Original Article

Effects of the Slow-release Curcumin-loaded Selenium Nanoparticles on Experimental Peritonitis

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ABSTRACT

Background: New pharmaceutical forms of natural compounds such as curcumin can be an effective intervention to control peritonitis and abdominal adhesion.

Objectives: This study investigates the effects of slow-release curcumin-loaded selenium nanoparticles (Cur@S.N) on some inflammatory biomarkers in experimental peritonitis.

Methods: After synthesizing selenium nanoparticles (S.N) and (Cur@S.N), experimental peritonitis was surgically induced in 80 adult male rats. The control group received no treatment, whereas the other groups received single intraperitoneal doses of 0.25 mg/kg S.N, 50 mg/kg curcumin, and 0.25+50 mg/kg (Cur@S.N). Blood malondialdehyde (MDA), nitric oxide (NO), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNFα) were measured on days 3, 7 and 14, and also intra-abdominal adhesion assessment was done.

Results: On day 3, NO levels in all treatment groups significantly decreased ($P>0.05$), while the lowest level was seen on day 14 in the S.N group ($P<0.05$). MDA was significantly lower in the S.N and Cur@S.N groups than in the control on days 3, 7 and 14 ($P<0.05$). TNF-α levels in S.N and Cur@S.N groups were significantly lower than in the control group on day 3 ($P\leq0.05$). Meanwhile, the S.N group had the lowest level on day 14. IL-6 significantly decreased on days 3 and 7 in the Cur@S.N and curcumin groups compared to the control group ($P<0.05$).

Conclusion: Cur@S.N group possesses significant anti-inflammatory efficacy by reducing MDA, NO, IL-6 and TNF-α, decreasing peritonitis and intra-abdominal adhesion.

Keywords: Adhesion, Interleukin 6 (IL-6), Malondialdehyde (MDA), NO, Tumor necrosis factor-alpha (TNF-α)

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Introduction

Peritonitis is a major surgical complication with numerous consequences and a high mortality rate despite invasive antimicrobial and supportive treatments. It involves various pathophysiological processes, many of which are connected to inflammatory and immune responses such as the release of cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) (Raftery, 1973; Ingersoll et al., 2011; Yildirim et al., 2016).

Peritonitis can result in adhesions in the abdominal cavity. The complex process of adhesion formation involves the migration and proliferation of different cell types, including inflammatory cells, mesothelial cells, and fibroblasts, then the construction of an extracellular matrix, and finally, the response and transformation of these cells during a series of subsequent processes to form fibrous adhesions (Raftery, 1973; Yildirim et al., 2016). Histamine and vasoactive kinins are released after peritonitis, increasing vascular permeability and secreting a fibrin-rich fluid into the peritoneal cavity to start healing. Following the migration of inflammatory cells into these bands, fibroblasts proliferate and produce persistent sticky bands along with angiogenesis. The tissue, including its fibroblasts, macrophages, and giant cells, is replaced as the fibrin matrix gradually undergoes reorganization. Adhesion results from the fibrin bundles' gradual organization. Eosinophils, macrophages, erythrocytes, tissue fragments, fibroblasts, and mast cells constitute the adhesion tissue (Milligan & Raftery, 1974; Raftery, 1973). An increased inflammatory response results in a pathogenic reaction that damages cell membranes, generates oxidative stress, increases lipid peroxidation and produces free radicals and malondialdehyde (MDA) as the final product. Additionally, cytokine release stimulates NO production by macrophages and endothelial cells (Raftery, 1973; Ingersoll et al., 2011; Yildirim et al., 2016). Numerous chemical elements with antioxidant and anti-inflammatory properties, including the essential micronutrient selenium, have been suggested for inflammatory conditions. Selenium nanoparticles (S.N) seem to be a good substitute for other forms of selenium due to their chemical stability, excellent biocompatibility, and lower toxicity than selenite and selenate (Skalickova et al., 2017). They increase glutathione peroxidase, superoxide dismutase, glutathione S-transferase, and thyroxine reductase activities, leading to much less MDA production. Also, they increase and facilitate selenium transport to the target site and are crucial for the adherence of monocytes to endothelial cells, tissue infiltration, and transformation into macrophages, which are the primary immunological components of inflammation (Hasan et al., 2023; Wu et al., 2011). Curcumin is the main active substance of the turmeric plant and is a very old and widely used food spice with anti-inflammatory, immune modulation and anti-mitotic functions (Huang et al., 1991; Liju et al., 2011; Lee et al., 2019). Generally, therapeutic effects depend on the drug concentration at the target site, so delivering a sufficient therapeutic concentration to the target tissue (s) is crucial. Slow-release pharmaceutical forms provide an initial loading dose, then gradually release maintenance doses over time, resulting in more comfortable drug administration, decreased side effects and improved drug tolerability (Adepu & Ramakrishna, 2021). This study aimed to synthesize S.N and curcumin-loaded S.N (Cur@S.N) and examine their effects on some inflammatory mediators during experimental peritonitis.

