berberine loaded zein polysaccharide Nanoparticle

Drug loading and % Entrapment Efficiency

Based on the % absorbance measurements, the data shows the percentage of drug loading and entrapment effectiveness of berberine into zein polysaccharide berberine nanoparticles at various time periods (Figure 8). Following 10-, 20-, and 30-minute time points, the percentages of drug loading and entrapment efficiency for berberine Nps were 54%, 39% (after 10 minutes), 64.4%, 45.7% (after 20 minutes), and 72.9%, 52.6% (after 30 minutes), respectively. With the passage of time the % drug loading and % entrapment efficiency of berberine NPs remained almost constant till 60 minutes and was recorded as 73.2%, and 53.1%, respectively. A non-significant increase was recorded for berberine Nps % drug loading and % entrapment efficiency from 10-60 minutes' time frame. Following is the data of drug loading entrapment efficiency absorbance 55 and its entrapment efficiency is10, 65 absorbance and and its entrapment efficiency is 20, 70 absorbance and its entrapment efficiency is30, 70absorbance and its entrapment efficiency is 40, 70absorbance and its entrapment efficiency is 50, 70 absorbance and its entrapment efficiency is 60.

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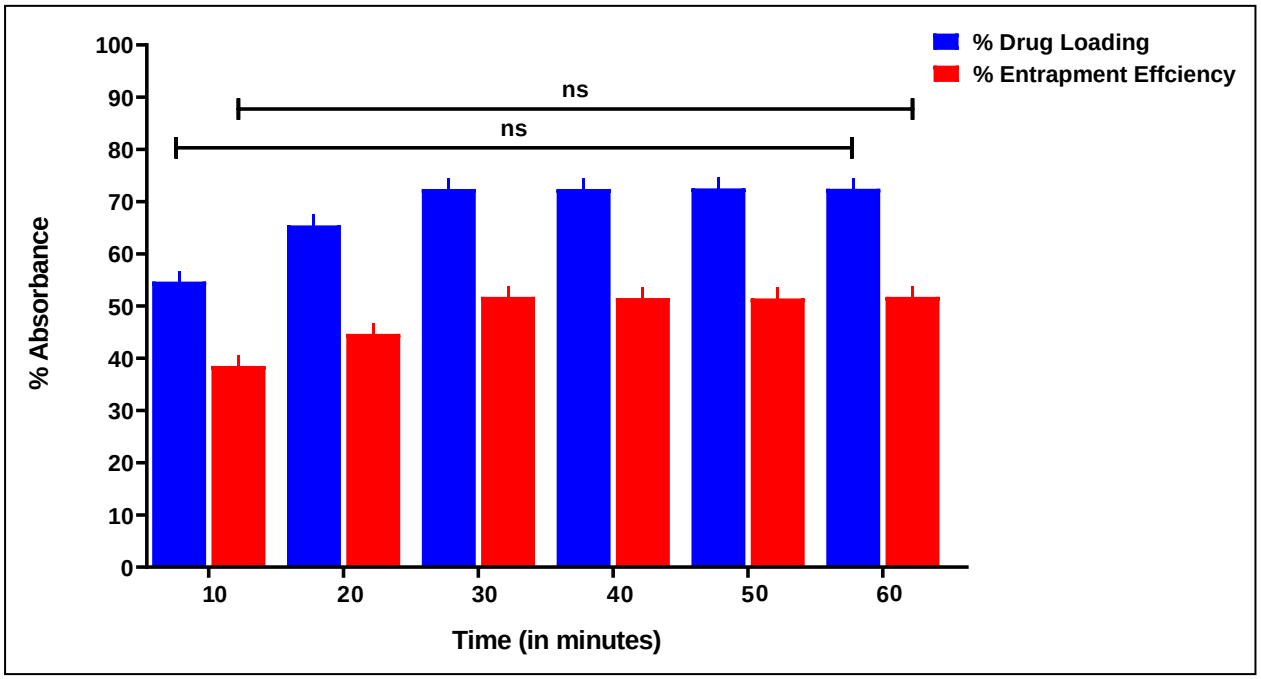


Figure 8: % drug loading and % entrapment efficiency of crude berberine and berberine loaded zein polysaccharide NPs as obtained from the percent absorbance measurements at different contact times

In vitro activities of berberine loaded zein polysaccharide nanoparticles
Antioxidant potential

The figure 9 and 10 present the DPPH· and ABTS radical scavenging efficacy of crude berberine and berberine loaded zein polysaccharide NPs. From figure 4.8, it was found that the percent activity of crude berberine and berberine loaded zein polysaccharide NP at sample concentration 10 was 37.9 and 81.6%, respectively. In the same tentative, at sample concentration 20 (µL/ml) the % activity (517nm) of crude berberine and berberine loaded zein polysaccharide NPs are 41.7 % and 90.6% respectively. Furthermore, at sample concentration 30 and 60 (µL/ml) the % activity (517nm) of crude berberine and berberine loaded zein polysaccharide NPs were 53.6, 93.8 % and 57.7 and 95.9 respectively. Finally, at sample concentration 70 and 80 (µL/ml) the percentage activity (517nm) of crude berberine and berberine loaded zein polysaccharide NPs were 63.3, 96.3 % and 68.2, 98.7, respectively.

