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Effects of Curcumin Nanoparticles Against Indomethacin Induced Gastric Ulcer in Rat

Gufran K. Abdulkareem[1], Bushra F. Hasan[2], Wasfi A. Al-Masoudi[3]

[1]Southern Technical University, Iraq
[2,3]University of Basrah, Iraq

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ABSTRACT

Objective: *Gastric ulcers (GUs) are a primary disorder affecting the upper gastrointestinal tract and are caused by gastric acid. The corrosive effects of pepsin and hydrochloric acid on the gastric mucosa can lead GUs. Compare the effect of curcumin and nanocurcumin with cimetidine on serum TC, TG, LDL, and HDL total protein and albumin levels in male rats with gastric ulcer.* ***Method:*** *Fifty male adult albino rats, with body weights ranging between 195–205 g where all the animals were categorized into five equal groups (each group containing 10 rats). Group 1: normal group, Group 2: indomethacin group, Group 3: indomethacin with curcumin, Group 4: indomethacin with nanocurcumin, Group 5: indomethacin with cimetidine. Blood samples (4 ml) were then placed into tubes without any anticoagulant, after centrifuging serum samples were then used for determining TC, TG, LDL, HDL, total protein and albumin levels in the animals.* ***Results:*** *Se/NP had a spherical, smooth nanoparticles, nanometre-sized. Oral administration of nanocurcumin caused marked improvement in HDL concentration and LDL concentration compared with gastric ulcer group and there were non-significant changes compared with normal group. Oral administration of nanocurcumin and cimetidine revealed a significant increase at ($p \leq 0.05$) level in serum albumin concentration when compared with gastric ulcer group and reach to normal group.* ***Novelty:*** *In rats with gastric ulcers caused by Indomethacin, the prepared nanocurcumin proved to be much more effective than curcumin. These results serve as a foundation for additional pharmacological investigation that could result in the creation of novel drug formulations.*

INTRODUCTION

Gastric ulcers (GUs) are a primary disorder affecting the upper gastrointestinal tract and are caused by gastric acid. It occurs when the stomach mucosa gets ruptured. The corrosive effects of pepsin and hydrochloric acid on the gastric mucosa can lead GUs. This disorder still has a significant effect on our society's healthcare system. Gastric ulcers are characterized by the following typical symptoms: nocturnal pain that is alleviated by food intake, antacids, or antisecretory compounds; pain that occurs on an empty stomach or 2-5 h after meals; and episodic gnawing or burning epigastric pain. The most prevalent gastrointestinal disorder ever documented [1]. It is caused by the stomach being exposed to gastrointestinal toxicity caused by the intake of non-steroidal anti-inflammatory drugs (NSAIDs), high acid and severe pepsin activity, and toxic chemicals such as alcohol. The pathogenesis of GUs was believed to be primarily caused by an imbalance between aggressive (excessive gastric acid secretion, bile salts, alcohol consumption, NSAIDs, abnormal motility, and *Helicobacter pylori* infections) and defensive (mucus secretion, bicarbonate production, gastroprotective prostaglandin synthesis, and normal tissue microcirculation) factors [2]. A few NSAIDs, such as Indomethacin and aspirin, are

commonly used as analgesics and anti-inflammatory agents. They help in treating many diseases like cardiovascular and rheumatic musculoskeletal disorders. However, they can lead to a few gastrointestinal issues like erosions and GUs. Additionally, they generate oxygen-free radicals, and play a vital part in the pathogenesis of a mucosal disorder. Furthermore, a few factors like a decreased expression of cyclooxygenases and prostaglandin synthesis are all associated with an Indomethacin -induced GUs in the glandular pattern. Many pharmacological therapies have been introduced into the market for GUs treatment. PPI act by preventing H/K ATPase in parietal cells [1]. By blocking histamine receptor-2 antagonists inhibit the acid-secreting activity of histamine. Antacids decrease stomach acidity, while mucosal protectants form barriers that shield the mucosa. However, these drugs display several adverse effects, including increased risk for gastric cancer, decreased vitamin absorption leading to dementia, increased risk for enteric infections, and hypersensitivity reactions [3].

Few researchers have recently looked into the use of medicinal plants as bio-factories to produce desired biomedical and pharmaceutical compounds, despite the fact that they have long been used for a variety of clinical, biological, pharmaceutical, and therapeutic purposes. It has been noted that the phytochemicals found in different plant parts like roots, leaves, stems, seeds, flowers, and fruits help protect the plant, animals, and people. Some of these phytochemicals include chemicals like alkaloids, terpenoids, and phenols that support the use of medicinal plants in traditional and alternative medicines [4].