Materials and Methods

Nanoparticles synthesis

Around 50 mL of a 44 mM ascorbic acid solution (Merck, Germany) was added dropwise to the 500 mL aqueous solution of 1 mM selenium oxide (Sigma-Aldrich, USA) to form S.N. For curcumin loading on the S.N, 10 mg of curcumin (Sigma-Aldrich, USA) dissolved in 5 mL of acetone (Sigma-Aldrich, USA) was added to 150 mL of S.N, stirred and mixed carefully for 24 h in a fridge (Anvar et al., 2022; Koohian et al., 2022; Vahdati et al., 2020; Kojouri et al., 2013; Baum & Ng, 2004). Figure 1, represented the synthesis process, characterization and effects of Cur@S.N on experimental peritonitis

Characterization of the nanoparticles

S.N and Cur@S.N morphologies were studied by field emission scanning electron microscopy and a Tescan MIRA3 electron microscope (Czech Republic) with an energy-dispersive spectroscopy analytical system. An x-ray diffraction analysis was performed using an x-ray diffractometer (Philips-PW1730, Netherlands). Nanoparticles (NPs) content was determined by inductively coupled plasma optical emission spectrometry (Varian Vista-Pro 7410, USA) and zeta potential was determined (VASCO-2 Cordouan Technologies, France). The calibration curve of the supernatant solution of the NPs was determined using a spectrophotometer (Unico SQ-2800, China) at 430 nm, and curcumin loading was measured (Baum & Ng, 2004).

Table 1. Grading scheme for evaluation of intra-abdominal adhesion

Grade	Definition	Point
0	No adhesion	5
1	Thin filmy adhesion	4
2	Thick adhesions in a limited area	3
3	Widespread adhesions	2
4	Widespread adhesions plus adherence of visceral organs to the abdominal wall	1

In vitro release study

Around 5 mg of the produced NPs was added to 5 mL of phosphate buffer (pH=5.5 or 4.7) and Tween 80% (Sigma-Aldrich, USA) and the mixture was thoroughly stirred (100 rpm, 37 ˚C). Then, 1 mL of fresh buffer was added to 1 mL of sample and spectrophotometry was performed after 0.5, 1, 2, 3, 4, 5, 6, 12, 24, 48 and 72 hours at 430 nm wavelength (Baum & Ng, 2004).

Animal experiments

According to international guidelines, 80 adult male Wistar rats weighing 200–250 g were housed in metal cages under standard conditions (Zimmermann, 1983). After one week, when animals adapted to the environmental conditions, the cecal abrasion method induced experimental peritonitis and abdominal adhesion (Deng et al., 2020). Anesthesia was induced by intraperitoneal administration of 80 mg/kg of ketamine and 10 mg/kg of xylazine (Merck, Germany). A 2 cm long incision was made in the abdominal midline. Subsequently, the cecum was separated from surrounding tissues and scratched with a sterile sponge on the anti-mesenteric surface until small petechial hemorrhages were seen; then, the incision was sutured (Deng et al., 2020). Next, the animals were divided into four equal groups randomly. The control group did not receive any treatment, while in the other groups, single doses of 0.25 mg/kg of S.N, 50 mg/kg of curcumin, and Cur@S.N (0.25+50 mg/kg) were administered intraperitoneally. On days 3, 7 and 14, blood samples were taken from all groups for biochemical measurements by cardiac puncture (Parasuraman et al., 2010). Finally, the animals were euthanized by the intraperitoneal injection of 150 mg/kg sodium pentobarbital (Sigma-Aldrich, USA) (Zimmermann, 1983) and the adhesion pattern was evaluated (Skalickova et al., 2017) (Table 1).

