Research article

Anti-inflammatory action of silver nanoparticles *in vivo*: systematic review and meta-analysis

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ABSTRACT

The aim of this study was to systematically review the literature to investigate whether silver nanoparticles (AgNPs) have an anti-inflammatory effect *in vivo*. The guidelines of PRISMA were applied, and a registration was made in PROSPERO. A personalized search of the PubMed, Web of Science, Scopus, Embase, Lilacs, and Google Scholar databases was conducted in September 2023. For the data analysis, the inverse variance in the random effects model was used. The tools of SYRCLE and GRADE were used to assess the risk of bias and the certainty of evidence, respectively. From the 9185 identified studies, 5685 duplicate studies were excluded; 52 were read in full text, and 7 were included in this review. Six studies were evaluated by the meta-analysis, and an increase in anti-inflammatory molecules (SMD -5.22; PI [-6.50, −3.94]) and an increase in anti-inflammatory ones (SMD 5.75; PI [3.79, 7.72]) were observed. Qualitative analysis showed a reduction in pro-inflammatory proteins and in the COX-2 pathway. It was concluded that AgNPs present an anti-inflammatory action *in vivo* through mechanisms involving the reduction of pro-inflammatory molecules and proteins, the increase of anti-inflammatory molecules, and selective inhibition of the COX-2 pathway.

1. Introduction

Silver nanoparticles (AgNPs), initially studied as antimicrobial agents to obtain biomedical devices and materials for the treatment and prevention of infections [1], also show anti-inflammatory and antioxidant activity at low concentrations [2–7]. Its *in vitro* mechanism of action shows potential to eliminate free radicals [6,8–10], express anti-inflammatory molecules, and suppress pro-inflammatory ones, overcoming the drawbacks of current drugs such as the induction of gastrointestinal, renal, and cardiovascular pathologies [11–13].

The synthesis of AgNPs can be achieved through the reduction of silver ions (Ag+), using chemical, physical, photochemical and biological methods [14–17]. The method of synthesizing nanoparticles (NPs) influences parameters such as size, shape, topography, stability, concentration, purity and release of Ag + ions, which in turn influences their anti-inflammatory activity [14–17]. Green methods (phytochemical and biological) use leaves, flowers, fruits, bark, stems, roots, microorganisms, enzymes and other bio-molecules to synthesize more biocompatible NPs [14–17]. The improved biological properties are due to the presence of natural anti-inflammatory and antioxidant compounds that bind and coat the NPs [14–17].

In vitro studies have compared the ingestion of AgNPs at low concentrations (0.012 % per kg) with gold standard drugs

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(glucocorticoids; 0.1 % per kg) and observed higher efficacy of NPs in promoting therapeutic effect [18,19]. An *in vitro* research demonstrated that low amount of NPs does not induce cytotoxicity in human keratinocytes and fibroblasts present in inflammatory and scarring processes [20], and another study has shown that chronic *in vivo* application of AgNPs at the minimum concentration necessary to promote therapeutic effect does not cause toxic effects [21].

The investigation of the therapeutic properties of AgNPs has allowed studies to be carried out between 2013 and 2023 to understand their mechanisms for modulating cytokines and enzymes involved in the inflammatory process. This research could allow the development of new treatments, define the effective therapeutic concentration and indications for use, as well as evaluate the cytotoxic, genotoxic, and carcinogenic potential and associated environmental impact. The objective of this study was answer the following question, "Do silver nanoparticles show anti-inflammatory action *in vivo*?". The study of AgNPs as anti-inflammatory agents could complement current treatments and be used in combination with antioxidants and anti-tumor agents to optimize tissue regeneration. However, the heterogeneity of studies, methods of application of NPs, and evaluation of their anti-inflammatory activity may make it difficult to understand their real effect. As a novelty, this review presents a literature data compilation on the current status, mechanism of action, and efficacy of AgNPs as anti-inflammatory agents to contribute to the understanding of the scientific community.

2. Material and methods

2.1. Project guidelines and registration

This review was conducted in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and was registered in the PROSPERO (International Prospective Register of Systematic Reviews) under the code CRD42023461888 [22].

2.2. Formulating the review question

The PICOS strategy was employed to formulate the review question: population (male and female mice with no restrictions on weight or age), intervention (AgNPs administration), comparison (no treatment or use of placebo vehicles), outcome (anti-inflammatory effect), and study (*in vivo* studies).

2.3. Databases and search strategy

A comprehensive search was conducted on September 8, 2023, using the Google Scholar, Scopus, Web of Science, PubMed, Lilacs, and Embase databases. The combination terms were applied: ("silver OR "silver nanoparticles") AND ("animal" OR "animal cell" OR "tissue") AND (inflammatory OR "anti-inflammatory" OR "antioxidant" OR "anti-oxidant"). No date or language restrictions were applied.

In the initial stage, the first researcher (J.M.C.S.) selected the articles based on the analysis of abstracts and titles using the Rayyan software [23], after removing duplicates using EndNote. In the second stage, the first researcher selected the included articles by reading the full text. Each stage was supervised by the second researcher (A.C.R).

2.4. Inclusion and exclusion criteria

The following eligibility criteria were applied: (1) Studies evaluating the anti-inflammatory action of AgNPs in mice of both sexes with different weights and ages; (2) Studies evaluating the potential of AgNPs to modulate the anti-inflammatory pathways of cyclooxygenase 1 and 2; (3) Studies evaluating the ability of AgNPs to inhibit or stimulate the expression of pro-inflammatory or anti-inflammatory cytokines; (3) Potential elimination of oxidant products or induction of antioxidant mediators; and (4) Published studies in peer-reviewed journals. Exclusion criteria included: (1) *In vivo* studies using other animal models, *in vitro* articles, review articles, book chapters, congress abstracts, editorials, human clinical trials, observational studies, short communications, letters to the editor, and patents; (2) Using of other AgNPs-based compounds combined or not with other chemical components; and (3) Studies evaluating anti-inflammatory or anti-oxidant action using histological techniques.

2.5. Risk of bias

The domains or queries of the SYRCLE tool were used to classify the articles included with an uncertain, low, or high risk of bias [24]. To check the certainty of evidence on the anti-inflammatory action after administration of AgNPs in mice, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool was used [25].

2.6. Data extraction, synthesis strategy, and meta-analyses

The following qualitative data were extracted from the studies: (1) author and year of publication; (2) journal; (3) production process and size of AgNPs; (4) method; (5) results; and (6) conclusion.

The data analysis of the quantification of pro- and anti-inflammatory cytokines after treatment with AgNPs and non-treatment was conducted using the Review Manager Web [26,27]. The median and confidence interval data were transformed into the mean and

standard deviation, and the data on the mean, standard deviation, and participants were employed as the statistical measures [26,27]. The WebPlotDigitizer software was used to obtain the quantitative data presented in figures and graphs [28]. The inverse variance method and random effect (RE) model were employed to assess the outcome. The meta-analysis was conducted using the standardized mean difference (MD) and prediction interval (PI) as the statistical units ($\alpha = 0.05$). In addition, the heterogeneity was informed by the I^2 index after the application of the Q test.

3. Results

3.1. Included articles

A total of 9185 articles were identified, of which 1474 were found in PubMed, 1558 in Web of Science, 3097 in Scopus, 287 in Lilacs, 2669 in Embase, and 100 in Google Scholar. The 5685 duplicates were excluded using the EndNote software; 52 studies were full-text read; and 7 studies were eligible for inclusion in this review (Fig. 1). Of the studies included, 28.57 % were carried out in Iran
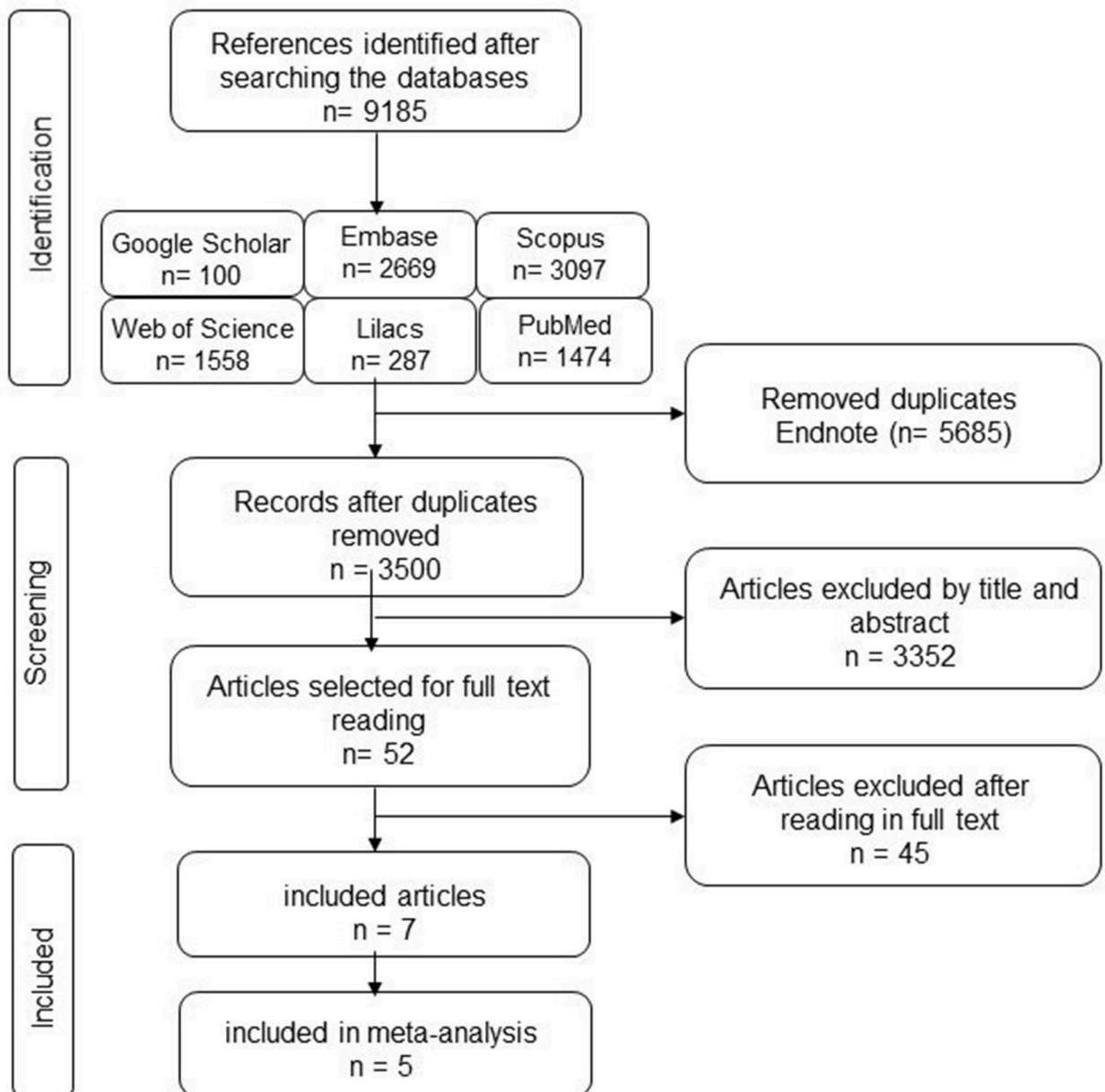