Curcumin is a yellow pigment and used as a dietary compound that can be used extensively to treat several disorders. Epidemiological research has indicated that curcumin may lower the risk of inflammatory diseases like GUs and cancer. A few past studies have revealed that curcumin is sensitive to physiological pH fluctuations and cannot be easily dissolved in water, despite its medicinal properties [5]. Therefore, it is important to develop techniques so improve the solubility of the efficient herbal chemicals that are poorly soluble.

Nanotechnology can be considered a very effective approach for increasing curcumin's water solubility, which improves its absorption, dispersibility, and bioavailability. Several techniques were explored in the past few years to improve the effectiveness and efficacy of the curcumin compound. Some of these techniques include the development of curcumin nanoparticles, curcumin phospholipid complex, liposomal curcumin, and curcumin nano-capsules. Nanoparticles can easily penetrate through the cell membranes in organisms and interact with their biological processes. Nanotechnology has emerged as a feasible solution for overcoming the limitations of conventional pharmaceutical delivery methods. The nano-formulations are made up of several platforms, such as micelles, liposomes, polymeric nanoparticles, and nano-emulsions. Every platform has unique biological effects and physicochemical characteristics [6]. Aim of study to compare the effect of curcumin and nanocurcumin with cimetidine on serum TC, TG, LDL, and HDL total protein and albumin levels in male rats with gastric ulcer.

RESEARCH METHOD

Plant Materials

Curcumin (purity>95%) was purchased from Friendship Joint-stock Company (Hoan Kiem, HaNoi, Vietnam), whereas Cremophor RH40 was procured from Sigma-Aldrich Company.

Biosynthesis of Selenium Nanoparticle-Loaded Curcumin (Se/NP/Cur)

The researchers used an eco-friendly technique for green biogenesis of selenium nanoparticles (Se/NP) using curcumin. They added the curcumin solution (10 ml) to sodium selenite (90 ml) of 2 mM to yield a test combination. On the other hand, a control sample (DW; 10 ml) to Na_2SeO_3 (90 ml of 2 mM solution) [7].

Study Design

In this study, 50 male adult albino rats, with body weights ranging between (195–205 g) where all the animals were categorized into five equal groups (each group containing 10 rats) defined below. Group 1: normal group, administration normal saline. Group 2: gastric ulcer group, received 40 mg/kg of Indomethacin for two days. Group 3: received 40 mg/kg of Indomethacin for two days, then curcumin using of 50 mg/kg for 2 weeks. Group 4: administration of Indomethacin 40 mg/kg for two days, then using nano-curcumin of 0.4 mg/kg for 2 weeks. Group 5: administration of Indomethacin 40 mg/kg for two days, followed by using cimetidine 50 mg/kg for 2 weeks.

Gastric Ulcers' (GUs) Induction

The researchers induced GUs in 40 non-starved rats by orally administering Indomethacin (Safa Co., Diala-Iraq) using a 1 ml syringe at the standardized (40 mg/kg) for two days. These 40 rats were then categorized into 4 groups.

Blood Sample Collection

Blood samples (4 ml) were then put into anticoagulant-free tubes, and serum samples were obtained by centrifuging the tubes for 15 minutes at 3000 rpm. The serum samples were then stored at -20^{o}C in polyethylene Eppendorf tubes, which were used to study total cholesterol, triglycerides, HDL, LDL, total protein, and albumin.

Statistical Analysis

The two-way covariance (ANOVA) test was used to analyze the current study's findings across all studies. With the use of the statistical software SPSS V. 22.0, all statistical computations were completed. The data were presented as X ±SD, or means ± standard deviation. The difference between group and subgroup means was tested using the least significant difference test (LSD).

RESULTS AND DISCUSSION

Results

Samples were analysed using the scanning electron microscopy (SEM) technique, and the results revealed that Se/NP had a spherical, smooth, nanometre-sized shape and size, see Figure 1. The SEM images indicated that the Se/NPs were of different sizes, such as 75.99, 76.66, and 99.76 nm.