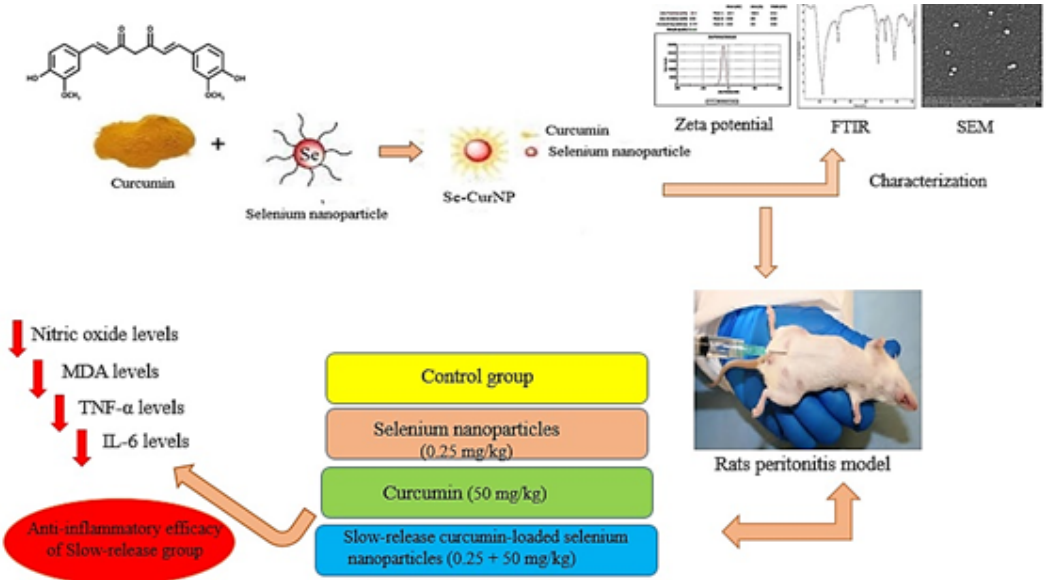

Figure 1. Schematic illustration of the synthesis process, characterization and effects of Cur@S.N on experimental peritonitis

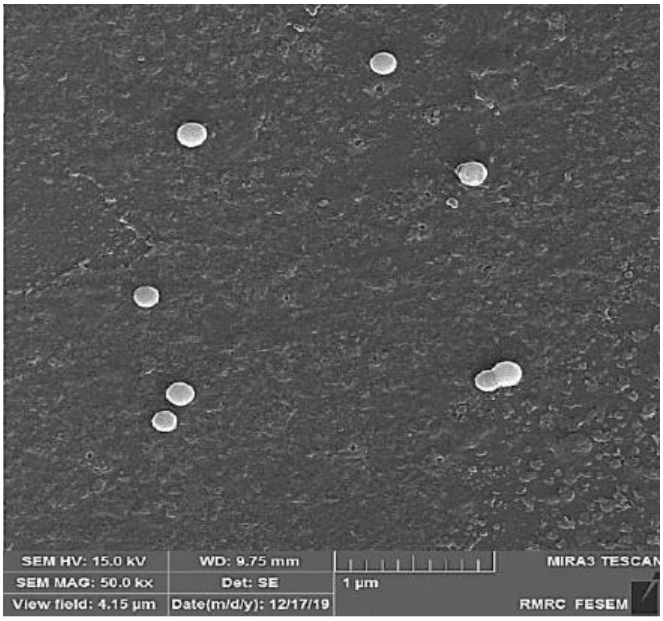

Figure 2. Scanning electron microscopic image of S.N, with an average size of about 200 nm

Biochemical analysis

TNF-α and IL-6 were measured using the ELISA method with Karmania Pars Gene (KPG®) kits, while MDA and nitric oxide (NO) were estimated using the TBA and Griess methods, respectively (Lindamood et al., 1990; Yin et al., 2015; Yazdi et al., 2019).

Statistical analysis

Data were shown as Mean±SD and analyzed using one-way ANOVA and Tukey's post-hock test by statistical package SPSS software, version 16 ($P<0.05$).

Results

Physiochemical characterization of S.N

The morphology examination of S.N by scanning electron microscope showed a spherical shape and uniform distribution, with an average size of about 200 nm (Figure 2). Dynamic light scattering analysis revealed 206-nm nanoparticle size and a 0.231 particle size distribution, indicating particle size uniformity (Figure 3). The zeta potential of the NPs was -20.4 mV (Figure 4).