Fig. 1. Flowchart of articles included in the systematic review.

[29,30], 28.57 % in Saudi Arabia [19,31], and the same percentage (17.28 %) in Egypt [32], United States of America [33], and Romania [18].

3.2. Risk of bias evaluation

A high risk of bias has been observed in the studies in the following domains: D1 (generation of the distribution sequence of mice), D3 (use of an appropriate blinding method to distribute the mice), D4 (random placement of mice during the methodology), D5 (the researchers' knowledge of the treatment), D6 (random selection of the mice for result assessment), and D7 (data on the assessment of the outcome) [18,19,29–33]. The risk of bias was found to be low for D2 (adjustment of confounding factors and lack of information about similarity at baseline), D8 (outcomes treatment), D9 (study reports without individualized results), and D10 (absence of factors that might lead to a high risk of bias for the results) [18,19,29–33] (Figs. 2 and 3). The studies had a high recommendation for certainty of evidence according to the GRADE scale.

3.3. Anti-inflammatory activity of AgNPs

The present review included *in vivo* articles using female [32] and male [18,29,31] Wistar rats and unspecified male and female rats [29,30,33] weighing from 38 to 200 g (Table 1). The animals were subjected to inflammatory reactions induced by carrageenan [18] and cisplatin [31]. The leukemia was induced by an intravenous injection of 40 mg/kg of 7,12-dimethylbenz [*a*]anthracene (DMBA), while 50 mg/kg streptozotocin (STZ) was injected intraperitoneally to induce diabetes. The animals were also infected with *Pseudomonas aeruginosa* by inoculation of 10^6 CFU/mL [32] and respiratory syncytial virus (RSV) [33].

After induction of inflammation, treatment protocols were applied intravenously, intraperitoneally, by aspiration, and by swallowing with AgNPs of varying duration (1–30 days) and concentration (0.19 mg/kg [18,19] to 40 mg/kg of AgNPs [29,30,33] and 5–10 ppm [31]). The AgNPs ranged in size (5–80 nm) and methods of production with extracts of *Melissa officinalis* [29], *Nigella sativa* [19], *Sambucus nigra* [18], *Arthrospira* spp. [32], and *Spinacia oleracea* L. [30]. After the treatment period, the biological molecules were quantified using the ELISA enzyme-linked immunosorbent assay and complemented or not with Western Blot on blood serum samples [18,19,29–33].

The anti-inflammatory action of AgNPs was measured by quantifying pro- and anti-inflammatory molecules (cytokines, chemokines, enzymes, and proteins). An increase was observed in the anti-inflammatory molecules IL-4, IL-5, and IFN-α [29,30], IL-10 and IL-13 [29,30,33], GM-CSF and G-CSF, and CXCL1 [33]. AgNPs promoted a decrease in the pro-inflammatory molecules IL-1 [29,30, 32], IL-1-α, IL-1-β [18,33], IL-6 [18,29–31,33], IL-9 [33], IL-12[29,30,33], IL-18 [29,30], IFN-γ [29–31], TNF- α [18,19,29–33] and the proteins C-reactive [31], Nuclear factor Kappa B (NF-kB) [19,32] and S–100 B [19] and the enzyme COX-2 [32].

3.4. Random effect meta-analysis: anti- and pro-inflammatory cytokines

A meta-analysis was conducted on 5 studies to assess the overall effect of a decrease in pro-inflammatory cytokines and an increase in anti-inflammatory ones after the treatment of inflammation with AgNPs [19,29–31,33] (Figs. 4–7). Subgroup analyses were performed for each cytokine, where a decrease was observed for IL-1 (−6.21 [−11.99, −0.43]), IL-1α (−12.58 [−18.44, −6.71]), IL-1β (−1.12 [−3.10, 0.87]), IL-6 (−4.35 [−7.86, −0.85]), IL-12 (−6.01 [−11.79, −0.24]), IL-18 (−6.88 [−15.19, 1.44]), IFN-γ (−4.12

Fig. 2. Risk of bias graph. D1: generation of the mice's allocation sequence; D2: similarity of the mice at baseline and adjustments made to minimize confounding factors; D3: Randomization of the allocation; D4: Randomization of the mice; D5: blinding of caregivers and researchers to the intervention in the mice; D6: random selection of mice to evaluate outcomes; D7: blinding of researcher evaluating outcomes; D8: treatment of outcomes; D9: study reports free of bias in reporting outcomes; and D10: absence of other methodological problems that would result in a high risk of bias. yellow (uncertain); green (low risk); and red (high risk).

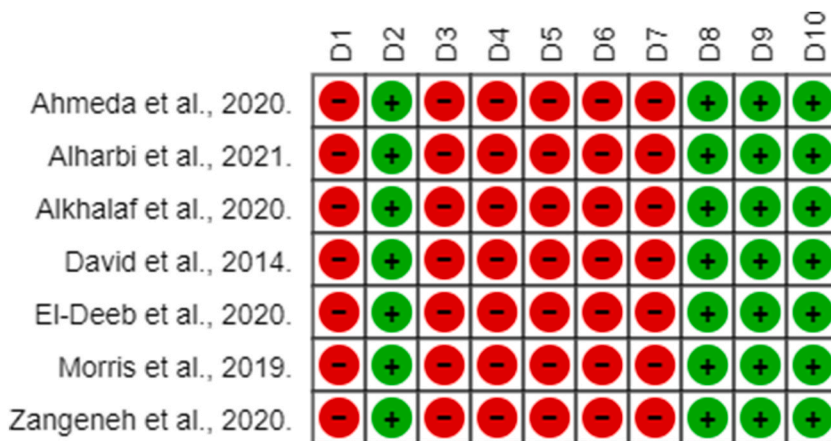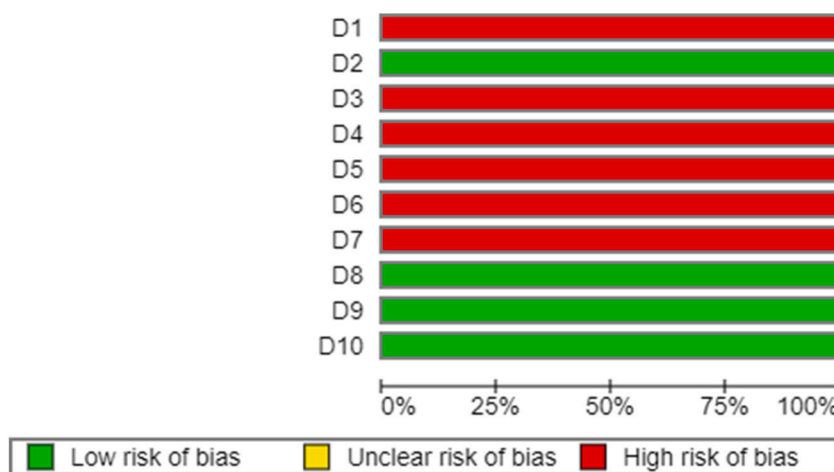**Fig. 3.** Summary of risk of bias. D1: generation of the mice's allocation sequence; D2: similarity of the mice at baseline and adjustments made to minimize confounding factors; D3: Randomization of the allocation; D4: Randomization of the mice; D5: blinding of caregivers and researchers to the intervention in the mice; D6: random selection of mice to evaluate outcomes; D7: blinding of researcher evaluating outcomes; D8: treatment of outcomes; D9: study reports free of bias in reporting outcomes; and D10: absence of other methodological problems that would result in a high risk of bias.