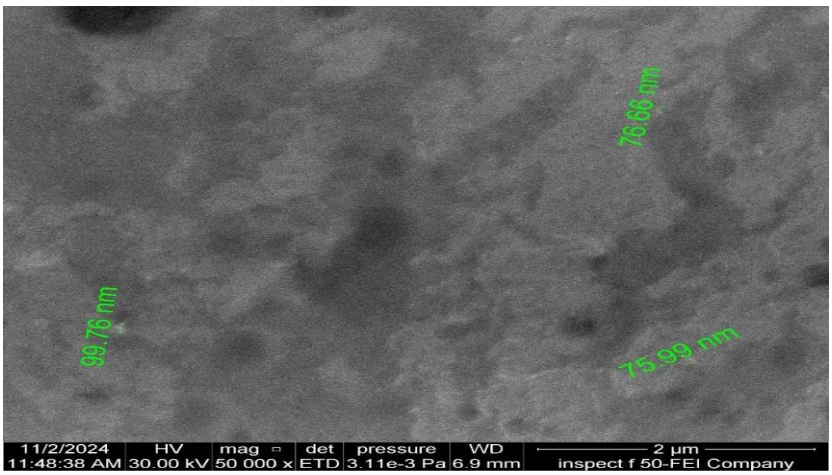

Figure 1. The field emission SEM (FeSEM) image-based morphology and size of the Cur Se/NP.

The biogenic Selenium nanoparticles (SeNPs) in Figure 2 exhibit a range of optical absorbance values with distinct peaks at 237, 262, and 290 nm. The reduction of Selenium ions is indicated by the distinct peak at 290 nm.

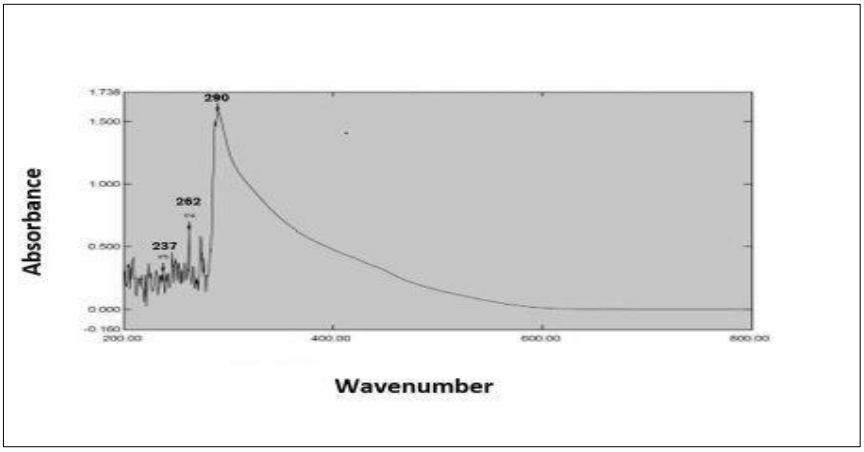

Figure 2. UV-Vis Spectrum of Biogenic Selenium Nanoparticles after 72 Hours of Incubation.

The generated Se-NPs' crystal structure and phase were investigated using XRD analysis. The pattern clearly shows that the original precursors did not have any distinguishable peaks. In Figure 3, the XRD diffraction peaks of Se-NPs are displayed along with the diffraction characteristics pertaining to 2θ at 24.83◦, 29.95◦, and 51.65◦, which correspond to the Bragg's reflections at (100), (101), and (201), respectively.

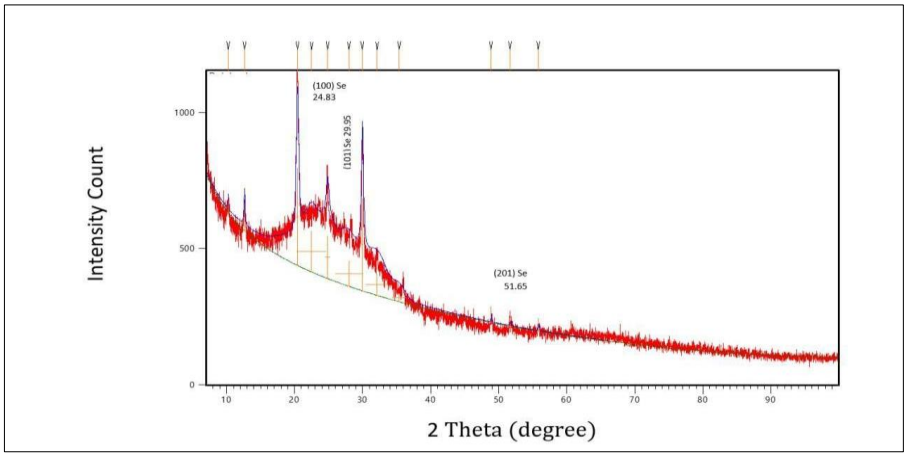

Figure 3. X-ray Diffraction Pattern of Biogenic Nanoparticles (SeNPs).