Likewise, using ABTS scavenging assay and outcomes elucidated in Figure 4.9 the absorbance Percentage of crude berberine and berberine zein loaded polysaccharide NPs at 10µL/ml sample conc. was 31.2 and 78.6% respectively. Likewise, at sample concentration 20 (µL/ml) the % activity (734nm) of crude berberine and berberine loaded zein polysaccharide NPs were 34.3 and 90.3% respectively. Furthermore, at sample concentration 30 and 60 (µL/ml) the % activity (734nm) of crude berberine and berberine loaded zein polysaccharide NPs were; 41.1, 91.8 and 56.7, 93.9, respectively. Finally, at sample concentration 70 and 80 (µL/ml) the % activity (734 nm) of crude berberine and berberine loaded zein polysaccharide NPs were 61.5, 95.3% and 66.8, 97.7% respectively. In summary, these outcomes indicate that

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compared with crude form, the berberine loaded zein polysaccharide NPs have a significantly improved antioxidant property.

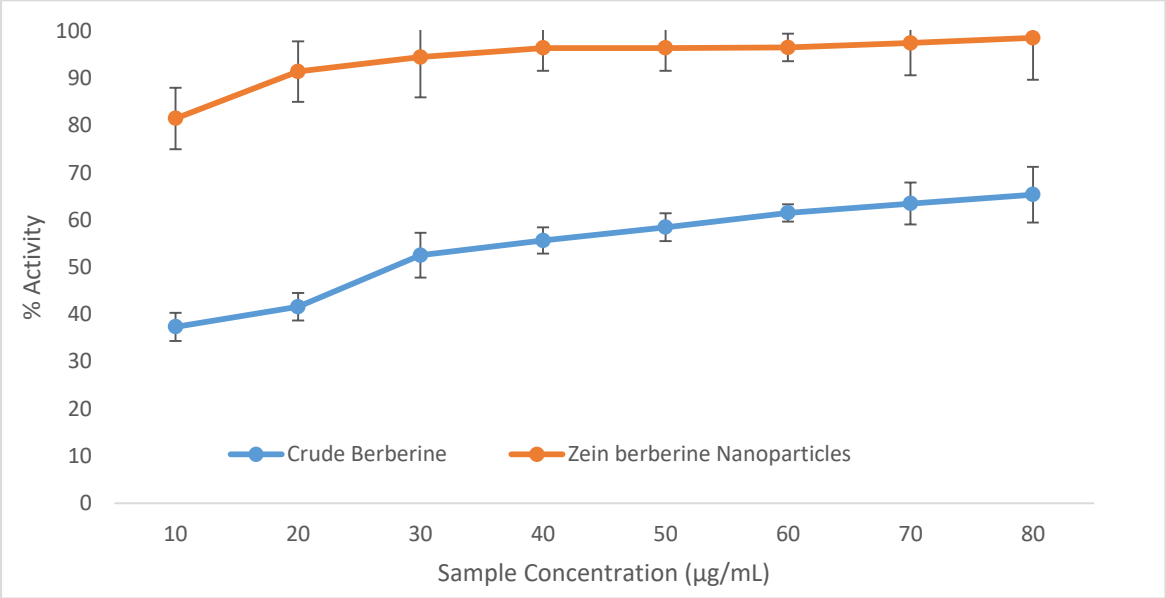


Figure 9: The DPPH• scavenging capacity of crude berberine and berberine loaded zein polysaccharide NPs