[−7.42, −0.83]) and TNF-α (−6.15 [−10.08, −2.22]), consistent with the overall effect (SMD -5.22; PI [−6.50, −3.94]; P < 0.00001; $I^2 = 94$ %). Moderate heterogeneity was observed between the groups (Chi^2 = 18.91, df = 7 (P = 0.008), $I^2 = 63.0$ %). The increase in the anti-inflammatory molecules IL-4 (5.61 [3.37, 7.85]), IL-5 (3.17 [1.33, 5.01]), IL-10 (8.72 [3.77, 13.66]), IL-13 (3.48 [−2.47, 9.43]), and IFN-α (8.25 [5.39, 11.10]) with an overall effect evidenced by a decrease in anti-inflammatory cytokines in the forest plot for non-treatment (SMD 5.75; PI [3.79, 7.72]). Moderate heterogeneity was observed between the groups (Chi^2 = 11.42, df = 4 (P = 0.02), $I^2 = 65.0$ %).

4. Discussion

This systematic review assessed the anti-inflammatory action of AgNPs in mice with tissue lesions associated or not with bacterial [32] and viral infections [33] by quantifying the expression of cytokines, chemokines, enzymes, and proteins [18,19,29–31]. The use of these NPs is promising due to their mechanism of action to control inflammation and associated pathologies, as well as their optimized effect when combined with antioxidant and anti-tumor drugs [18,19,29–45].

The inflammatory process is a fundamental response for tissue repair in the presence of lesions [46], infections [47], and tumors [48]. The failure to treat this condition contributes to the incidence of autoimmune diseases, cancer, and metabolic disorders [49]. It is believed that AgNPs will enable treatment, improve quality of life, and reduce the gastrointestinal, renal, and cardiovascular pathological effects associated with conventional drugs.

The anti-inflammatory mechanism of AgNPs can be elucidated by their binding affinity and penetration into cell membranes stimulated by inflammatory processes [50–53]. They release Ag + ions and generate ROS that suppress the NF-κB transcription factor pathway, which reduces the production of cytokines IL-1 [29,30,32], IL-1-α, IL-1-β [18,33], IL-6 [18,29–31,33], IL-9 [33], IL-12 [29, 30,33], IL-18 [29,30], IFN-γ [29–31], and TNF-α [18,19,29–33], and are subsequently inactivated by intracellular glutathione (GSH) to reduce cytotoxicity to healthy cells [19,32] (Fig. 8). The results of this review corroborate Crisan et al. [54], who reported a decrease in NF-κB in epidermal cells from patients with psoriasis, and these results correlate with a decrease in C-reactive protein produced by the liver [31] and S–100 B produced by the brain [19]. Suppression of this protein is an effective strategy for treating inflammation without interfering with the immune system or cellular homeostasis [19,32].

Another process to consider is that M1 macrophages, associated with the release of pro-inflammatory molecules, phagocytize the NPs, which generates intracellular ROS and induces their apoptosis or repolarization to M2, which in turn produces anti-inflammatory molecules (Fig. 9) [50–53]. In addition, activation of regulatory T cells and electrostatic interactions with surface receptors [50] increase the levels of IL-4, IL-5, IFN-α [29,30], IL-10, IL-13 [29,30,33], CXCL1, GM-CSF, and G-CSF [33], which optimize tissue repair. Studies have also reported that the use of NPs at low concentrations is effective for tissue repair and reduction of edema and pain without inducing side effects similar to steroid and non-steroid drugs (Fig. 10) [29,30,33].

In this review, it was observed that AgNPs selectively inhibit the cyclooxygenase-2 (COX-2) enzyme by inducing a structural change that blocks the production of prostaglandins from arachidonic acid and by inhibiting NF-κB, which reduces leukocyte chemotaxis and exacerbates inflammation [32]. David et al. [55] reported that pre-treatment with the nanomaterial also reduced the presence of COX-2 *in vivo*. In addition, *in vitro* studies have also reported a decrease in this enzyme in fibroblast cell lines [56], keratinocytes [57], and human BV-2 microglial cells [58]. The low concentration of NPs to interrupt the COX-2 pathway compared to conventional drugs demonstrates that this compound could be effective for therapies through biological investigations that support its clinical application.

Table 1
Data extraction: *In vivo* anti-inflammatory activity of silver nanoparticles (AgNPs).

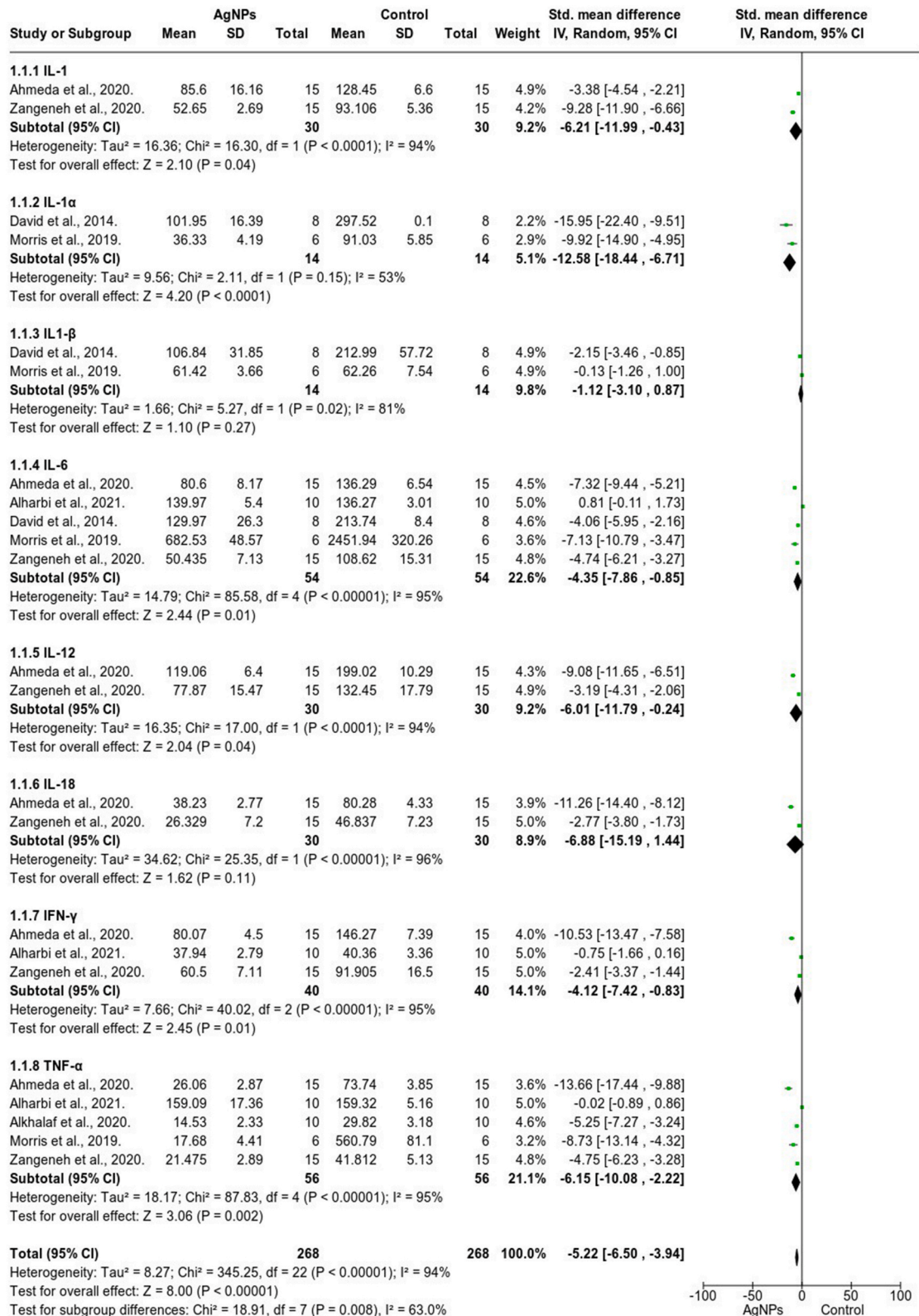| Author, Year, Country.	Journal.	AgNPs	Method	Results	Conclusion
Ahmeda et al., 2020. Iran.	Appl. Organometal Chem.	5–30 nm.*Melissa officinalis*.	Quantification of anti-inflammatory and pro-inflammatory enzymes.	AgNPs and mitoxantrone increased levels of anti-inflammatory cytokines (IL4, IL5, IL10, IL13, and IFNα) and decreased pro-inflammatory cytokines (IL1, IL6, IL12, IL18, IFNY and TNFα). The best results were observed for AgNPs for IL4, IL5 and IL10 (p ≤ 0.01).	AgNPs showed anti-inflammatory activity *in vivo*.
Alharbi1 et al., 2021. Saudi Arabia.	Journal of Pharmaceutical Research International.	30–50 nm.	Inflammatory mediators TNF-α, IFN-γ, IL-6, C-reactive protein by ELISA.	AgNPs (5 and 10 ppm) reduced pro-inflammatory mediators in a dose-dependent manner.	The AgNPs showed a dose-dependent anti-inflammatory action.
Alkhalaf et al., 2020. Saudi Arabia.	Saudi Journal of Biological Sciences.	n/a.*Nigella sativa*.	Rats with induced neuropathic diabetes (streptozotocin 50 mg/kg) and 21-day treatment with oral AgNPs (0.25 mg/kg): Inflammatory mediators TNF-a, Nuclear factor Kappa B (NFkB), S–100 B in brain tissues.	Treatment with AgNPs showed a reduction in inflammatory mediators, with better results for the green synthesized nanoparticles.	The AgNPs obtained from the green synthesis of N. sativa were effective in reducing pro-inflammatory cytokines.
David et al., 2014. Romania.	Colloids and Surfaces B: Biointerfaces.	20–80 nm.*Sambucus nigra*.	Reduction of carrageenan-induced paw edema in Wistar rats and measurement of pro-inflammatory cytokine levels, IL-1α, IL-1β and IL-6 with AgNPs pretreatment.	AgNPs inhibited the rate of inflammatory edema (12.61 %) 2 h after carrageenan injection. Pretreatment with AgNPs reduced IL-1α levels at 24 h (87 %) and 48 h (49 %). A similar effect was observed for IL-1β at 24 h (92 %). IL-6 secretion was inhibited after 2 h (83 %) of inflammation induction.	AgNPs had an anti-inflammatory effect and pre-treatment with AgNPs promoted inhibition of inflammatory cytokine secretion, which was sustained for 48 h.
El-Deeb et al., 2020. Egypt.	Frontiers in Bioengineering and Biotechnology.	9.7 nm.*Arthrospira* sp polysaccharides.	In vivoquantification of COX-1 and COX-2 (ELISA) in tissue and serum, and IkBα, IL-1α, IL-1β, and TNF-α.	AgNPs decreased COX-2 expression from 14.38 to 10.16 μg/mL in tissues and 11.66 to 4.34 μg/mL in serum and had no effect on COX-1. Treatment with NPs reduced the expression of inflammatory cytokines.	The AgNPs promoted anti-inflammatory action by acting on the COX-2 pathway and reducing the expression of inflammatory cytokines.
Morris et al., 2019. USA.	Viruses.	8–12 nm.	Measurement of Cytokines, Chemokines, Interferon, Total Protein and Elastase with AgNPs treatment (2 mg/kg or4 mg/kg in mice) and subsequent viral infection.	Inflammatory and immunomodulatory cytokines (IL-1α, IL-6, IL-9, IL-10, IL-12p40, IL-12-p70, IL-13 and TNF-α were significantly decreased with AgNPs treatment. The cytokines G-CSF and GM-CSF, and chemokine CXCL1 (KC) increased significantly in all mice inoculated with AgNPs. Chemokines associated with viral replication (CCL3 (MIP-1), eVdirCusCesL 2051 (9R, 1A1, Nx FTOERS P)E, EwRe RrEeVsIiEgWn) decreased significantly.	AgNPs are effective in reducing pro-inflammatory cytokines and chemokines, with an effect on reducing chemokines associated with viral infection.
Zangeneh et al., 2020. Iran.	Appl Organometal Chem	50 nm.*Spinacia oleracea* L.	Measurement of anti-inflammatory cytokines (IL4, IL5, IL10, IL13, and IFNα) and pro-inflammatory cytokines (IL1, IL6, IL12, IL18, IFNY, and TNFα) cytokines) by ELISA after leukemia treatment.	AgNPs were more effective than doxorubicin in increasing anti-inflammatory cytokines and decreasing pro-inflammatory cytokines.	AgNPs were effective in regulating inflammatory cytokines close to normal.