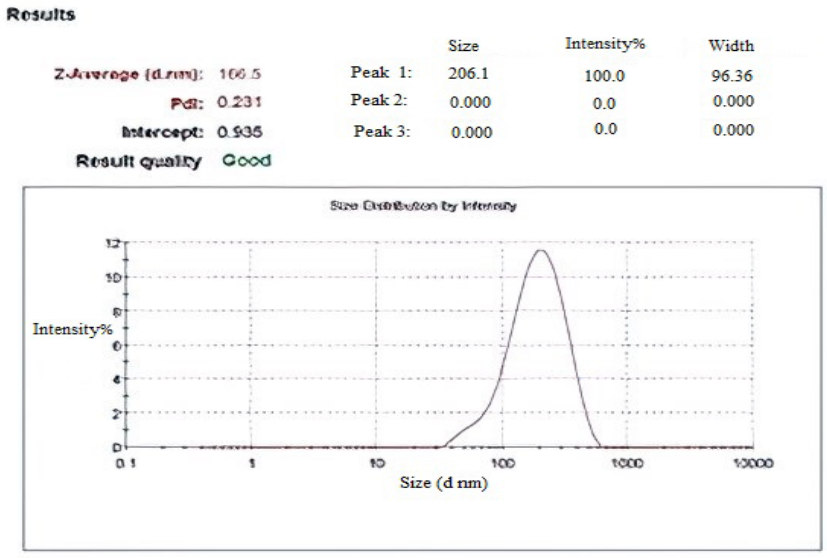

Figure 3. Size distribution of the S.N

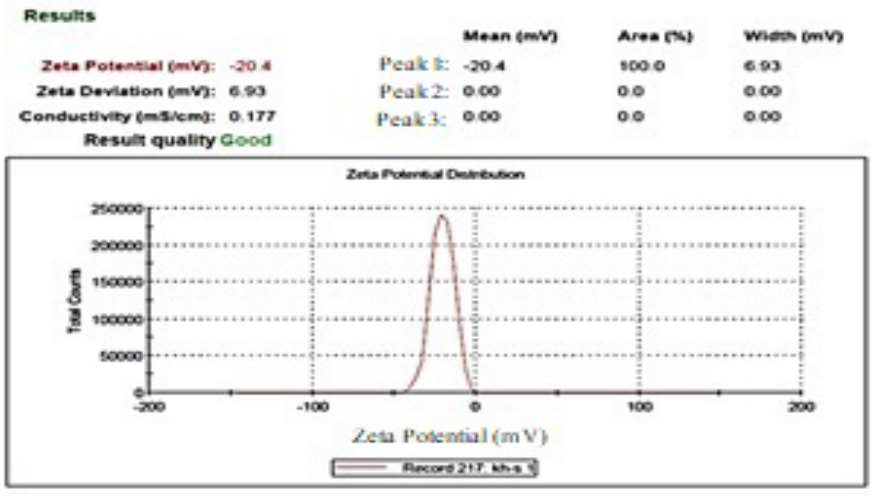

Figure 4. Zeta potential of the S.N

Fourier-transform infrared spectroscopy of S.N

The peaks at 1105 cm^{-1}, 1613 cm^{-1}, and 470 cm^{-1} are related to Se-O stretching and bending vibration, respectively. High-intensity bands at 3437 cm^{-1} and 11631 cm^{-1} are related to O-H stretching and bending vibrations, while the peak at 1380 cm^{-1} is associated with C-O stretching vibration. The vibrations at 2870 cm^{-1} and 2927 cm^{-1} are related to symmetric and asymmetric C-H stretching vibrations (Figure 5).

Loading capacity and efficacy

Loading capacity was estimated at 32.89%, with an efficacy of 98.23%, indicating effective synthesis and loading of the S.N. The standard curve of curcumin in ethanol was drawn using UV spectrophotometry at 430. It was linear in the concentration range of 0.004 to 0.009 µg/mL. Moreover, all measurements were carried out in triplicate (R^2=0.9857) (Figure 6).

In vitro curcumin release profile

The graph obtained from Cur@S.N released in buffer medium with pH 5.5 and 7.4 shows that release was pH dependent, though the difference was not significant. The burst effect is also seen in the nanoparticle release at both pH levels in the first 24 hours (Figure 7).