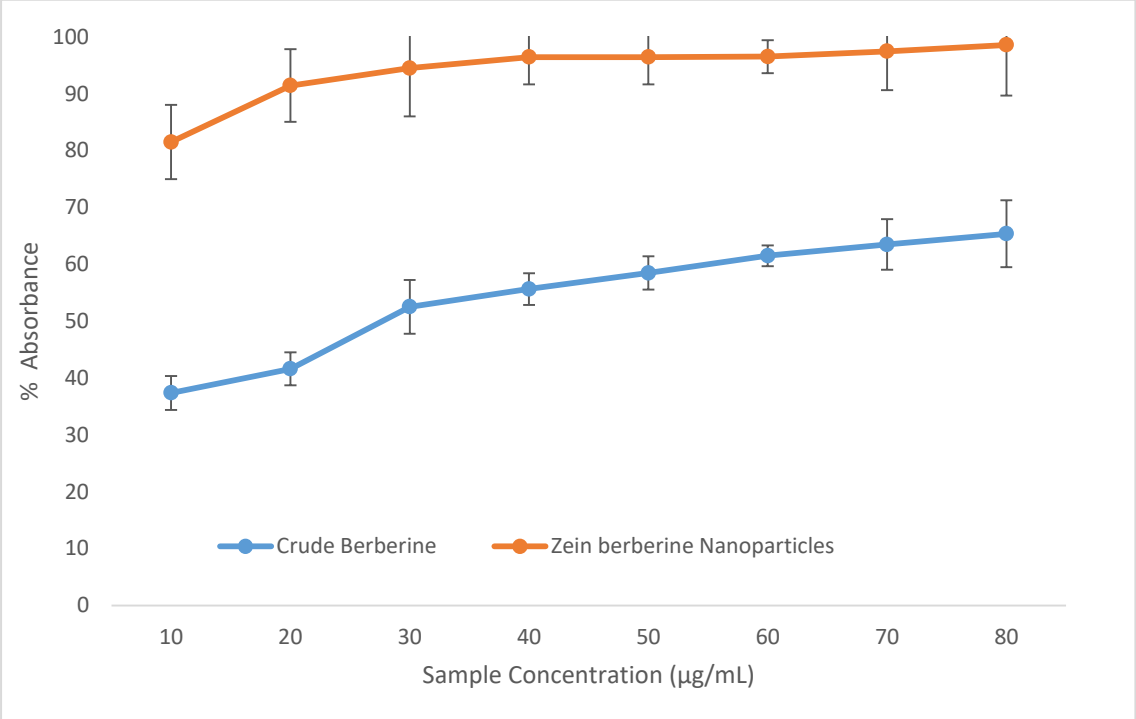


Figure 10: The ABTS radical scavenging capacity of crude berberine and berberine loaded zein polysaccharide NPs

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Antibacterial assay

Antibacterial assay of crude berberine and berberine loaded zein polysaccharide NPs against tested bacterial strains is shown in Figure 11 and Table 2 In contrast to crude berberine, berberine loaded zein polysaccharide NP showed enhanced antimicrobial activity against the tested strains namely; Salmonella typhi, Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, and Klebsiella pneumoniae. With an inhibition percentage of 78%, loaded zein polysaccharide nanoparticles, particularly berberine, demonstrated greater inhibitory action against Pseudomonas aeruginosa, which is comparatively resistant. Furthermore, zein polysaccharide nanoparticles loaded with berberine demonstrated antibacterial activity, exhibiting a zone of inhibition of 21.2 mm against Salmonella typhi, 21.1 mm against Streptococcus aureus, 20.3 mm against Escherichia coli, 15.3 mm against Pseudomonas aeruginosa, and 25.7 mm against Klebsiella pneumoniae. Loaded NPs of zein polysaccharide containing berberine resulted in 91.3% inhibition against Klebsiella pneumonia, 88.6% inhibition against Salmonella typhi, 94.2% against Staphylococcus aureus and 68.1% against Escherichia coli while crude berberine inhibited 79.3, 72.6, 81.2 and 68. The fabricated berberine loaded zein polysaccharide NPs have also shown the good percent antibacterial activity against Pseudomonas aeruginosa which was 78.6%, while the percent antibacterial activity of crude berberine was much less, which recorded only 29.9%, respectively. As compared to raw berberine, berberine incorporated zein polysaccharide NPs have demonstrated higher increased percent antimicrobial activity against S. typhi, S. aureus, K. pneumoniae, P. aeruginosa and E. coli.

Table 2: Antibacterial assay of crude berberine and berberine loaded zein polysaccharide NPs

Bacterial Species	Standard (mm)	**Growth inhibition by crude berberine and berberine loaded zein polysaccharide NPs**			
		Crude berberine		Berberine Nanoparticles	
		Zone of Inhibition (mm)	% Inhibition	Zone of Inhibition (mm)	% Inhibition
Klebsiella pneumonia	29	21.9 ± 1.26	79.3	25.7 ± 1.21	91.3
Salmonella typhi	27	17.2 ± 1.78	72.6	22 ± 1.26	88.6
Staphylococcus aureus	24	16.5 ± 1.18	81.2	21.1 ± 1.11	94.2

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Escherichia coli	26	14.8 ± 2.32	68.1	20.3 ± 1.22	83.9
Pseudomonas aeruginosa	19	7.3 ± 1.02	29.9	15.3 ± 1.54	78.6