Study or Subgroup	AgNPs Mean	SD	Total	Control Mean	SD	Total	Weight	Std. mean difference IV, Random, 95% CI
1.1.1 IL-1								
Ahmeda et al., 2020.	85.6	16.16	15	128.45	6.6	15	4.9%	-3.38 [-4.54 , -2.21]
Zangeneh et al., 2020.	52.65	2.69	15	93.106	5.36	15	4.2%	-9.28 [-11.90 , -6.66]
Subtotal (95% CI)			30			30	9.2%	-6.21 [-11.99 , -0.43]
Heterogeneity: Tau² = 16.36; Chi² = 16.30, df = 1 (P < 0.0001); I² = 94%								
Test for overall effect: Z = 2.10 (P = 0.04)								
1.1.2 IL-1α								
David et al., 2014.	101.95	16.39	8	297.52	0.1	8	2.2%	-15.95 [-22.40 , -9.51]
Morris et al., 2019.	36.33	4.19	6	91.03	5.85	6	2.9%	-9.92 [-14.90 , -4.95]
Subtotal (95% CI)			14			14	5.1%	-12.58 [-18.44 , -6.71]
Heterogeneity: Tau² = 9.56; Chi² = 2.11, df = 1 (P = 0.15); I² = 53%								
Test for overall effect: Z = 4.20 (P < 0.0001)								
1.1.3 IL1-β								
David et al., 2014.	106.84	31.85	8	212.99	57.72	8	4.9%	-2.15 [-3.46 , -0.85]
Morris et al., 2019.	61.42	3.66	6	62.26	7.54	6	4.9%	-0.13 [-1.26 , 1.00]
Subtotal (95% CI)			14			14	9.8%	-1.12 [-3.10 , 0.87]
Heterogeneity: Tau² = 1.66; Chi² = 5.27, df = 1 (P = 0.02); I² = 81%								
Test for overall effect: Z = 1.10 (P = 0.27)								
1.1.4 IL-6								
Ahmeda et al., 2020.	80.6	8.17	15	136.29	6.54	15	4.5%	-7.32 [-9.44 , -5.21]
Alharbi et al., 2021.	139.97	5.4	10	136.27	3.01	10	5.0%	0.81 [-0.11 , 1.73]
David et al., 2014.	129.97	26.3	8	213.74	8.4	8	4.6%	-4.06 [-5.95 , -2.16]
Morris et al., 2019.	682.53	48.57	6	2451.94	320.26	6	3.6%	-7.13 [-10.79 , -3.47]
Zangeneh et al., 2020.	50.435	7.13	15	108.62	15.31	15	4.8%	-4.74 [-6.21 , -3.27]
Subtotal (95% CI)			54			54	22.6%	-4.35 [-7.86 , -0.85]
Heterogeneity: Tau² = 14.79; Chi² = 85.58, df = 4 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 2.44 (P = 0.01)								
1.1.5 IL-12								
Ahmeda et al., 2020.	119.06	6.4	15	199.02	10.29	15	4.3%	-9.08 [-11.65 , -6.51]
Zangeneh et al., 2020.	77.87	15.47	15	132.45	17.79	15	4.9%	-3.19 [-4.31 , -2.06]
Subtotal (95% CI)			30			30	9.2%	-6.01 [-11.79 , -0.24]
Heterogeneity: Tau² = 16.35; Chi² = 17.00, df = 1 (P < 0.0001); I² = 94%								
Test for overall effect: Z = 2.04 (P = 0.04)								
1.1.6 IL-18								
Ahmeda et al., 2020.	38.23	2.77	15	80.28	4.33	15	3.9%	-11.26 [-14.40 , -8.12]
Zangeneh et al., 2020.	26.329	7.2	15	46.837	7.23	15	5.0%	-2.77 [-3.80 , -1.73]
Subtotal (95% CI)			30			30	8.9%	-6.88 [-15.19 , 1.44]
Heterogeneity: Tau² = 34.62; Chi² = 25.35, df = 1 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 1.62 (P = 0.11)								
1.1.7 IFN-γ								
Ahmeda et al., 2020.	80.07	4.5	15	146.27	7.39	15	4.0%	-10.53 [-13.47 , -7.58]
Alharbi et al., 2021.	37.94	2.79	10	40.36	3.36	10	5.0%	-0.75 [-1.66 , 0.16]
Zangeneh et al., 2020.	60.5	7.11	15	91.905	16.5	15	5.0%	-2.41 [-3.37 , -1.44]
Subtotal (95% CI)			40			40	14.1%	-4.12 [-7.42 , -0.83]
Heterogeneity: Tau² = 7.66; Chi² = 40.02, df = 2 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 2.45 (P = 0.01)								
1.1.8 TNF-α								
Ahmeda et al., 2020.	26.06	2.87	15	73.74	3.85	15	3.6%	-13.66 [-17.44 , -9.88]
Alharbi et al., 2021.	159.09	17.36	10	159.32	5.16	10	5.0%	-0.02 [-0.89 , 0.86]
Alkhalaf et al., 2020.	14.53	2.33	10	29.82	3.18	10	4.6%	-5.25 [-7.27 , -3.24]
Morris et al., 2019.	17.68	4.41	6	560.79	81.1	6	3.2%	-8.73 [-13.14 , -4.32]
Zangeneh et al., 2020.	21.475	2.89	15	41.812	5.13	15	4.8%	-4.75 [-6.23 , -3.28]
Subtotal (95% CI)			56			56	21.1%	-6.15 [-10.08 , -2.22]
Heterogeneity: Tau² = 18.17; Chi² = 87.83, df = 4 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 3.06 (P = 0.002)								
Total (95% CI)			268			268	100.0%	-5.22 [-6.50 , -3.94]
Heterogeneity: Tau² = 8.27; Chi² = 345.25, df = 22 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 8.00 (P < 0.00001)								
Test for subgroup differences: Chi² = 18.91, df = 7 (P = 0.008); I² = 63.0%								

Fig. 4. Forest plot of the reduction of pro-inflammatory enzymes.

