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Anti-inflammatory Effects of the Novel Slow-Release Curcumin-Loaded Selenium Nanoparticles on Experimentally Induced 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. 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 of 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, 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, nitric oxide 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 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 the control group on day 3 ($P <0.05$). 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, nitric oxide, IL-6, and TNF-α, decreasing peritonitis and intra-abdominal adhesion.

Keywords: Adhesion, IL-6, MDA, NO, TNF-α

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 TNF-α and 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; the construction of extracellular matrix; and 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 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 and AT, 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 MDA as the final product. Additionally, cytokine release stimulates nitric oxide 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 indicated for inflammatory conditions. S.N seem to be a good substitute for other forms of selenium due to 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 are planned to provide an initial loading dose, then release maintenance doses gradually over a given time, resulting in more comfortable drug administration, a decrease in side effects, and an improved drug tolerability (Adepu and Ramakrishna, 2021). This study aimed to S.N and Cur@S.N synthesis and examine their effects on some inflammatory mediators during experimental peritonitis.

Material and methods

Nanoparticles synthesis

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 hours in

the fridge (Anvar et al 2022., Kohian et al 2022., Vahdati et al 2020., Kojori et al 2013., Baum and Ng, 2004).

Characterization of the NPs

S.N and Cur@S.N morphology was studied by field emission scanning electron microscopy and a TESCAN MIRA3 electron microscope (Czech Republic) with an energy dispersive spectroscopy (EDS) analytical system. X-Ray diffraction analysis (XRD) investigation was achieved by an X-ray diffractometer (Philips-PW1730, Netherlands). NPs content was determined by inductively coupled plasma optical emission spectrometry (ICP-OES) (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 and Ng, 2004).

***In- vitro* release study**

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

Animal experiments

According to international guidelines, 80 adult male Wistar rats weighing 200–250 grams were housed in metal cages under standard conditions, approved by the institutional ethical committee (IR.SKU.REC.1401.016) (Zimmermann, 1983). After a week, and animals adaption to the environmental conditions, experimental peritonitis, and abdominal adhesion were induced by the cecal abrasion method (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). Then, 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 mg/kg + 50 mg/kg) were administered intraperitoneally. On days 3, 7, and 14, blood samples were taken in each group 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).

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

GRADE	DEFINITION	POINT
0	no adhesions	**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**

Biochemical analysis

TNF-α and IL-6 were measured using the ELISA method with Karmania Pars Gene (KPG®) kits, while MDA and 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 at the significance level of 0.05 (P<0.05).

Results

Physiochemical characterization of S.N

The morphology examination of S.N by SEM showed a spherical shape and uniform distribution, with an average size of about 200 nm (Figure 1).

Fig 1. SEM image of selenium nanoparticles, with an average size of about 200 nm

DLS analysis revealed 206 nm nanoparticle size and a 0.231 particle size distribution, indicating particle size uniformity (Figure 2).

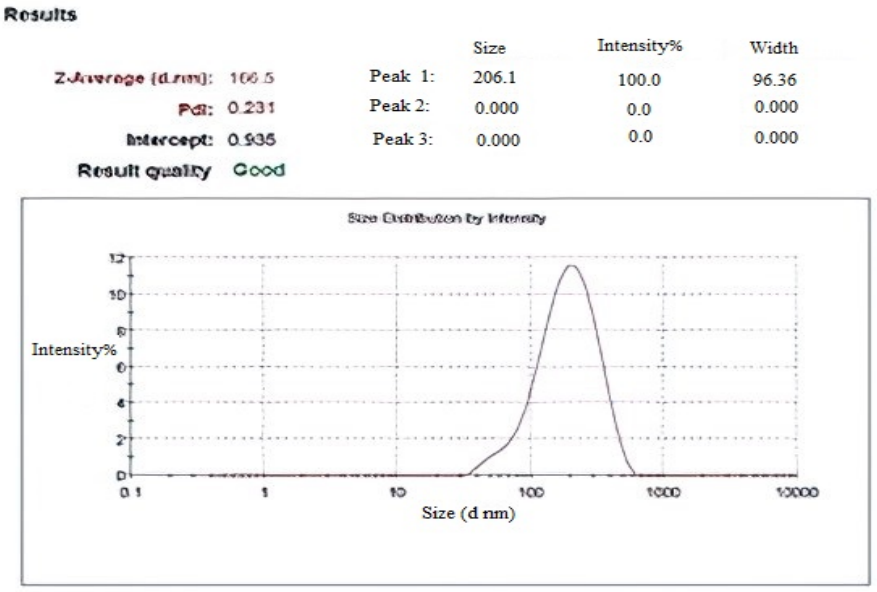

Fig2. Size distribution of the selenium nanoparticles

The zeta potential of the nanoparticles was -20.4 mV (Figure 3).