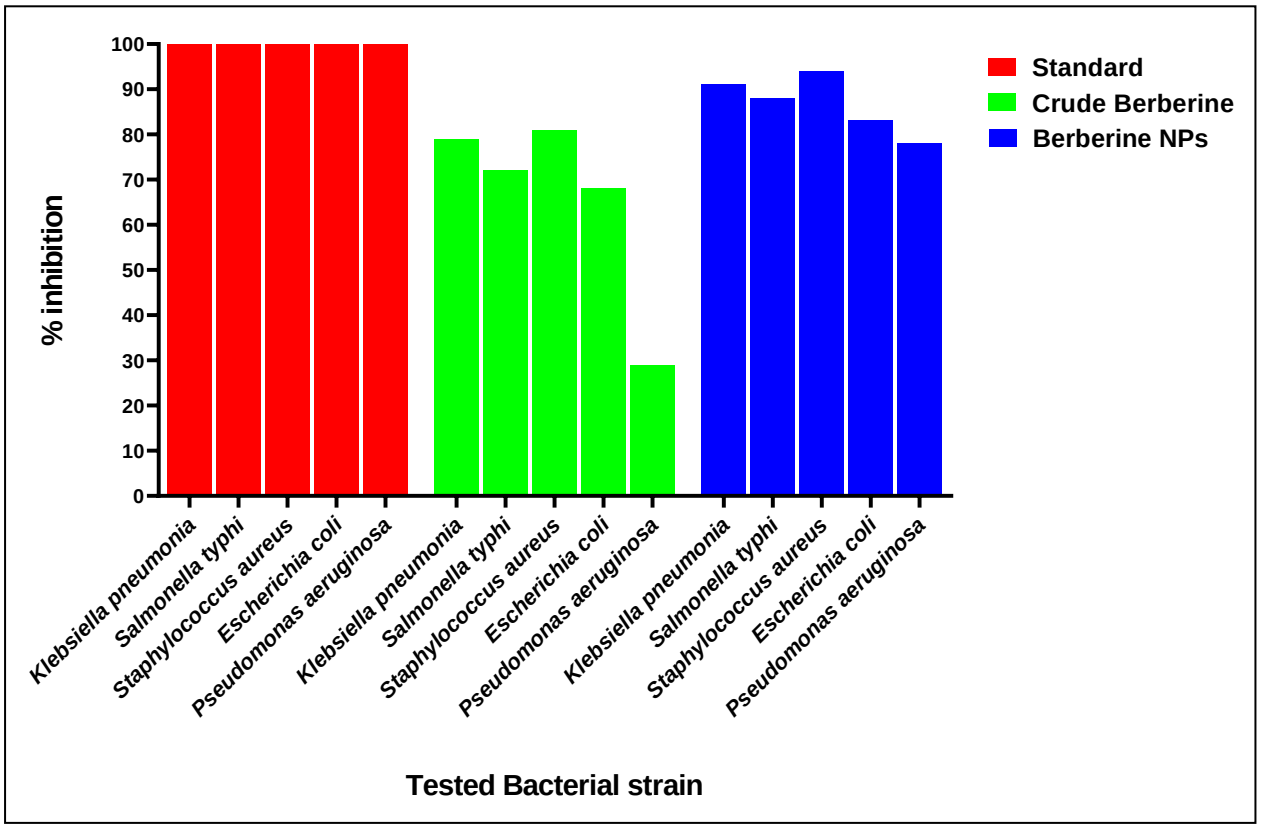


Figure 11 Antibacterial assay of crude berberine and berberine loaded zein polysaccharide NPs

Antifungal assay

Antibacterial assay of crude berberine and berberine loaded zein polysaccharide NPs against tested fungal species is shown in Figure 4.11 and Table 4.2. Berberine loaded zein polysaccharide NPs demonstrated 87% suppression of *Candida albicans*. They have also shown a promising antifungal activity against *Micosporum furfur*, which was 73%, while crude berberine only had a 28% percent inhibition of *Micosporum furfur* through antifungal assay, respectively. Furthermore, berberine loaded zein polysaccharide NPs exhibited 88% inhibition against *Aspergillus flavus* and 81% antifungal assay inhibition rate against *Fusarium solani*. *Aspergillus niger* and *Trichophyton spp.* growth were also significantly inhibited by berberine loaded zein polysaccharide NPs (68% and 52%, respectively). Berberine loaded zein polysaccharide NPs have shown enhanced antifungal growth inhibition activity (%)

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against the tested fungal species.