Table 1 shows the average TC, TG, HDL, and LDL levels for the control and treated groups noted during the study. Oral administration of nanocurcumin caused marked improvement in HDL concentration and LDL concentration compared with gastric ulcer group and reach to normal group. In comparison to the GU group, the curcumin and cimetidine therapy groups did not exhibit any significant changes in their HDL concentration. Furthermore, no significant difference was noted in total cholesterol and triacylglycerol concentrations in any of male rat groups. The results presented in the table also indicated that the LDL concentration in the male rats from the curcumin treatment group was not significantly different than that displayed by the rats in the (+ve) control group.

Table 1. Effect of curcumin and nanocurcumin in comparison with cimetidine on serum lipid profiles in Indomethacin-induced GUs male rats (n=10), (mean ± SD).

Parameters treatment	Total Cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
Control (-ve)	84.19 ±8.17	80.16±9.15	45.03±3.81	40.33±2.36
Normal Saline (0.9% NaCl)	NS	NS	A	BC
Control (+ve)	92.59±31.01	89.37±28.33	33.10±10.25	53.87±13.59
Indomethacin (40mg/kg)	NS	NS	C	A
Indomethacin + Curcumin (50mg/kg)	89.00±5.99	82.00±4.18	38.00±5.02	46.80±3.13
	NS	NS	BC	AB
Indomethacin + Nanocurcumin (0.4mg/kg)	88.90±5.037	82.00±8.42	42.00±6.51	38.50±7.31
	NS	NS	AB	C
Indomethacin + Cimetidine (50mg/kg)	88.50±9.99	81.50±16.02	38.50±7.83	46.50±7.48
	NS	NS	BC	B
LSD			6.353	7.09

Table 2 illustrates the mean value of total protein and albumin concentration in the control and treated groups through the experimental period. The results of serum total protein concentration revealed non-significant changes in all experiment study groups of male rats. Also, the table shows a significant decrease at ($p \leq 0.05$) level in serum albumin concentration in gastric ulcer group compared with normal group. Oral administration of nanocurcumin and cimetidine revealed a significant increase at ($p \leq 0.05$) level in serum albumin concentration when compared with gastric ulcer group and reach to normal group. From the same table, albumin concentration data revealed non-significant changes in treatment group with curcumin when compared with gastric ulcer group.

Table 2. Effect of Curcumin and nanocurcumin in comparison with cimetidine on serum Total Protein and Albumin in Indomethacin induced Gastric ulcer male Rats (n=10), (means ±SD).

Parameters treatment	Total protein (g/dl)	Albumin (g/dl)
Control (-ve)	6.24±0.59	3.95±0.46
Normal Saline (0.9% NaCl)	NS	A
Control (+ve)	5.75±0.34	3.35±0.79
Indomethacin (40mg/kg)	NS	B
Indomethacin + Curcumin	5.80±0.62	3.30±0.29
(50mg/kg)	NS	B
Indomethacin + Nanocurcumin (0.4	6.00±1.04	3.92±0.36
mg/kg)	NS	A
Indomethacin + Cimetidine	6.20±0.74	4.05±0.50
(50mg/kg)	NS	A
LSD		0.4643

Discussion

Gastric ulcers are caused by disruptions in the digestive system's bioactivities and the body's defenses, which include blood flow, mucus content, mucosal membrane cell regeneration, and endogenous defense enzymes. The aforementioned conditions may result in submucosal erosion, decreased cyclooxygenase, and damage to the stomach's mucosal layers [8]. Nonsteroidal anti-inflammatory drug (NSAID) use is thought to be the primary risk factor for stomach ulcers [9]. All of the rats that received Indomethacin displayed decreased feed intake, lethargy, and an unthrifty appearance. The gastric damage caused by indomethacin has been confirmed by histopathologic analysis. To effectively manage therapeutic drug toxicity, such as gastric ulcers, there has been a lot of interest in finding natural antioxidants from plant materials to replace synthetic ones. In this work, we examined the impact of curcumin and nanocurcumin on rats' gastric damage caused by indomethacin. It is well known that curcumin, a compound high in phenolics, has antioxidant qualities. Curcumin lessens NSAID-induced gastric damage. By blocking Indomethacin's peroxidase inactivation effect and scavenging the reactive

oxygen this enzyme produces, curcumin has been shown to reduce gastric damage [10]. Nevertheless, curcumin has very little aqueous solubility and is extremely sensitive to physiological pH variations. However, these kinds of obstacles can be effectively overcome with the aid of curcumin nanoparticles, allowing for longer-term topical delivery of the agent. A significant improvement was noted in the serum HDL and LDL values after the rats were orally administered nano-curcumin. Earlier studies showed that nano-curcumin could have a hypolipidemic effect, which inhibits the liver's production of low-density lipoproteins (LDL) [11].