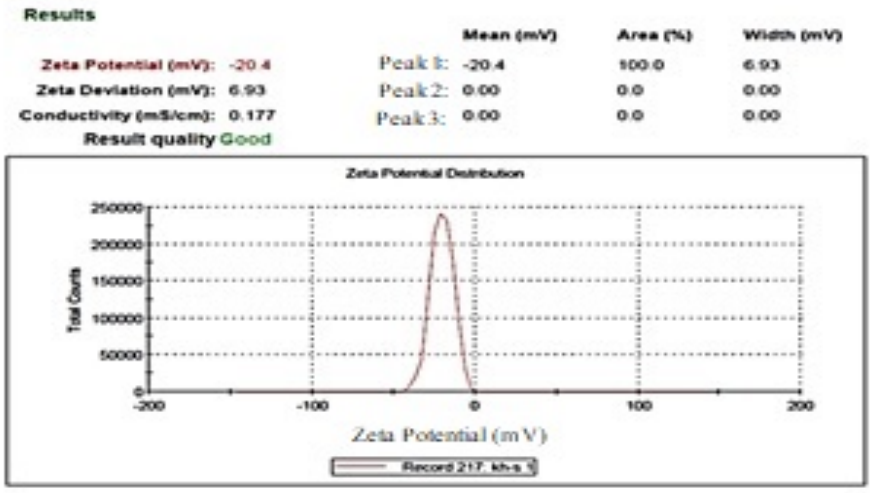

Fig3. Zeta potential of the selenium nanoparticles

FTIR 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 related to 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 4).

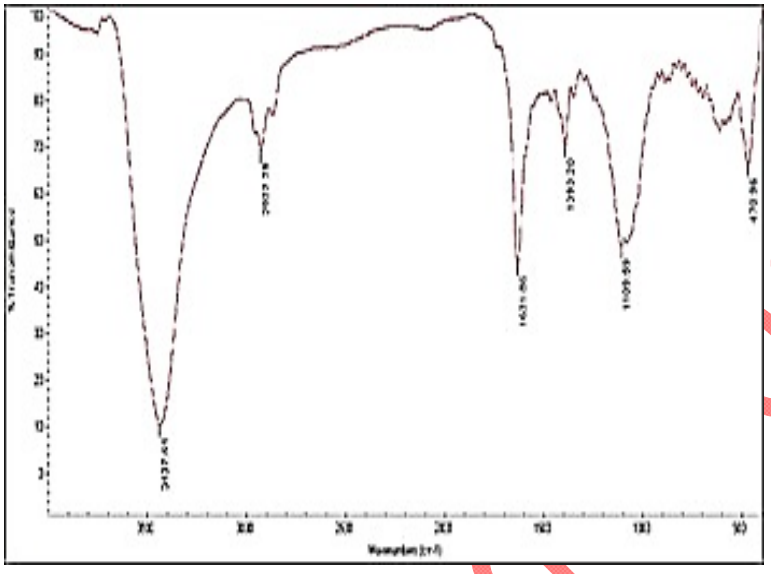

Fig 4. FTIR spectrum of the selenium nanoparticles

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 Cur 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 of the measurements were carried out in triplicate. ($R^2 = 0.9857$) (Figure 5).