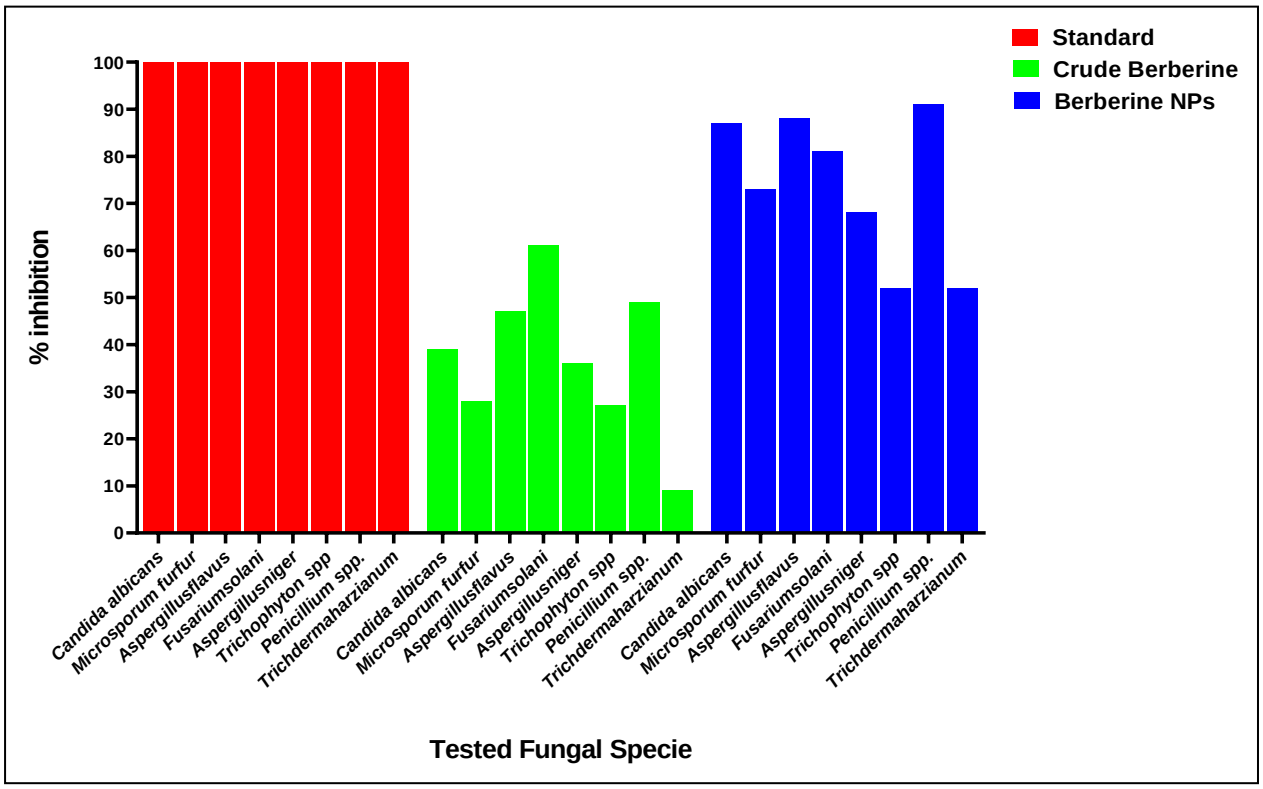


Figure 12: Antifungal assay of crude berberine and berberine loaded zein polysaccharide NPs

DISCUSSIONS

Berberine is an active constituent of Berberis lyceum. This study investigated the enhancement of berberine therapeutic efficacy through the synthesis of zein polysaccharide core-shell nanoparticle. Employing sodium alginate for stability and controlled release, and zein for biocompatibility, five variants of nanoparticles were produced with different ratios of sodium alginate to pectin. In addition, the nanoparticles were characterized and evaluated for in vitro potentials.

Zein polysaccharide nanoparticles loaded with berberine were created in the polysaccharide solution with a 100% pectin ratio. Figure 4.2a: 50% alginate solution and 50% pectin Figure 4.2c: 30% alginate solution and 70% pectin the 100% alginate solution with Figure 4.2d Figure 4.2e were all irregular, non-uniform in shape with size ranging between 30-120nm. However, Berberine loaded zein polysaccharide nanoparticles formed in a polysaccharides solution with a (30% alginate solution & 70% pectin) Figure 4.2b, displayed best results as it were all spherical, uniform in size and shape, with average diameter of 80-90nm. Our findings align with those of earlier research. Shah and colleagues established the anatomy of NP1 and NP3. It was observed that the morphology of both NP1 and NP3 was tiny, regular, and spherical. Highly monodispersed particles were present (Shah et al., 2020). For the formation of

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the shell surrounding the zein nanoparticles, Huang et al. also utilized a mixture of pectin and alginate. They found that aggregation stability at pH 5 to 7 was significantly increased when alginate was substituted for 30% of the pectin. The produced nanoparticles were found to have a spherical, homogeneous size and to have a diameter of around 80 nm (Huang et al., 2016).