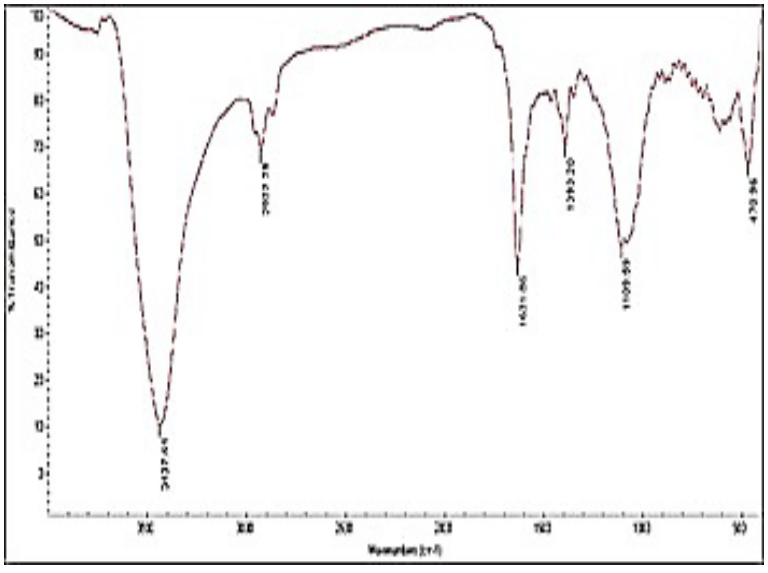

Figure 5. Fourier-transform infrared spectroscopy spectrum of the S.N

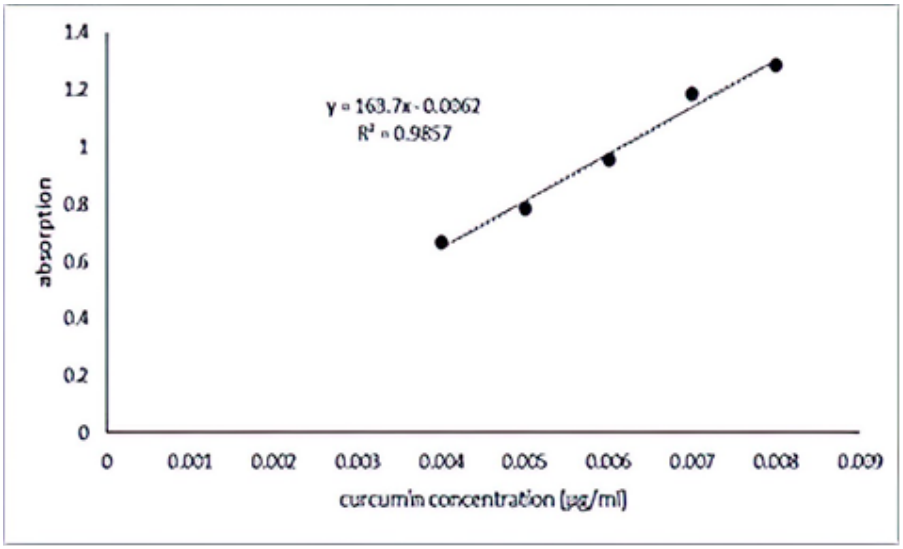

Figure 6. Standard UV spectrophotometry curve of curcumin in ethanol

NO levels

On day 3, the highest level of NO was seen in the control group, which was significantly higher than in other groups (P<0.05). On day 7, no significant difference was seen between the treatment groups (P>0.05). On day 14, the lowest level of NO was seen in the S.N group, which was significantly lower than in other groups (P<0.05) (Table 2).

MDA levels

On days 3, 7 and 14, a significant decrease in MDA level was seen between the S.N and Cur@S.N groups compared with the control group (P<0.05), and the lowest level was seen in the Cur@S.N group. On day 3, a significant difference was seen between the curcumin and Cur@S.N groups (P<0.05). Also, a significant difference was seen between curcumin with S.N and Cur@S.N groups on days 7 and 14 (P<0.05); meanwhile, there was no significant difference between S.N and Cur@S.N groups (P>0.05) (Table 3).

TNF-α levels

On days 3 and 14, TNF-α was significantly lower in the S.N and slow-release groups than in the control (P<0.05). On day 7, no significant difference was seen among the groups (P>0.05). On day 14, a significant decrease was seen between the S.N, cur and Cur@S.N groups (P<0.05) (Table 4).

