Selenium Nanoparticles in Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a common chronic inflammation-mediated disorder having systematic complications. RA triggers a self-directed inflammatory and immunological cascade that culminates in joint destruction. Though a range of treatment options are available, none of them are without adverse effects, leading researchers to search for alternative solutions. Nanomedicine has emerged as a powerful therapeutic alternative, and selenium (Se) is an essential micronutrient trace element that has a crucial role in human health and disease. The potential of SeNPs can be attributed to the effect of functional groups bound to them, concentration, and most importantly to their nano range size. The antirheumatic effect of SeNPs is considerable due to its potential in amelioration of oxidative stress-mediated inflammation via downregulation of radical and nonradical species, markers of inflammation, and upregulation of inherent antioxidant defenses.

Keywords: selenium ; nanoparticles ; biological methods ; inflammation ; oxidative stress ; rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is a common chronic inflammation-mediated disorder [1]. It is a long-lasting condition described as the inflammation of diarthrodial joints leading to symmetrical polyarthritis and synovial hyperplasia (swelling) that results in progressive destruction of cartilage and bones and loss of articular function that leads to the eventual deformation of joints [2]. Moreover, it is a systematic autoimmune disorder that can alter multiple organ systems [3].

The exact etiological milieu for RA is still not certain, but as an example of a chronic inflammation-mediated autoimmune disorder, it has been correlated to oxidative stress (OS), a state wherein a pool of reactive oxidative species (ROS) upregulates actively, either due to their enhanced generation, the decline in antioxidative defense mechanisms, or the combined effects of both, thus leading to altered redox signaling that is involved in the maintenance and progression of the disorder [4][5]. The therapeutic options for patients suffering from RA include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GC), and disease-modifying antirheumatic drugs (DMARDs), but all of these available therapeutic remedies have associated adverse effects [1]. Thus, there is a prominent need to develop and test novel drugs that intend to ameliorate inflamed synovial joints and mitigate bone damage. Selenium (Se) is an essential micronutrient trace element having a crucial role in normal human functioning and has prominent relevance to several pathophysiological conditions [2].

In this regard, one of the most promising therapeutic solutions for RA is ‘nanomedicine’ [3] and has captured quite the amount of attention. Selenium nanoparticles (SeNPs) have become the centerpiece of attention due to their exclusive physical and chemical properties [6]. The SeNPs play an essential role in the antioxidant defense system that is crucial for reduction of oxidative stress [7].

2. Serum Selenium Status in Rheumatoid Arthritis

In the past, lowered serum concentration of trace micronutrients has been demonstrated as a frequent event in autoimmune diseases [8]. Epidemiological reports proved that a low Se status can be a risk factor for RA, indicating the significance of antioxidants in controlling the maintenance and progression of the disease [9][10][11][12][13][14][15][16][17][18].

It has been reported that Se supplementation improves the condition of patients as well as reduces inflammation levels in experimental models, such as the granuloma pouch exudate, and in lupus mice or in adjuvant arthritis in rats [19]. Evidence has suggested that Se can decrease inflammation in autoimmune disorders [20].

3. Current RA Medication

Conventional treatment options for RA patients comprise NSAIDs, GC, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), and biologic DMARDs (bDMARDs), and all these available therapeutic remedies have associated side effects. **Table 1** summarizes the diverse treatment options available for RA and their associated side effects.

Table 1. Current treatment options for RA and related side effects.

Drugs	Mode of Mechanism	Side Effects
NSAIDs	**Inhibition of COXs**	**Cardiovascular risk, gastro-intestinal disorders, and renal malfunction**
GCs	**Inhibition of phospholipid release**	**Cardiovascular disorders, osteoporosis, insulin resistance, skin thinning, hypertension, and obesity**
Conventional synthetic DMARDs	**Disease altering activities**	**Interstitial pneumonitis, myelosuppression, hepatic cirrhosis, retinopathies, hypersensitivity, and allergic reactions**
Biologic DMARDs	**Inhibitors to immune mediators**	**Bacterial infections and high costs**
Targeted synthetic DMARDs	**Intracellular blockers of tyrosine kinase**	**Infections, headaches, hypertension, nausea, diarrhea, and high cholesterol levels**

4. Nanomedicine as a Potential Solution

RA continues to be a challenging disorder because all the above-mentioned recommended therapies do not often lead to a cure and are linked to frequent drug resistance and related side effects [21]. Hence, it is crucial to develop and test novel drugs that target inflamed joints and mitigate damage. In this regard, one of the most promising therapeutic solutions for RA is nanomedicine [3]. Hundreds of diverse nanomedicine formulations have been prepared and assessed over the years for various kinds of maladies. However, about 50 of such formulations are at present approved for clinical usage, and several nanomedicines are going through trials [22]. Nanoparticles (NPs) are defined as nano-range submicroscopic particles that have unique properties such as large surface area, nano size, surface charge, and chemistry, solubility, and multifunctionality [23]. NPs are deemed as being in a transitional stage between individual molecules and the analogous bulk materials, which allows them to possess peculiar properties that are unique from their molecular and bulk analogue counterparts [23][24]. Based on their unique properties, nanoscale materials and devices can interact with biomolecules from both the inside and on the cell surface that has the potential to detect disorders and deliver treatments. Hence, NPs have revolutionized healthcare as they facilitate research and development, help with early detection, enhance molecular imaging, and enable prevention, diagnosis, and control [25].