Study or Subgroup	AgNPs Mean	SD	Total	Control Mean	SD	Total	Weight	Std. mean difference IV, Random, 95% CI	Std. mean difference IV, Random, 95% CI
2.1.1 IL-4									
Ahmeda et al., 2020.	16.03	0.39	15	11.27	0.87	15	9.9%	6.87 [4.87 , 8.87]	
Zangeneh et al., 2020.	13.14	1.55	15	7.73	0.5	15	10.4%	4.57 [3.14 , 6.00]	
Subtotal (95% CI)			**30**			**30**	**20.3%**	**5.61 [3.37 , 7.85]**	
Heterogeneity: Tau² = 1.86; Chi² = 3.36, df = 1 (P = 0.07); I² = 70%									
Test for overall effect: Z = 4.90 (P < 0.00001)									
2.1.2 IL-5									
Ahmeda et al., 2020.	19.1	1.52	15	13.93	0.77	15	10.5%	4.18 [2.83 , 5.52]	
Zangeneh et al., 2020.	11.9	1.26	15	9.2	1.02	15	10.8%	2.29 [1.34 , 3.24]	
Subtotal (95% CI)			**30**			**30**	**21.3%**	**3.17 [1.33 , 5.01]**	
Heterogeneity: Tau² = 1.42; Chi² = 5.05, df = 1 (P = 0.02); I² = 80%									
Test for overall effect: Z = 3.38 (P = 0.0007)									
2.1.3 IL-10									
Ahmeda et al., 2020.	36.02	1.91	15	24.91	1.46	15	10.0%	6.36 [4.49 , 8.23]	
Zangeneh et al., 2020.	33.71	1.88	15	15.68	1.09	15	8.6%	11.42 [8.24 , 14.60]	
Subtotal (95% CI)			**30**			**30**	**18.6%**	**8.72 [3.77 , 13.66]**	
Heterogeneity: Tau² = 11.02; Chi² = 7.22, df = 1 (P = 0.007); I² = 86%									
Test for overall effect: Z = 3.46 (P = 0.0006)									
2.1.4 IL-13									
Ahmeda et al., 2020.	16.24	0.84	15	11.27	0.61	15	10.0%	6.59 [4.66 , 8.51]	
Zangeneh et al., 2020.	13.49	1.21	15	12.88	1.09	15	10.9%	0.52 [-0.21 , 1.24]	
Subtotal (95% CI)			**30**			**30**	**20.9%**	**3.48 [-2.47 , 9.43]**	
Heterogeneity: Tau² = 17.88; Chi² = 33.39, df = 1 (P < 0.00001); I² = 97%									
Test for overall effect: Z = 1.15 (P = 0.25)									
2.1.5 IFN-α									
Ahmeda et al., 2020.	14.87	0.75	15	8.32	0.52	15	9.0%	9.88 [7.10 , 12.65]	
Zangeneh et al., 2020.	13.77	1.19	15	6.27	0.89	15	9.9%	6.94 [4.93 , 8.96]	
Subtotal (95% CI)			**30**			**30**	**18.9%**	**8.25 [5.39 , 11.10]**	
Heterogeneity: Tau² = 2.76; Chi² = 2.80, df = 1 (P = 0.09); I² = 64%									
Test for overall effect: Z = 5.66 (P < 0.00001)									
Total (95% CI)			**150**			**150**	**100.0%**	**5.75 [3.79 , 7.72]**	
Heterogeneity: Tau² = 9.10; Chi² = 157.89, df = 9 (P < 0.00001); I² = 94%									
Test for overall effect: Z = 5.74 (P < 0.00001)									
Test for subgroup differences: Chi² = 11.42, df = 4 (P = 0.02), I² = 65.0%									

Fig. 5. Forest plot of the increase in anti-inflammatory enzymes.

Furthermore, they demonstrate an antioxidant effect in eliminating free radicals, including ABTS (2,2′-azino-bis [3-ethylbenzothiazoline-6-sulfonic acid]) [59] and DPPH (2,2-diphenyl-1-picrylhydrazyl) [29,59] which helps to reduce inflammation. These data confirm findings in the literature where AgNPs reduce biomarkers of oxidative stress [55], such as malondialdehyde (MDA) and cell membrane peroxidation [19,31] and increase intracellular GSH [19]. The synergy of these NPs and the molecules derived from their use is advantageous because it allows the suppression of compounds that exacerbate tissue injury, unlike conventional drugs that induce dose- and time-dependent citotoxic effects.

The included articles demonstrated that the green synthesis of AgNPs using *M. officinalis* [29], *N. sativa* [19], *S. nigra* [18], *Arthrospira* sp. [32], and *S. oleracea* L. [30]. makes them more biocompatible and imparts a surface coating of anti-inflammatory and antioxidant chemical components (polyphenols, ascorbic acid, anthocyanins, and flavonoids), which contribute to the nanoparticles' inherent therapeutic mechanism of action [19–21,60–62]. This method also permits the alteration of physicochemical characteristics, including size, distribution, crystallinity, charge, and surface coating. These modifications can influence the release of Ag + ions and reduce their cytotoxic potential [21].

The mechanisms of action of AgNPs, such as suppression of NF-κB and pro-inflammatory molecules, increase in anti-inflammatory molecules, repolarization of macrophages, selective inhibition of COX-2, and antioxidant effect, show the promising potential of this nanomaterial for biological modulation in tissue repair, whether related to microbial infections or not. However, it is advisable to exercise caution when producing and utilizing these nanoparticles, as high concentrations may result in the development of allergies, citotoxicity, microbial resistance, and adverse environmental impacts [63–65].

This review presented limitations, including (1) In the meta-analyses, heterogeneity was reported among the studies included in this review; (2) the use of different methods for synthesizing AgNPs, different particle sizes, variation in concentrations, and treatment
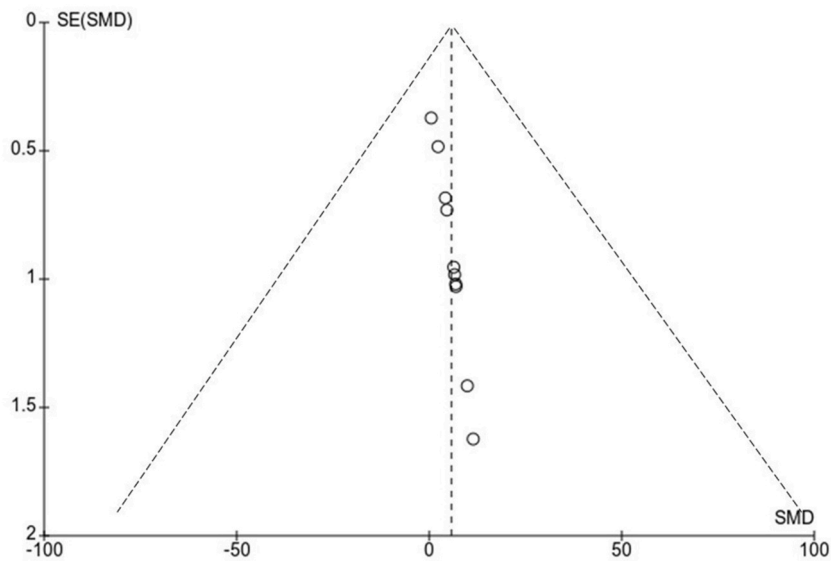
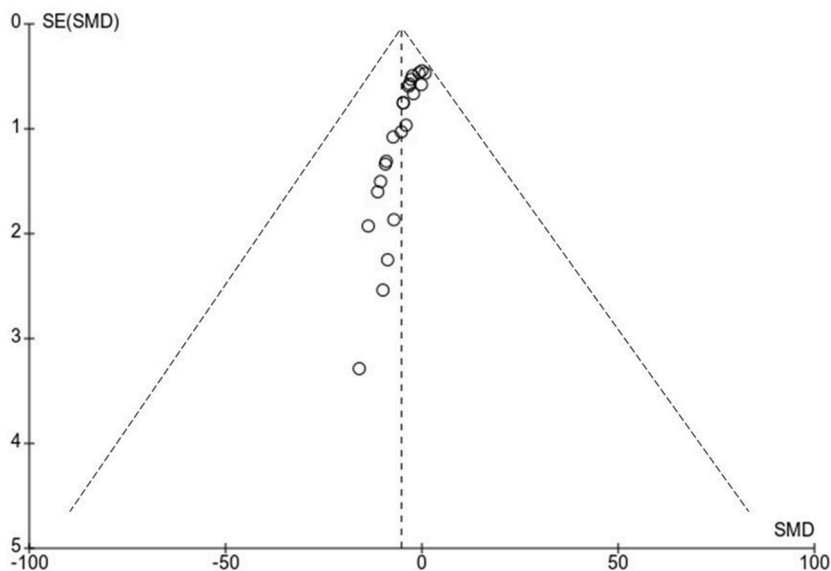**Fig. 6.** Funnel plot of the decrease in pro-inflammatory cytokines.

Fig. 7. Funnel plot of the increase in anti-inflammatory cytokines.

time; (3) heterogeneity of the mice including species, sex, weight and age; and (4) high risk of bias in articles regarding the randomization method. Despite the limitations, it was observed that AgNPs have a promising anti-inflammatory effect, and the meta-analysis showed consistency between the results individually and in combination. In addition, the presence of new pre-clinical studies in mice could improve the statistically significant level of the findings reported in this review, as well as contribute to updating the literature to support or avoid their use as a drug.