According to SEM pictures, the resultant nanoparticles were spherical in size and shape, ranging from 80 to 90 nm. According to Li et al., plain zein colloidal nanoparticles were 80–100 nm in size, spherical in shape, and had a smooth surface. Silver nanoparticles with a dimensional restriction of 50 nm were synthesized by Paul and Yadav. According to SEM examination, the produced silver nanoparticles had a spherical form and ranged in size from 3 to 36 nm (Paul & Yadav, 2015).

The characterization of the functional groups and investigation of the interactions in nanoparticles tend to utilize FTIR frequently. From the vibrations of the repeat units in proteins of fibres, various unique infrared absorption bands such as the amide A,B, I to VII and more are generated (Kong & Yu,2007). However, the most important among them are the amide I and II bands due to their relation with the secondary conformational changes in the protein, The Amide II, N-H bending mode in conjunction with C-N stretch, is found to be between 1600 and 1500 cm−1 for Amide I, predominantly C=O stretch, it is found between 1700 and 1600 cm−1. Carbon-hydrogen stretching varies between 2800 and 3200 cm−1, while hydroxyl group's O-H stretching vibration is another band of 3100 to 3500 cm−1(Li et al., 2019). In the context of the present work, the spectral region of 3000–2800 cm −1 is characteristic for symmetric and antisymmetric stretching vibrations of CH2. The decrease in the band's peak from 3100 to 3500 cm−1 may suggest the presence of hydrogen bonding. Discriminations of a bands of amide I and amide II indicate hydrogen bond formations and conformational modifications of the zein secondary structure. Hasni et al., in their study pointed out that the stretching of the band in the regions of 3000-2800 cm−1 may be useful in the determination of the hydrophobic forces (Hasni et al., 2011).nctive infrared absorption bands, including amide A, amide B, amide I to VII, and so forth, are produced by the vibrations of repeat units in proteins (Kong & Yu, 2007). The amide I and II bands are the most significant ones among them because of their sensitivity to the secondary structure of the protein. The amide II band (C-N stretch coupled with N-H bending mode) occurs in the 1600–1500 cm−1 area, whereas the amide I peak position (mostly C=O stretch) occurs in the 1700–1600 cm−1 range. The hydroxyl group's O-H stretching vibration is responsible for the band at 3100 to 3500 cm−1 (Li et al., 2019). The region of 3000 to 2800 cm−1 is where the spectrum of symmetric and antisymmetric stretching vibrations in CH2 is found. The band's peak shift from 3100 to 3500 cm−1 often indicates the presence of hydrogen bonding. Changes in the bands of amide I and amide II often signify both the emergence of hydrogen bonds and a change in zein secondary structure. According to Hasni et al., the band between 3000 and 2800 cm−1 could provide information on hydrophobic forces (Hasni et al., 2011). The presence of methoxyl group was confirmed in the FTIR spectra of berberine NPs (a broad peak at 2.844 cm−1) and the hypothetical iminium (C=N+) double bond of the molecule was assigned to 1.635 cm−1 peak. Moreover, the furyl group and the aromatic bending of C=C are presented by the peaks at 1569 and 1506 cm−1. XRD spectrum for Berberine

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loaded zein polysaccharide NPs of 70% pectin and 30% alginate solution displayed nanoparticles peaks at 30.0, 39.0, 45.0 having sharper humps and at 20.5,21.0 and 39.0 showing additional peaks. Improved peak sharpness at 30.0,39.0 and 45.0 shows the presence of a very big crystalline structure. Other small additional peaks at 20.5, 21.0, 39.0 imply that phase distribution and composition can have different values.

Phase, structure and other structural characteristics of crystal materials can be studied through the XRD technique when studying crystal materials (Rajeshkumar et al., 2019). In the case of zein/polysaccharide nanoparticles, a state of the encapsulated compounds such as the resveratrol by Khan et al., (2019), curcumin by Li et al.,(2019), PTX by Ngo et al., (2019) and CoQ10 by Wei et al., (2019) have been determined using XRD. Interestingly, after being encapsulated into nanoparticles, all of these chemicals were found to be in the amorphous state. Additionally, when the sample developed into amorphous complexes, the peak strength of the zein/polysaccharide complexes was diluted, which provided some evidence of the intermolecular interaction between zein and polysaccharides (Khan et al., 2019). X-ray diffraction pattern revealed crystalline structure of the sample with highest sharp intensity peaks at diffraction angles 30.0, 39.0 and Further peaks at 20.5, 21.0 and 39.0 indicate that both phase distribution and composition may not necessarily be related to each other. According to the XRD analysis, the resulting NPs formulation has a higher degree of crystallinity as well as better phase distribution because the peaks are sharper. Comparing the percent absorbance after various contact times, it can be concluded that zein polysaccharide nanoparticles of berberine display the higher and more rapid extent of absorption compared to the crystalline crude berberine. These outcomes indicate that zein polysaccharide nanoparticles can improve the bioavailability (90%) and efficiency effects of berberine.