Murthy *et al*., designed an oral nano micelle incorporating curcumin and conducted their clinical trial [12]. They noted that nano-curcumin could become a powerful tool for decreasing different lipid profile markers. Furthermore, their results also showed that oral administration of nano-curcumin (1 g/day) to obese adults could help them significantly decrease their blood TG levels. The researchers further stated that every participant in the group that received nano-curcumin treatment showed significantly lower serum liver enzymes. Shamsi-Goushki *et al*., examined the outcome of diverse nano-curcumin concentrations in serum lipid profile [13]. Furthermore, they noted that the animal group that underwent nano-curcumin treatment displayed significantly higher average serum HDL levels. Both studies highlighted the significance of nano-curcumin therapy in preserving the serum lipid profile levels. Fakhri *et al*., discovered that the effects of nano-curcumin administration were significantly better in rats with nicotine-induced toxicity [14]. Their results showed that the ameliorative effect of nano-curcumin improved the blood serum HDL level and normalized the serum TC, TG, LDL, and VLDL levels. The above studies showed curcumin nanoparticles plays a vital part in preserving lipid profile levels.

Oral administration of curcumin did not show any significant changes in serum albumin, while Oral administration of nanocurcumin and cimetidine caused marked improvement in the serum albumin as compared with (+ve) control group (Table 2). The antioxidant activity of the liver's mitochondria was compared between curcumin and nanocurcumin using aluminum phosphide (AIP)-induced toxicity [15]. The study's findings demonstrated that exposure to AIP had serious oxidative toxic effects on the liver mitochondria. However, using nanocurcumin to treat oxidative stressors could result in significant improvements. With the aid of free radical scavenging and liver oxidative status stabilization, nanocurcumin administration may be advantageous in cases of the detrimental effects of AIP-induced toxicity. It was discovered that curcumin nanoencapsulation could be a very successful strategy for preventing the toxicity that lead exposure causes in the body [16]. Both the reduced and oxidized levels of glutathione were restored by administering nanocurcumin and lead, which also resulted in a decrease in ROS. The removal of lead from soft tissues and blood was likely due to the chelation property and improved bioavailability of nanocurcumin. Fakhri *et al*., examined the protective properties of curcumin and nanocurcumin against lung damage brought on by exposure to paraquat [14]. The study discovered that nanocurcumin had a far

greater protective effect than curcumin in preventing lung damage brought on by paraquat, primarily by regulating the amount of oxidative stress and gene expression.

Bladé *et al*., examined how curcumin nanocrystals' antioxidant properties protected Wister rats' circulatory systems from harmful effects [15]. The study's findings demonstrated that curcumin nanocrystals at a dose of 40 mg were more effective at lowering the level of lipid peroxidation while also boosting antioxidant activity and detoxifying enzymes like glutathione peroxidase, catalase, and superoxide dismutase.

CONCLUSION

Fundamental Finding : Oral administration of nanocurcumin led to a significant improvement in HDL and LDL serum levels in rats with gastric ulcers. The treatment also showed a marked increase in serum albumin compared to the ulcer group. These results demonstrate the superior efficacy of nanocurcumin over conventional curcumin in mitigating lipid profile disturbances and supporting protein balance under ulcer-inducing conditions. **Implication :** Nanocurcumin offers a promising alternative to conventional therapies by enhancing curcumin's solubility, absorption, and bioavailability. Its ability to penetrate cellular membranes and exert biological effects suggests potential for clinical application in gastrointestinal disorders, especially as a safer and more effective delivery platform than current treatments. **Limitation :** Curcumin's therapeutic application is limited by its poor water solubility and high sensitivity to physiological pH. In this study, curcumin alone did not significantly improve albumin levels, indicating limitations in its standalone efficacy without formulation enhancement. **Future Research :** Further studies are needed to explore optimized nanoformulations of curcumin and assess long-term safety and efficacy in diverse models. Investigating the molecular mechanisms behind nanocurcumin's protective effects will also support its development into clinical-grade pharmaceuticals.

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***Gufran K. Abdulkareem (Corresponding Author)**
Southern Technical University, Iraq
Email: gufran.kadhim@stu.edu.iq

Bushra F. Hasan
University of Basrah, Iraq
Email: bushra.hasan@uobasrah.edu.iq

Wasfi A. Al-Masoudi
University of Basrah, Iraq
Email: wasfi.masoudi@uobasrah.edu.iq