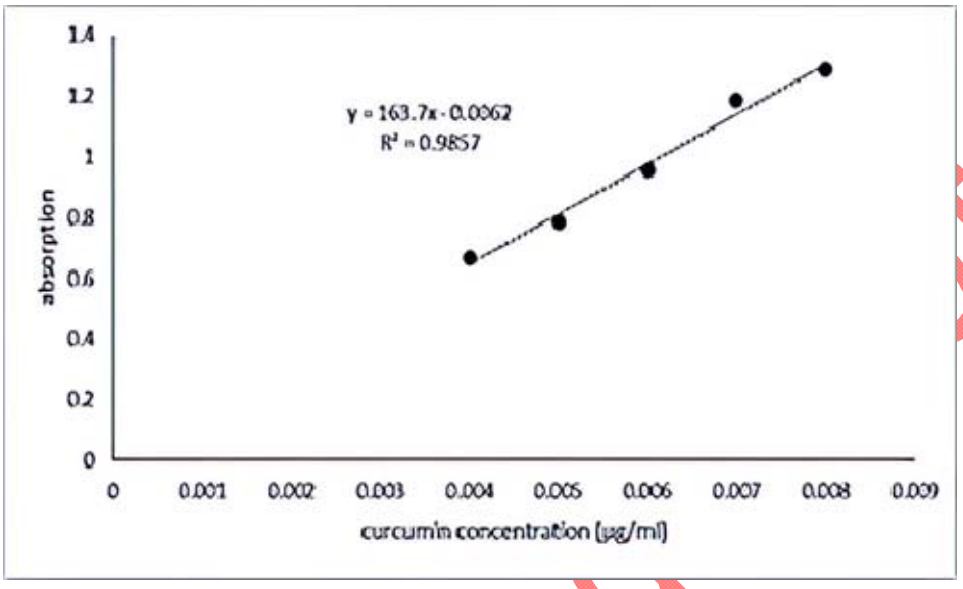

Fig5. Standard UV spectrophotometry curve of curcumin in ethanol

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 6).

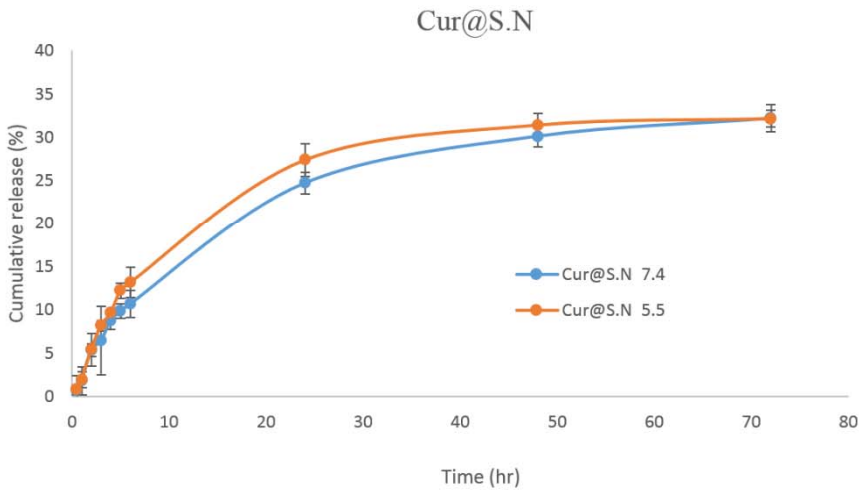

Fig 6. Curcumin release from selenium nanoparticles at pH= 7.4 & 5.5.

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).

Table 2. Nitric oxide level in the control, Curcumin, Selenium nanoparticles, and Slow-resale groups (mM/mL)

Groups	Day 3	Day7	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
Selenium nanoparticles	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

* Indicates significant Vs control group. Different letters (A&B) in each column indicate significant differences between different treatment groups ($P< 0.05$); data are presented as mean ± SD

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)

Table 3. Malondialdehyde (MDA) level in the control, Curcumin, Selenium nanoparticles, and Slow-resale groups (nM/mL)

Groups	Day 3	Day7	Day 14
Control	602±96.7	550±130.1	496±119.2
Curcumin	510±140.3	502±6 ^{A}	398±14.5 ^{A}
Selenium nanoparticles	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*}

* Indicates significant Vs control group. Different letters (A&B) in each column indicate significant differences between different treatment groups ($P< 0.05$); data are presented as mean ± SD.

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)

Table 4. TNF-α level in the control, Curcumin, Selenium nanoparticles, and Slow-resale groups (pg/mL)

Groups	Day 3	Day7	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}
Selenium nanoparticles	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*}

* Indicates significant Vs control group. Different letters (A&B) in each column indicate significant differences between different treatment groups ($P< 0.05$); data are presented as mean ± SD.

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, in all treatment groups, IL-6 was significantly lower than the control ($P< 0.05$), while 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)

Table 5. IL-6 level in the control, Curcumin, Selenium nanoparticles, and Slow-resale groups (pg/mL)

Groups	Day 3	Day7	Day 14
Control	30.24±3.7	30.03±3.6	19.71±3.8
Curcumin	25.08±1.	23.61±2.07 ^{A*}	20.82±1.6
Selenium nanoparticles	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

* Indicates significant Vs control group. Different letters (A&B) in each column indicate significant differences between different treatment groups (P< 0.05); data are presented as mean ± SD.

Intra-abdominal adhesion assessment

On day 3, there was no significant difference between any of the groups (P> 0.05). The least 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).