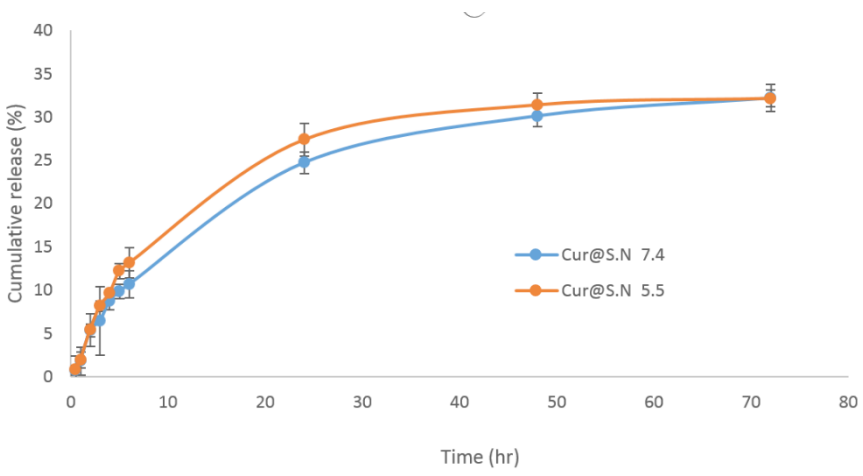

Figure 7. Curcumin release from S.N at pH=7.4 & 5.5

Table 2. NO levels in the control, curcumin, S.N and slow-release groups (mM/mL)

Groups	Mean±SD		
	Day 3	Day 7	Day 14
Control	134.674±38.	94.01±19.7	83.81±38.7
Curcumin	101.472±28.1*	86.23±20.4	55.52±16.2
S.N	65±13.9*	63.09±22.9	20.42±11.8*
Slow release	93.69±17.5*	80.62±1.4	56.01±14.8

*Significant vs control group.

Table 3. MDA levels in the control, curcumin, S.N and slow-release groups (nM/mL)

Groups	Mean±SD		
	Day 3	Day 7	Day 14
Control	602±96.7	550±130.1	496±119.2
Curcumin	510±140.3	502±6^{A}	398±14.5^{A}
S.N	370±6^{AB*}	188±26.8^{B*}	126±18.1^{B*}
Slow release	304±48.2^{B*}	194±27.01^{B*}	122±20.4^{B*}

*Significant vs control group; ^{A,B}Significant differences between different treatment groups (P<0.05).

Table 4. Tumor necrosis factor-α levels in the control, curcumin, S.N, and slow-release groups (pg/mL)

Groups	Mean±SD		
	Day 3	Day 7	Day 14
Control	33.27±7.6	19.19±4.9	28.82±3.3
Curcumin	25.72±2.3	23.24±2.8	23.68±3.3^{A}
S.N	23.45±2.7*	17.26±3.7	16.65±3.4 ^{B*}
Slow release	26.16±3.07*	18.68±3.5	20.17±4.05^{AB*}

*Significant vs control group; ^{A,B}Significant differences between different treatment groups (P<0.05).

Table 5. Interleukin 6 levels in the control, curcumin, S.N and slow-release groups (pg/mL)

Groups	Mean±SD		
	Day 3	Day 7	Day 14
Control	30.24±3.7	30.03±3.6	19.71±3.8
Curcumin	25.08±1.4	23.61±2.07^{A*}	20.82±1.6
S.N	26.9±1.6	16.5±2.2^{B*}	17.2±1.8
Slow release	24.71±34.6*	21.41±1.7^{A*}	20.82±1.6

*Significant vs control group, ^{A,B}Significant differences between different treatment groups (P<0.05).

Table 6. Median intra-abdominal adhesion grades in different groups using the Kruskal–Wallis test

Group	Day 3	Day 7	Day 14
Control	4(4-5)	2(2-4)^{A}	2(1-3)^{A}
Curcumin	4(4-5)	3(3-4)^{A}	2(1-3)^{A}
S.N	4(4-5)	3(3-5)^{B}	4(3-5)^{B}
Slow release	4(4-5)	3(3-4)^{A}	4(2-5)^{B}

*Significant vs control group; ^{A,B}Significant differences between different treatment groups (P<0.05).

IL-6 levels

On day 3, there was a significant difference between the curcumin and Cur@S.N groups compared to the control group (P<0.05). Additionally, the Cur@S.N group had the lowest level of IL-6. On day 7, IL-6 was significantly lower in all treatment groups than in the control (P<0.05). At the same time, there was no significant difference between the curcumin and Cur@S.N groups (P>0.05) and the lowest level of IL-6 was seen in the S.N group. On day 14, no significant difference was seen between the control and treatment groups (P>0.05) (Table 5).