5. Conclusion

The studies included in this systematic review have led to the conclusion that AgNPs have an anti-inflammatory action *in vivo* by suppressing NF-κB and pro-inflammatory molecules, increasing anti-inflammatory molecules, selectively inhibiting COX-2, and exerting an antioxidant effect.
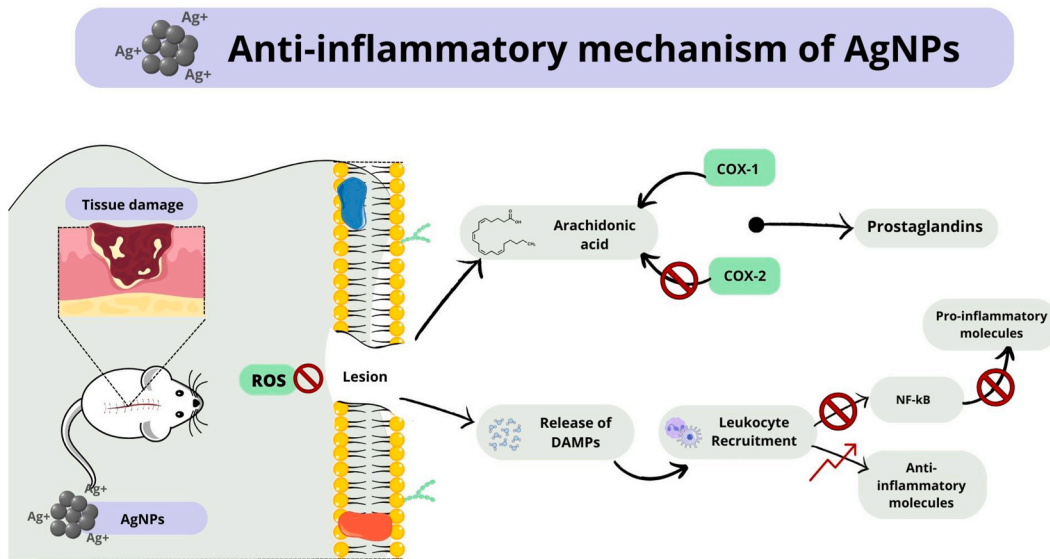
Fig. 8. Graphical abstract. AgNPs selectively inhibit COX-2 and the NF-kB pathway.
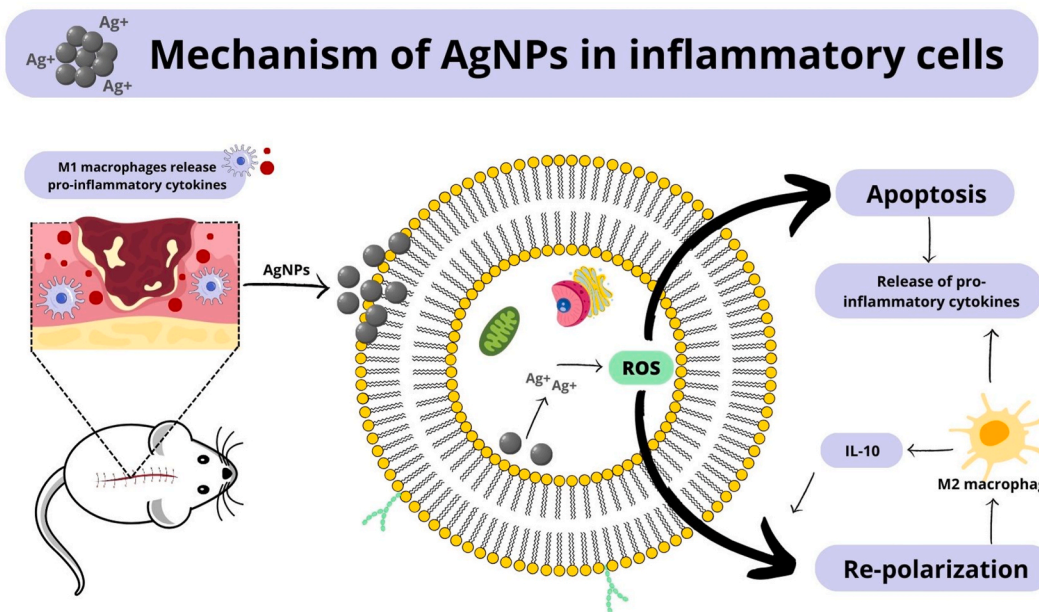
Fig. 9. Graphical abstract. Mechanism of action of AgNPs on inflammatory cells. Legend: M1 macrophages are recruited to the affected tissue and release pro-inflammatory cytokines that attenuate local inflammation. The application of AgNPs allows the release of Ag + ions and the subsequent generation of ROS, which induce the repolarization of cells to M2 macrophages. This cell line releases anti-inflammatory cytokines and phagocytizes pro-inflammatory ones, which reduces local inflammation.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

João Marcos Carvalho-Silva: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Andréa Cândido dos Reis:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis,
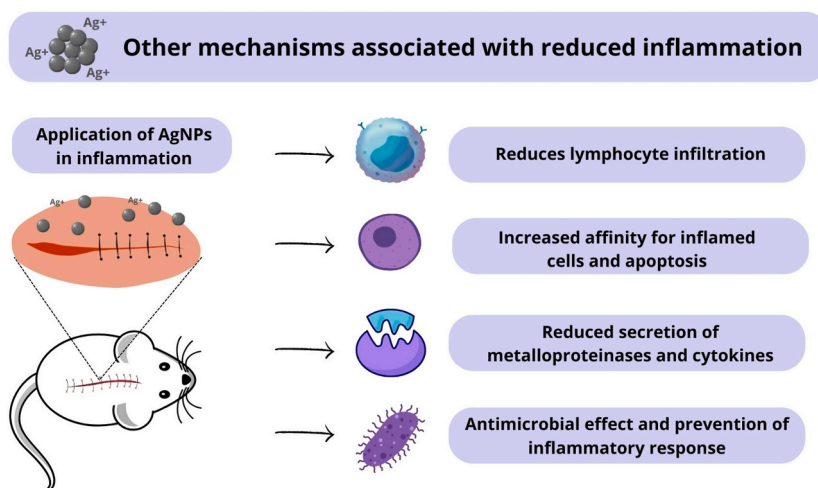
Fig. 10. Graphical abstract. Other mechanisms of AgNPs associated with reducing local tissue inflammation.

Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] F. Furno, K.S. Morley, B. Wong, B.L. Sharp, P.L. Arnold, S.M. Howdle, R. Bayston, P.D. Brown, P.D. Winship, H.J. Reid, Silver nanoparticles and polymeric medical devices: a new approach to prevention of infection? J. Antimicrob. Chemother. 54 (2004) 1019–1024, https://doi.org/10.1093/jac/dkh478.
[2] Y. Xiong, Y. Xu, F. Zhou, Y. Hu, J. Zhao, Z. Liu, Q. Zhai, S. Qi, Z. Zhang, L. Chen, Bio-functional hydrogel with antibacterial and anti-inflammatory dual properties to combat with burn wound infection, Bioeng. Transl. Med. 8 (2023) 1–19, https://doi.org/10.1002/btm2.10373.
[3] S. Vijayakumar, B. Malaikozhundan, K. Saravanakumar, E.F. Durán-Lara, M.H. Wang, B. Vaseeharan, Garlic clove extract assisted silver nanoparticle – antibacterial, antibiofilm, antihelminthic, anti-inflammatory, anticancer and ecotoxicity assessment, J. Photochem. Photobiol. B Biol. 198 (2019) 111558, https://doi.org/10.1016/j.jphotobiol.2019.111558.
[4] S. Sivakumar, M. Subban, R. Chinnasamy, K. Chinnaperumal, I. Nakouti, M.A. El-Sheikh, J.P. Shaik, Green synthesized silver nanoparticles using Andrographis macrobotrys Nees leaf extract and its potential to antibacterial, antioxidant, anti-inflammatory and lung cancer cells cytotoxicity effects, Inorg. Chem. Commun. 153 (2023) 110787, https://doi.org/10.1016/j.inoche.2023.110787.
[5] S. Manimegalai, V.D. Rajeswari, R. Parameswari, M. Nicoletti, S. Alarifi, M. Govindarajan, Green synthesis, characterization and biological activity of Solanum trilobatum-mediated silver nanoparticles, Saudi J. Biol. Sci. 29 (2022) 2131–2137, https://doi.org/10.1016/j.sjbs.2021.11.048.
[6] D. Khullar, N. Ahmed, Green Synthesis , Characterization and Assessment of Anti-inflammatory and Antioxidant Properties of Silver Nanoparticles Prepared Using Amla Extracts-An In-Vitro Study, vol. 10, 2022, pp. 47–52.
[7] M.A. Antonysamy Johnson, T. Shibila, S. Amutha, I.R.A. Menezes, J.G.M. Da Costa, N.F.L. Sampaio, H.D.M. Coutinho, Synthesis of silver nanoparticles using odontosoria chinensis (L.) J. sm. and evaluation of their biological potentials, Pharmaceuticals 13 (2020) 1–10, https://doi.org/10.3390/ph13040066.
[8] M.A. Solaiman, M.A. Ali, N.M. Abdel-Moein, E.A. Mahmoud, Synthesis of Ag-NPs developed by green-chemically method and evaluation of antioxidant activities and anti-inflammatory of synthesized nanoparticles against LPS-induced NO in RAW 264.7 macrophages, Biocatal. Agric. Biotechnol. 29 (2020) 101832, https://doi.org/10.1016/j.bcab.2020.101832.
[9] F. Jalilian, A. Chahardoli, K. Sadrjavadi, A. Fattahi, Y. Shokoohinia, Green synthesized silver nanoparticle from Allium ampeloprasum aqueous extract: characterization, antioxidant activities, antibacterial and cytotoxicity effects, Adv. Powder Technol. 31 (2020) 1323–1332, https://doi.org/10.1016/j.apt.2020.01.011.
[10] J. Vishal, S. Ranjani, R.J. Karunya, S. Hemalatha, Synthesis, characterization and evaluation of antioxidant, anticancer and toxicity properties of silver nanoparticles synthesized from syzygium aromaticum, arch, Breast Cancer 10 (2023) 291–300, https://doi.org/10.32768/abc.2023103291-300.
[11] C.O. Stiller, P. Hjemdahl, Lessons from 20 years with COX-2 inhibitors: importance of dose–response considerations and fair play in comparative trials, J. Intern. Med. 292 (2022) 557–574, https://doi.org/10.1111/joim.13505.
[12] R. Sohail, M. Mathew, K.K. Patel, S.A. Reddy, Z. Haider, M. Naria, A. Habib, Z.U. Abdin, W. Razzaq Chaudhry, A. Akbar, Effects of non-steroidal anti-inflammatory drugs (NSAIDs) and gastroprotective NSAIDs on the gastrointestinal tract: a narrative review, Cureus 15 (2023) 1–14, https://doi.org/10.7759/cureus.37080.
[13] J.A. Mitchell, N.S. Kirkby, B. Ahmetaj-Shala, P.C. Armstrong, M. Crescente, P. Ferreira, M.E. Lopes Pires, R. Vaja, T.D. Warner, Cyclooxygenases and the cardiovascular system, Pharmacol. Ther. 217 (2021) 107624, https://doi.org/10.1016/j.pharmthera.2020.107624.
[14] S.N. Nandhini, N. Sisubalan, A. Vijayan, C. Karthikeyan, M. Gnanaraj, D.A.M. Gideon, T. Jebastin, K. Varaprasad, R. Sadiku, Recent advances in green synthesized nanoparticles for bactericidal and wound healing applications, Heliyon 9 (2023) e13128, https://doi.org/10.1016/j.heliyon.2023.e13128.
[15] S.M. Mousavi, S.A. Hashemi, Y. Ghasemi, A. Atapour, A.M. Amani, A. Savar Dashtaki, A. Babapoor, O. Arjmand, Green synthesis of silver nanoparticles toward bio and medical applications: review study, Artif. Cells, Nanomedicine Biotechnol. 46 (2018) S855–S872, https://doi.org/10.1080/21691401.2018.1517769.
[16] F. Arshad, G.A. Naikoo, I.Nanomed. Biotechnol.U. Hassan, S.R. Chava, M. El-Tanani, A.A. Aljabali, M.M. Tambuwala, Bioinspired and green synthesis of silver nanoparticles for medical applications: a green perspective, Appl. Biochem. Biotechnol. (2023), https://doi.org/10.1007/s12010-023-04719-z.
[17] E. Abbasi, M. Milani, S.F. Aval, M. Kouhi, A. Akbarzadeh, H.T. Nasrabadi, P. Nikasa, S.W. Joo, Y. Hanifehpour, K. Nejati-Koshki, M. Samiei, Silver nanoparticles: synthesis methods, bio-applications and properties, Crit. Rev. Microbiol. 42 (2016) 173–180, https://doi.org/10.3109/1040841X.2014.912200.