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

Groups	Day 3	Day7	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}
Selenium nanoparticles	4 (4-5)	3 (3-5)^{B}	4 (3-5)^{B}
Slow release	4 (4-5)	3 (3-4)^{A}	4 (2-5)^{B}

* Indicates significant Vs control group. Different letters (A&B) in each column indicate significant differences between different treatment groups ($P< 0.05$); data are presented as mean ± SD.

Discussion

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

Assessment of the severity of the peritonitis complications and the impact of treatment is possible by measuring specific factors that are produced when peritoneal adhesion processes to stop the damage and initiate healing. IL-6 is an inflammatory cytokine linked to acute infection and inflammation that is 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; Mani 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 those of NSAIDs and reduces NF-κB activity, which encourages the expression of proinflammatory gene products (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 (Mani et al 2015).

Inhibition of IL-6 slows the adhesion process because it induces an increase in 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, while 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 necrosis, bleeding, hyperemia, lipid peroxidation, and the number of neutrophils (Mani 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; Mani et al., 2015). NO, TNF-α, and PGE_2 all have been demonstrated to decrease after oral administration of S.N to rats (Funk et al.,

2006). Selenium nanoparticles boost antioxidant activity by blocking COX-2 activity and thus reducing the generation of PGE2 (Agarwal et al., 2019). S.N decrease TNF-α, monocyte, and granulocyte migration in the experimental inflammation (Zaafan et al., 2016). Oral S.N supplementation for six weeks decreased inflammation and the expression of TNF-α and TGF-β genes in diabetics (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 have anti-inflammatory efficacy, they are a good choice for this application (Liakakos et al., 2001).

5-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 number of biological markers of inflammation in experimental peritonitis. S.Ns increase curcumin absorption and therapeutic concentration,

enhanced anti-inflammatory effects leading to a decline in peritoneal adhesion, so can be used as a therapeutic solution alongside conventional treatments.

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

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چکیده

زمینه مطالعه: اشکال دارویی جدید ترکیب های طبیعی همچون کورکومین می تواند مداخله ای کارامد برای ساماندهی پریتونیت و چسبندگی شکمی باشد.

هدف: این پژوهش به بررسی اثر نانوذره های سلنیوم آهسته رهش بارگذاری شده با کورکومین بر برخی شاخص های زیستی آماس در پریتونیت تجربی می‌پردازد.

روش کار: پس از ساخت نانوذره های سلنیوم و نانوذره های سلنیوم بارگذاری شده با کورکومین (فرمولاسیون آهسته رهش)،

پریتونیت تجربی با جراحی در 80 موش صحرایی نر بالغ ایجاد شد. گروه کنترل هیچ درمانی دریافت نکردند، در حالی که گروه های دیگر0/25 میلی گرم بر کیلوگرم نانوذره های سلنیوم، 50 میلی گرم بر کیلوگرم کورکومین و0/25 + 50 میلی گرم بر کیلوگرم نانوذره های سلنیوم آهسته رهش با کورکومین به صورت تک دوز درون صفاقی دریافت کردند. سنجش مالون دی آلدهید(MDA)، نیتریک اکسید(NO)، اینترلوکین 6 (IL-6) و TNF-α خون در روزهای 3، 7 و 14 و همچنین ارزیابی چسبندگی داخل شکمی انجام می شد.

نتایج: در روز سوم، سطح اکسید نیتریک در همه گروه‌های درمانی به‌طور معنی‌داری کاهش یافت($P<0.05$) ، در حالی که کمترین میزان آن در گروه نانوذره های سلنیوم در روز 14 دیده شد. در گروه های نانوذره های سلنیوم و آهسته رهش میزان مالون دی آلدهید نسبت به گروه کنترل در روزهای 3، 7 و 14 به طور معنی داری کمتر بود ($P<0.05$) .سطح TNF-α در گروه های نانوذره های سلنیوم و آهسته رهش به طور معنی‌داری کمتر از گروه کنترل در روز سوم بود($P<0.05$) ، در حالی که گروه نانوذره های سلنیوم کمترین سطح را در روز 14 داشت. میزان IL-6 به طور معنی‌داری در روزهای 3 و 7 در گروه های آهسته رهش و کورکومین نسبت به گروه کنترل کهش معنی داری نشدان داد($P<0.05$)

نتیجه گیری: نانوذره های سلنیوم آهسته رهش بارگیری شده با کورکومین دارای اثر پاد آماسی چشمگیری هستند و با کاهش مالون دی آلدهید، نیتریک اکسید، اینترلوکین 6 و .TNF-α سبب کاهش پریتونیت و چسبندگی درون شکمی می گردند.

واژگان کلیدی: چسبندگی، اینترلوکین 6، مالون دی آلدهید، نیتریک اکسید، TNF-α