The percentage of drug loading was calculated after 10 min found to be 55% this means the extent of berberine incorporated into the zein polysaccharide nanoparticles. At the same time, the relative percent entrapment efficiency of berberine in the developed nanoparticles was also found to be 39% at this time point. Till 20 minutes, percent drug loading and percent entrapment efficiency was also improved. The percent drug loading increased to 67% by the end of 40 minutes, which pointed to the fact that more of berberine was loaded in the nanoparticles. The percent entrapment efficiency also enhance to 45%, this reveal an increasing efficiency in entrapping berberine by zein polysaccharide nanoparticles. Depending on their area of expertise, each of these analytic tools mentioned above can offer some significant information. Combining and evaluating these data points may help identify a potential mechanism for the zein/polysaccharide nanoparticle production process. Hydrophobic forces accompanied by zein structural alterations are often the primary cause of zein molecule aggregation into nanoparticles. Zein and polysaccharides interact primarily through hydrophobic, electrostatic, and hydrogen-bonding adsorption forces. The number of polysaccharides also causes a modification in the zein structure. Instead of continuing crystal form, the chemicals that are encapsulated in nanoparticles remain in their amorphous condition. Furthermore, hydrophobic forces dominate the interactions between chemicals and zein, however hydrogen bonds may also be implicated for some molecules.

Wang et al. prepared chitosan nanoparticles modified with folate acid and loaded

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them with berberine hydrochloride using the ionic cross-linking technique. The physicochemical characteristics and the impact of BH/FA-CTS NPs on the migration, apoptosis, and proliferation of human nasopharyngeal carcinoma CNE-1 cells were examined both in vitro and in vivo. The diameter of the sphere-shaped BH/FA-CTS nanoparticles, measured by scanning electron microscopy (SEM) images, was found to be 258.2±9.1 nm. The encapsulation efficiency was 87.73±4.21% and the drug loading efficiency was 8.17±1.12%, respectively. Over the course of 48 hours, the drug release kinetics showed a slower and more consistent release. Additionally, the MTT and scratch test findings showed that BH/FA-CTS NPs significantly reduced the migration and proliferation of CNE-1 cells (Wang et al., 2018).

Berberine loaded zein polysaccharide NPs possessed enhanced bioavailability in contrast to crude berberine. The NPs form possessed 80-90% bioavailability after 40 min of contact time. After 60 min of contact time, the bioavailability was found to be more than 90%. At various contact times, the results were obtained from the percent absorbance measurements. In addition, the %drug loading and % entrapment efficiency of berberine loaded zein polysaccharide NPs increased with the passage of time. Deng et al., synthesized berberine-loaded nanostructured lipid carriers through high-pressure homogenization were assessed. In vivo, berberine-loaded nanostructured lipid carriers demonstrated outstanding biocompatibility. Experiments on cellular uptake demonstrated that berberine-loaded nanostructured lipid carriers enhanced berberine uptake by Caco-2 and RAW 264.7 cells. Furthermore, oral administration of Berberine-loaded nanostructured lipid carriers upregulated the tight junction protein, downregulated pro-inflammatory cytokines through NF-κB inhibition, thus offering impressive amelioration of colitis (Deng et al., 2020). According to Niu et al. (2020), transdermal treatment of Berberine-Loaded Thiolated Pluronic may effectively control ear edema generated by dimethyl benzene. Berberine-Loaded Thiolated Polymeric Micelles exhibited a very high safety profile with no potentially harmful skin irritation (Niu et al., 2020).

Berberine loaded zein polysaccharide NPs possessed better antioxidant potential in contrast to crude berberine, as evident from DPPH and ABTS radical scavenging results. The greatest values of total antioxidants in terms of ascorbic acid equivalents/mg were found to be 67.6 ± 1.44 for ZnO and 72.6 ± 1.32 for Ag–ZnO at the measured dose of 1000 μg/ml, according to Hameed et al. (Hameed et al., 2019). Superior antibacterial action against Salmonella typhi, Streptococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae was shown by zein polysaccharide nanoparticles loaded with berberine. The NPs form was found to be more effective as decrease in MIC and MBC concentrations are evident from the given results. Berberine loaded zein polysaccharide NPs possessed excellent antifungal activity in contrast to crude berberine against different fungal species such as *Aspergillus flavus, Candida albicans, Fusarium solani, and Aspergillus Niger. In addition,* berberine loaded zein polysaccharide NPs *showed intermediate action against Penicillium spp. Trichophyton spp.* and *Trichdermaharzianum,* respectively. The antifungal effectiveness of ZnO–NPs and Ag–ZnO heterostructures inspired by Berberius lycium against four harmful fungus strains—Aspergillus flavus, Aspergillus niger, Aspergillus fumigatus, and Fusarium solani—was recently shown by Hameed et al. The DPPH Free Radical Scavenging Activity of Berberus lycium Methanol