[18] L. David, B. Moldovan, A. Vulcu, L. Olenic, M. Perde-Schrepler, E. Fischer-Fodor, A. Florea, M. Crisan, I. Chiorean, S. Clichici, G.A. Filip, Green synthesis, characterization and anti-inflammatory activity of silver nanoparticles using European black elderberry fruits extract, Colloids Surf. B Biointerfaces 122 (2014) 767–777, https://doi.org/10.1016/j.colsurfb.2014.08.018.

[19] M.I. Alkhalaf, R.H. Hussein, A. Hamza, Green synthesis of silver nanoparticles by Nigella sativa extract alleviates diabetic neuropathy through anti-inflammatory and antioxidant effects, Saudi J. Biol. Sci. 27 (2020) 2410–2419, https://doi.org/10.1016/j.sjbs.2020.05.005.

[20] H. Haidari, Z. Kopecki, R. Bright, A.J. Cowin, S. Garg, N. Goswami, K. Vasilev, Ultrasmall AgNP-impregnated biocompatible hydrogel with highly effective biofilm elimination properties, ACS Appl. Mater. Interfaces 12 (2020) 41011–41025, https://doi.org/10.1021/acsami.0c09414.

[21] M. Noga, J. Milan, A. Frydrych, K. Jurowski, Toxicological aspects, safety assessment, and green toxicology of silver nanoparticles (AgNPs)—critical review: state of the art, Int. J. Mol. Sci. 24 (2023), https://doi.org/10.3390/ijms24065133.

[22] M.J. Page, D. Moher, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, et al., PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews, BMJ 29 (2021), https://doi.org/10.1136/bmj.n160, 372:n160.

[23] M. Ouzzani, H. Hammady, Z. Fedorowicz, A. Elmagarmid, Rayyan-a web and mobile app for systematic reviews, Syst. Rev. 5 (2016) 1–10, https://doi.org/10.1186/s13643-016-0384-4.

[24] C.R. Hooijmans, M.M. Rovers, R.B.M. De Vries, M. Leenaars, M. Ritskes-Hoitinga, M.W. Langendam, SYRCLE's risk of bias tool for animal studies, BMC Med. Res. Methodol. 14 (2014) 1–9, https://doi.org/10.1186/1471-2288-14-43.

[25] L. Zeng, R. Brignardello-Petersen, G. Guyatt, When applying GRADE, how do we decide the target of certainty of evidence rating? Evid. Base Ment. Health 24 (2021) 121–123, https://doi.org/10.1136/ebmental-2020-300170.

[26] M. Richardson, P. Garner, S. Donegan, Interpretation of subgroup analyses in systematic reviews: a tutorial, Clin. Epidemiol. Glob. Heal. 7 (2019) 192–198, https://doi.org/10.1016/j.cegh.2018.05.005.

[27] H. Kamioka, Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015 statement, Jpn. Pharmacol. Ther. 47 (2019) 1177–1185.

[28] D. Drevon, S.R. Fursa, A.L. Malcolm, Intercoder reliability and validity of WebPlotDigitizer in extracting graphed data, Behav. Modif. 41 (2017) 323–339, https://doi.org/10.1177/0145445516673998.

[29] A. Ahmeda, A. Zangeneh, M.M. Zangeneh, Preparation, formulation, and chemical characterization of silver nanoparticles using Melissa officinalis leaf aqueous extract for the treatment of acute myeloid leukemia in vitro and in vivo conditions, Appl. Organomet. Chem. 34 (2020) 1–14, https://doi.org/10.1002/aoc.5378.

[30] M.M. Zangeneh, Green synthesis and formulation a modern chemotherapeutic drug of Spinacea oleracea L. leaf aqueous extract conjugated silver nanoparticles; Chemical characterization and analysis of their cytotoxicity, antioxidant, and anti-acute myeloid leukemia propert, Appl. Organomet. Chem. 34 (2020) 1–16, https://doi.org/10.1002/aoc.5295.

[31] H.Y. Alharbi, N.W. Helmi, N.A. Salem, Possible protective effect of silver nanoparticles against cisplatin induced pulmonary inflammation in rat model, J. Pharm. Res. Int. 33 (2021) 453–463, https://doi.org/10.9734/jpri/2021/v33i46a32888.

[32] N.M. El-Deeb, M.A. Abo-Eleneen, L.A. Al-Madboly, M.M. Sharaf, S.S. Othman, O.M. Ibrahim, M.S. Mubarak, Biogenically synthesized polysaccharides-capped silver nanoparticles: immunomodulatory and antibacterial potentialities against resistant Pseudomonas aeruginosa, Front. Bioeng. Biotechnol. 8 (2020) 1–18, https://doi.org/10.3389/fbioe.2020.00643.

[33] D. Morris, M. Ansar, J. Speshock, T. Ivanciuc, Y. Qu, A. Casola, R. Garofalo, Antiviral and immunomodulatory activity of silver nanoparticles in experimental rsv infection, Viruses 11 (2019), https://doi.org/10.3390/v11080732.

[34] A. Parveen, N. Kulkarni, M. Yalagatti, V. Abbaraju, R. Deshpande, In vivo efficacy of biocompatible silver nanoparticles cream for empirical wound healing, J. Tissue Viability 27 (2018) 257–261, https://doi.org/10.1016/j.jtv.2018.08.007.

[35] J. Hedberg, M. Eriksson, A. Kesraoui, A. Norén, I. Odnevall Wallinder, Transformation of silver nanoparticles released from skin cream and mouth spray in artificial sweat and saliva solutions: particle size, dissolution, and surface area, Environ. Sci. Pollut. Res. 28 (2021) 12968–12979, https://doi.org/10.1007/s11356-020-11241-w.

[36] M.C. Silva, Silver-based Gels for Oral and Skin Infections : Antimicrobial Effect and Physicochemical Stability, 2023, https://doi.org/10.2217/fmb-2023-0034.

[37] M. Singh, V. Thakur, V. Kumar, M. Raj, S. Gupta, N. Devi, S.K. Upadhyay, M. Macho, A. Banerjee, D. Ewe, K. Saurav, Silver nanoparticles and its mechanistic insight for chronic wound healing: review on recent progress, Molecules 27 (2022) 1–16, https://doi.org/10.3390/molecules27175587.

[38] S.D. Bansod, M.S. Bawaskar, A.K. Gade, M.K. Rai, Development of shampoo, soap and ointment formulated by green synthesised silver nanoparticles functionalised with antimicrobial plants oils in veterinary dermatology: treatment and prevention strategies, IET Nanobiotechnol. 9 (2015) 165–171, https://doi.org/10.1049/iet-nbt.2014.0042.