Intra-abdominal adhesion assessment

On day 3, there was no significant difference between the groups (P>0.05). The lowest degree of adhesion was seen in the S.N group on day 7, while on day 14, it was seen in the S.N and Cur@S.N groups (Table 6).

Discussion

To our knowledge, this is the first report about the synthesis of Cur@S.N and its anti-inflammatory response in experimental peritonitis. Confirmatory tests revealed successful synthesis, alongside NO, MDA, IL-6, and TNF-α anti-inflammatory biomarkers reduction and lower intra-abdominal adhesion.

Assessment of the severity of the peritonitis complications and the impact of treatment is possible by measuring specific factors produced when peritoneal adhesion processes to stop the damage and initiate healing. IL-6 is an inflammatory cytokine linked to acute infection and inflammation released in response to peritoneal injury. TNF-α is an inflammatory cytokine that can be used to detect and confirm adhesion in a damaged area, and its elevation has been well-documented in both chronic and acute inflammation (Agarwal et al., 2019; Liakakos et al., 2001; Savitha et al., 2015; Plomgaard et al., 2005).

Curcumin treatment significantly reduced IL-6 and TNF-α in the current study. Curcumin affects the metabolism of arachidonic acid and has anti-inflammatory effects by inhibiting the PLA_2 enzyme, decreasing the COX_2 gene production, and inhibiting the 5-LO enzyme (Aghaei, 2008; Funk et al., 2006). Several inflammatory cytokines, such as chemokines, IL-1, IL-6, and TNF-α, are also inhibited by curcumin (Lindamood et al., 1990). It possesses anti-inflammatory properties comparable to NSAIDs and reduces NF-κB activity, encouraging pro-inflammatory gene product expression (Gaddipati et al., 2003; Lee et al., 2019). So, because of its anti-inflammatory properties, curcumin can reduce inflammation induced by experimental peritonitis in mice. Moreover, a distinctly anti-inflammatory effect of curcumin in the LPS-induced experimental peritonitis in rats has been indicated (Savitha et al., 2015).

Inhibition of IL-6 slows the adhesion process because it increases inflammation and adhesion in rats (Raftery, 1973; Saba et al., 1998). A 28-day intraperitoneal administration of curcumin in rheumatoid arthritis, decreased swelling, discomfort, and inflammatory cytokines such as TNF-α and chemokines (Huang et al., 1991). Because of the high surface area-to-volume ratio, NPs like S.N with anti-inflammatory properties can inhibit inflammatory cytokines (Agarwal et al., 2019; Jamilian et al., 2018; Shahabi et al., 2021; Peidaei et al., 2021).

After daily intraperitoneal administration of 5 and 10 mg/kg curcumin for 5 weeks, the pain and inflammation induced by the writhing test in mice were significantly reduced, with an impact on the inflammatory and oxidative stress markers (Liju et al., 2011). Superoxide dismutase activity was significantly increased by intraperitoneal administration of curcumin to rats with spinal cord injuries. At the same time, MDA, macrophage ED-1, and other inflammatory markers like IL-6, IL-8, and TNF-α were significantly decreased (Lee et al., 2019). The efficacy of curcumin in experimental peritonitis was investigated and showed that it markedly reduced ne-

crosis, bleeding, hyperemia, lipid peroxidation and the number of neutrophils (Savitha et al., 2015).

The current study showed a significant reduction in inflammatory biomarkers by S.N exposure to peritoneum with selenium, and S.N decreases the TNF-α as an excellent biomarker in peritonitis and abdominal adhesion (Liakakos et al., 2001; Savitha et al., 2015). NO, TNF-α, and Prostaglandin E2 all have decreased after oral administration of S.N to rats (Funk et al., 2006). S.N boost antioxidant activity by blocking COX-2 activity and thus reducing the generation of PGE2 (Agarwal et al., 2019). In the experimental inflammation, S.N decreases TNF-α, monocyte and granulocyte migration (Zaafan et al., 2016). Oral S.N supplementation for six weeks reduced inflammation and the expression of TNF-α and TGF-β genes in people with diabetes (Jamilian et al., 2018; Javanmardi et al., 2017). Selenium plays an important role in combating oxidative stress by enhancing the activity and expression of glutathione peroxidase and thioredoxin reductase and exhibits anti-inflammatory characteristics by inhibiting leukotriene and prostaglandin synthesis and infiltration of inflammatory cells (Shahabi et al., 2021; Khurana et al., 2019). Inflammation plays a significant and crucial role in the pathogenesis of intra-abdominal adhesion by releasing inflammatory factors, including cytokines; anti-inflammatory medications can reduce this process. Since S.N has anti-inflammatory efficacy, they are a good choice for this application (Liakakos et al., 2001).