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Extracts was 25, 30, 55, 75, and 85% at sample concentrations of 0.25, 0.05, 0.1, 0.25, and 0.5 (µg/ml) accordingly (Chandran, 2020).

Overall, this study suggests that zein polysaccharide could potentially enhance the therapeutic benefits of berberine. In literature, different studies have accomplished similar results by utilizing different types of nanocarrier systems.

When using hematoxylin and eosin staining, it was found that berberine solid lipid nanoparticles significantly reduced the sizes of lipid droplets and the accumulation of fats in the liver. In livers of BBR-SLN treated rats, lipogenic gene such as FAS, ACC and SCAP were significantly decreased while the lipofytic gene, CPT1 was up regulated. Some of these genes are SREBP1c, FAS and SCD1 genes among others (Xue et al., 2015). Breast tumor MDA-MB-231 cells are treated with curcumin (Cur) and berberine (Ber) associated nanopolymers where chitosan polysaccharide and zein protein are used as shell and core respectively. The resulting nanoparticles encapsulated more than 60% of Ber and 75% of Cur. After 4 months the Cur-Z-Ber-Ch nanoparticles showed the best storage stability as well as the redispersibility properties. Dependence of the drug release from the freeze-dried nanoparticles on pH was demonstrated. In the present study, the cytotoxic effect of Cur-Z-Ber-Ch nanoparticles was more pronounced in the case of MDA-MB-231 and A549 cancer cells, compared to normal MCF-10A cells, as determined through the in vitro cytoxicity assay. When compared to the free Cur + Ber bioactive compounds, in vitro experiments using MDA-MB-231 cells demonstrated that the Cur-Z-Ber-Ch nanoparticles could significantly reduce the pro-inflammatory cytokine IL-8 while also successfully increasing cellular absorption and death.

(Ghobadi-Oghaz et al., 2022). In cerebral ischemia, a lower dose of nano berberine formulation may be preferable to regular berberine formulation in order to reduce oxidative and inflammatory factors. Therefore, the production of micelles equipped with BBR could provide a possible protection against cerebral ischemia (Azadi et al., 2021).The suggested drug carrier significantly enhances berberine suppressive action on*H.pylori* development and precisely regulates its release, according to an analysis of a simulated gastrointestinal medium. This interaction occurs at the site of H. pylori infection. Based on an H. pylori-infected animal investigation, our results show that fucose-conjugated nanoparticles loaded with berberine significantly decrease stomach inflammation and have an H. pylori clearance effect (Lin et al., 2015). The prepared berberine chloride were found to have a spherical and homogeneous in shape. Furthermore, they showed good stability and appropriate releasing profile in vitro. When ONE intra-articular injection of BBR-loaded CNs was administered in rats, the plasma concentration of BBR declined and the synovial fluid concentration peaked at longer time points than free BBR solution. Following this, the in vivo evaluation of BBR-loaded CNs revealed higher apoptotic activity in the treatment of OA compared to BBR solution at the same concentration. In addition to TUNEL, real-time PCR, Western blot, and enhanced IHC staining of caspase-3, Bcl-2, and Bax, this was consistent with changes in gross morphology and histological staining in rat articular cartilage. Consequently, BBR-loaded CNs is potentially as therapeutic agents against OA. (Zhou et al., 2015).

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CONCLUSION

To sum up, this work successfully synthesizes zein-polysaccharide nanoparticles loaded with berberine, providing details regarding their physicochemical properties and their applications in the field of medicine. The best nanoparticle formulation was found by experimenting with several ratio combinations, which led to a consistent shape and improved drug encapsulation effectiveness. The structure of the nanoparticles was confirmed by the characterisation methods, suggesting a crystalline and stable form appropriate for future biological uses. Consistent with previous research, the results indicate that these nanoparticles have the potential to enhance therapeutic effectiveness and bioavailability, which makes them a promising option for a range of medical interventions, such as antibacterial, anticancer, and anti-inflammatory treatments. Further research regarding in vivo studies and clinical applications are warranted to fully comprehend the translational potential of these nanoparticles in medical practice

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