[39] A. Alali, A. Hosseini-Abari, A. Bahrami, M. Yazdan Mehr, Biosynthesis of copper oxide and silver nanoparticles by Bacillus spores and evaluation of the feasibility of their use in antimicrobial paints, Materials 16 (2023), https://doi.org/10.3390/ma16134670.

[40] F.A. Alamer, R.F. Beyari, Overview of the influence of silver, gold, and titanium nanoparticles on the physical properties of PEDOT:PSS-coated cotton fabrics, Nanomaterials 12 (2022), https://doi.org/10.3390/nano12091609.

[41] M.E. El-Naggar, S. Shaarawy, M.S. Abdel-Aziz, K.H. Abd El Moneim, A.M. Youssef, Functionalization of cotton fabrics with titanium oxide doped silver nanoparticles: antimicrobial and UV protection activities, Luminescence 37 (2022) 854–864, https://doi.org/10.1002/bio.4229.

[42] S. Kaabipour, S. Hemmati, A review on the green and sustainable synthesis of silver nanoparticles and one-dimensional silver nanostructures, Beilstein J. Nanotechnol. 12 (2021) 102–136, https://doi.org/10.3762/BJNANO.12.9.

[43] X. He, F. Chen, Z. Chang, K. Waqar, H. Hu, X. Zheng, Y. Wang, W. fei Dong, C. Yang, Silver mesoporous silica nanoparticles: fabrication to combination therapies for cancer and infection, Chem. Rec. 22 (2022), https://doi.org/10.1002/tcr.202100287.

[44] T. Bruna, F. Maldonado-Bravo, P. Jara, N. Caro, Silver nanoparticles and their antibacterial applications, Int. J. Mol. Sci. 22 (2021), https://doi.org/10.3390/ijms22137202.

[45] C.A. DinarelloAnti-inflammatory Agents, Present and future, Cell 19 (2010) 935–950, https://doi.org/10.1016/j.cell.2010.02.043.

[46] Y. Zhou, H. Huang, G. Chen, Q. Yuan, J. Ren, J. Wu, Y. Lin, Z. Lin, L. Xu, Promoting the healing of diabetic wounds with an antimicrobial gel containing AgNPs with anti-infective and anti-inflammatory properties, J. Biomater. Sci. Polym. Ed. 35 (2024) 1236–1257, https://doi.org/10.1080/09205063.2024.2324494.

[47] J. Xie, H. Li, X. Zhang, T. Yang, M. Yue, Y. Zhang, S. Chen, N. Cui, C. Yuan, J. Li, S.J. Zhu, W. Liu, Akkermansia muciniphila protects mice against an emerging tick-borne viral pathogen, Nat. Microbiol. 8 (2023) 91–106, https://doi.org/10.1038/s41564-022-01279-6.

[48] S.C. Shah, S.H. Itzkowitz, Colorectal cancer in inflammatory bowel disease: mechanisms and management, Gastroenterology 162 (2022) 715–730.e3, https://doi.org/10.1053/j.gastro.2021.10.035.

[49] S. Zappavigna, A.M. Cossu, A. Grimaldi, M. Bocchetti, G.A. Ferraro, G.F. Nicoletti, R. Filosa, M. Caraglia, Anti-inflammatory drugs as anticancer agents, Int. J. Mol. Sci. 21 (2020) 1–29, https://doi.org/10.3390/ijms21072605.

[50] Y. Yang, L. Guo, Z. Wang, P. Liu, X. Liu, J. Ding, W. Zhou, Targeted silver nanoparticles for rheumatoid arthritis therapy via macrophage apoptosis and Re-polarization, Biomaterials 264 (2021 Jan) 120390, https://doi.org/10.1016/j.biomaterials.2020.120390.

[51] A.N. Yilma, S.R. Singh, S. Dixit, V.A. Dennis, Anti-inflammatory effects of silver-polyvinyl pyrrolidone (Ag-PVP) nanoparticles in mouse macrophages infected with live Chlamydia trachomatis, Int. J. Nanomed. 8 (2013) 2421–2432, https://doi.org/10.2147/IJN.S44090.

[52] C. Kong, S. Chen, W. Ge, Y. Zhao, X. Xu, S. Wang, J. Zhang, Riclin-capped silver nanoparticles as an antibacterial and anti-inflammatory wound dressing, Int. J. Nanomed. 17 (2022 Jun 13) 2629–2641, https://doi.org/10.2147/IJN.S366899.

[53] O.V. Morozova, Silver nanostructures: limited sensitivity of detection, toxicity and anti-inflammation effects, Int. J. Mol. Sci. 22 (18) (2021 Sep 14) 9928, https://doi.org/10.3390/ijms22189928.

[54] D. Crisan, K. Scharffetter-Kochanek, M. Crisan, S. Schatz, A. Hainzl, L. Olenic, A. Filip, L.A. Schneider, A. Sindrilaru, Topical silver and gold nanoparticles complexed with Cornus mas suppress inflammation in human psoriasis plaques by inhibiting NF-κB activity, Exp. Dermatol. 27 (10) (2018 Oct) 1166–1169, https://doi.org/10.1111/exd.13707.

[55] L. David, B. Moldovan, I. Baldea, D. Olteanu, P. Bolfa, S. Clichici, G.A. Filip, Modulatory effects of Cornus sanguinea L. mediated green synthesized silver nanoparticles on oxidative stress, COX-2/NOS2 and NFkB/pNFkB expressions in experimental inflammation in Wistar rats, Mater. Sci. Eng., C 110 (2020 May) 110709, https://doi.org/10.1016/j.msec.2020.110709.

[56] J. Franková, V. Pivodová, H. Vágnerová, J. Juráňová, J. Ulrichová, Effects of silver nanoparticles on primary cell cultures of fibroblasts and keratinocytes in a wound-healing model, J. Appl. Biomater. Funct. Mater. 14 (2) (2016 May 18) e137–e142, https://doi.org/10.5301/jabfm.5000268.

[57] P. Singh, S. Pandit, M. Beshay, V.R.S.S. Mokkapati, J. Garnaes, M.E. Olsson, A. Sultan, A. Mackevica, R.V. Mateiu, H. Lütken, A.E. Daugaard, A. Baun, I. Mijakovic, Anti-biofilm effects of gold and silver nanoparticles synthesized by the Rhodiola rosea rhizome extracts, Artif. Cells, Nanomed. Biotechnol. 46 (sup3) (2018) S886–S899, https://doi.org/10.1080/21691401.2018.1518909.

[58] Z.D. Ozdal, E. Sahmetlioglu, I. Narin, A. Cumaoglu, Synthesis of gold and silver nanoparticles using flavonoid quercetin and their effects on lipopolysaccharide induced inflammatory response in microglial cells, 3 Biotech 9 (6) (2019 Jun) 212, https://doi.org/10.1007/s13205-019-1739-z.

[59] S.H. Shin, M.K. Ye, H.S. Kim, H.S. Kang, The effects of nano-silver on the proliferation and cytokine expression by peripheral blood mononuclear cells, Int. Immunopharm. 7 (2007) 1813–1818, https://doi.org/10.1016/j.intimp.2007.08.025.

[60] V. Lakkim, M.C. Reddy, V.D.V.V. Lekkala, V.R. Lebaka, M. Korivi, D. Lomada, Antioxidant efficacy of green-synthesized silver nanoparticles promotes wound healing in mice, Pharmaceutics 15 (2023), https://doi.org/10.3390/pharmaceutics15051517.

[61] N. Draginic, M. Andjic, J. Jeremic, V. Zivkovic, A. Kocovic, M. Tomovic, B. Bozin, N. Kladar, S. Bolevich, V. Jakovljevic, I. Milosavljevic, Anti-inflammatory and antioxidant effects of Melissa officinalis extracts: a comparative study, Iran. J. Pharm. Res. (IJPR) 21 (2022) 1–13, https://doi.org/10.5812/ijpr-126561.

[62] K. De Pádua Lúcio, A.C.S. Rabelo, C.M. Araújo, G.C. Brandão, G.H.B. De Souza, R.G. Da Silva, D.M.S. De Souza, A. Talvani, F.S. Bezerra, A.J. Cruz Calsavara, D. C. Costa, Anti-inflammatory and antioxidant properties of black mulberry (Morus nigra L.) in a Model of LPS-Induced Sepsis, Oxid. Med. Cell. Longev. 2018 (2018), https://doi.org/10.1155/2018/5048031.

[63] B. Amin, H. Hosseinzadeh, Black cumin (Nigella sativa) and its active constituent, thymoquinone: an overview on the analgesic and anti-inflammatory effects, Planta Med. 82 (2016) 8–16, https://doi.org/10.1055/s-0035-1557838.

[64] S. Marimuthu, A.J. Antonisamy, S. Malayandi, K. Rajendran, P.C. Tsai, A. Pugazhendhi, V.K. Ponnusamy, Silver nanoparticles in dye effluent treatment: a review on synthesis, treatment methods, mechanisms, photocatalytic degradation, toxic effects and mitigation of toxicity, J. Photochem. Photobiol. B Biol. 205 (2020) 111823, https://doi.org/10.1016/j.jphotobiol.2020.111823.

[65] S.S. Abdulsahib, Synthesis, characterization and biomedical applications of silver nanoparticles, Biomed 41 (2021) 458–464, https://doi.org/10.51248/. v41i2.1058.