Conclusion

Inflammation plays a healing predisposing function during peritonitis, but prolonged, severe inflammation hinders the healing process, so its control is necessary. Curcumin, S.N, and Cur@S.N significantly decrease the level of biological markers of inflammation in experimental peritonitis. S.N increases curcumin absorption and therapeutic concentration, enhancing anti-inflammatory effects and leading to a decline in peritoneal adhesion so that it can be used as a therapeutic solution alongside conventional treatments.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Shahrekord University (Code: IR.SKU.REC.1401.016).

Funding

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Authors' contributions

Study design: Jahangir Kaboutari and Moosa Javdai; Experiments: Maryam Ghorbani; Writing the initial draft: All authors; Model code development and simulations, review and editing: Jahangir Kaboutari.

Conflict of interest

The authors declared no conflict of interest.

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مطالعه پژوهشی

ارزیابی اثر پادآماسی نانوذره های نوین سلنیوم بارگذاری‌شده با کورکومین در پریتونیت تجربی

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چکیده

زمینه مطالعه: اشکال دارویی جدید ترکیب‌های طبیعی همچون کورکومین می‌تواند مداخله‌ای کارآمد برای ساماندهی پریتونیت و چسبندگی شکمی باشد.

هدف: این پژوهش به بررسی اثر نانوذره‌های سلنیوم آهسته رهش بارگذاری‌شده با کورکومین بر برخی شاخص‌های زیستی آماس در پریتونیت تجربی می‌پردازد.

روش کار: پس از ساخت نانوذره‌های سلنیوم و نانوذره‌های سلنیوم بارگذاری‌شده با کورکومین (فرمولاسیون آهسته رهش)، پریتونیت تجربی با جراحی در ۸۰ موش صحرایی نر بالغ ایجاد شد. گروه کنترل هیچ درمانی دریافت نکردند، درحالی‌که گروه‌های دیگر ۰/۲۵ میلی‌گرم بر کیلوگرم نانوذره‌های سلنیوم، ۵۰ میلی‌گرم بر کیلوگرم کورکومین و ۰/۲۵ + ۵۰ میلی‌گرم بر کیلوگرم نانوذره‌های سلنیوم آهسته رهش با کورکومین به‌صورت تک دُز درون صفاقی دریافت کردند. سنجش مالون‌دی‌آلدهید (MDA)، نیتریک اکسید (NO)، اینترلوکین (IL-6)6 و TNF-α خون در روزهای ۳، ۷ و ۱۴ و همچنین ارزیابی چسبندگی داخل شکمی انجام شد.

نتایج: در روز سوم، سطح اکسید نیتریک در همه گروه‌های درمانی به‌طور معنی‌داری کاهش یافت (P<۰/۰۵)، درحالی‌که کمترین میزان آن در گروه نانوذره‌های سلنیوم در روز ۱۴ دیده شد. در گروه‌های نانوذره‌های سلنیوم و آهسته رهش میزان مالون‌دی‌آلدهید نسبت به گروه کنترل در روزهای ۳، ۷ و ۱۴ به‌طور معنی‌داری کمتر بود (P<۰/۰۵). سطح TNF-αدر گروه‌های نانوذره‌های سلنیوم و آهسته رهش در روز سوم به‌طور معنی‌داری کمتر از گروه کنترل بود (P<۰/۰۵)، درحالی‌که گروه نانوذره‌های سلنیوم کمترین سطح را در روز ۱۴ داشت. میزان IL-6به‌طور معنی‌داری در روزهای ۳ و ۷ در گروه‌های آهسته رهش و کورکومین نسبت به گروه کنترل کاهش معنی‌داری نشان داد (P<۰/۰۵).

نتیجه‌گیری نهایی: نانوذره‌های سلنیوم آهسته رهش بارگیری‌شده با کورکومین دارای اثر پاد آماسی چشمگیری هستند و با کاهش مالون‌دی‌آلدهید، نیتریک اکسید، اینترلوکین ۶ و TNF-α، سبب کاهش پریتونیت و چسبندگی درون شکمی می‌شوند.

کلیدواژه‌ها: چسبندگی، اینترلوکین ۶، مالون‌دی‌آلدهید، نیتریک اکسید، TNF-α

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