5. Selenium Nanoparticles

SeNPs have received attention due to their exclusive physical and chemical properties (i.e., mechanical, electrical, catalytic, and opt-magnetic properties) that are exhibited when this element is scaled down to the nano range as a result of high spatial confinement of nanomaterials, high surface-to-volume ratio, and large surface energy [26][27][28]. SeNPs, due to remarkable photoreactive, biocidal, anticancer, antidiabetic, antioxidant, antimicrobial, and anti-inflammatory properties in the healthcare arena, is being used in antimicrobial coatings, diagnostics, medical devices, nutritional supplements, and nanotherapeutics [29][30]. SeNPs have significantly emerged as a dual-targeting modality with both pro-oxidant and antioxidant potential dependent on subsequent duration, dose, and frequency as well as oxidation state. The pro-oxidant potential of SeNPs has been exploited in anticancer agents (chemotherapeutic drugs carriers). These NPs fundamentally localize in the malignant cells and lead to the production of reactive oxygen species, and hence cause cytotoxicity. The pro-oxidant mechanism of SeNPs follows the reduction of nano selenium via thioredoxin- and glutaredoxin-mediated redox signaling that leads to the generation of Se^{2-} anion through the consumption of $NADPH+H^{+}$ and stimulated production of ROS [31]. SeNPs play an important role in the antioxidant defense system, which is essential for reducing oxidative stress [7]. Se is an integral part of selenoproteins, such as glutathione peroxidases (GPxs) and TrxRs, which are needed for several biochemical reactions involved in normal antioxidant defenses [32]. SeNPs have been studied in different inflammation and redox imbalance-mediated disorders, such as cancer, diabetes, nephritis, and arthritis, and showed potential remedial uses [29].

5.1. Pharmacokinetics and Toxicological Profile of SeNPs

Oral intake of NPs is regarded as the most suitable and cost-effective mode of supplementation. Nonetheless, the absorption of NPs is hindered by two gastrointestinal barriers: the intestinal mucosa and the mucus covering the intestinal mucosa [33]. In theoretical terms, NPs can pass through the intestinal epithelium via two transport methods: paracellular (between adjacent cells) or transcellular (through the cells) [34]. Intestinal epithelial cells can transfer NPs along with the mineral elements, though their ability is limited. Transcellular transport starts with endocytosis (pinocytosis or macropinocytosis) [35]. The absorption of the NPs depends on the size, surface hydrophobicity, and electric charge [36]. The epithelium of the digestive tract is comprised of lipids, resulting in a higher absorption rate of hydrophobic NPs than hydrophilic NPs. The absorption of 100 nm NPs in the digestive tract is about 15 to 250 times higher than that of larger NPs [37].

In a recent report, a comparison between SeNPs and selenomethionine (SeMet) in male C3H/HeJ mice to estimate the LD_{50} showed that SeNPs induce minor toxic effects compared to SeMet [38]. In short, SeNPs are less toxic, more bioavailable, and possess stronger biological properties than other organic and inorganic Se forms [39][40].

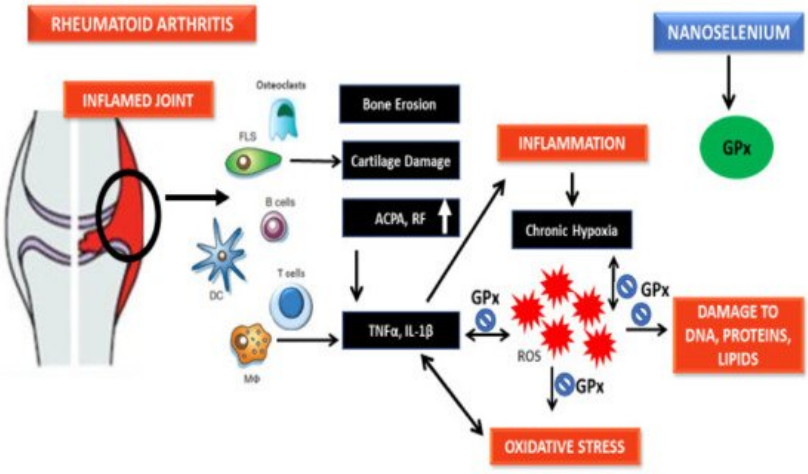
5.2. Protective Role of SeNPs against Rheumatoid Arthritis

Qamar et al. reported the potential of SeNPs prepared from *Trachyspermum ammi* against RA in BALB/c mice models. SeNPs exhibited correction in a manner independent of dose in the redox state through the upregulation of antioxidant defenses and a reduction of paw edema as compared to the diseased group [41]. Hence, the antiarthritic potential of SeNPs is perhaps due to the reduction of ROS, inflammation-related markers, and increase in antioxidant protection as established from recent research.

5.3. Role of SeNPs against ROS and Inflammation Markers

Selenoproteins P, K, and W might also have a substantial function in providing defense against damaging ROS and RNS [42][43][44][45]. Especially selenoprotein P, which functions as an extracellular antioxidant linked to vascular endothelium that reduces ONOO− levels [46]. Besides its notable antioxidant role, Se has also been described to have potential against inflammation-induced damage [47][48][49]. GPx and selenoprotein P are also implicated in the regulation of inflammation-related responses [50]. It has been reported that GPx has a role in the arachidonic acid breakdown and alters prostaglandin and leukotriene synthesis [51]. GPx degrades hydroperoxide intermediates in the cyclooxygenase and lipoxygenase pathways, reducing the production of inflaming prostaglandins and leukotrienes [52]. The endoplasmic reticulum (ER) transmembrane selenoproteins S and K are also reported to be linked to inflammation and immune regulation [53]. Selenoprotein K is especially sensitive to Se status in human peripheral leukocytes, suggesting that this protein might have a relevant function in immune cells in addition to its ER stress-associated functions [54].

Se has been studied at great length due to its function in the regulation of ROS/RNS and inflammation as well as its role as an antioxidant and anti-inflammatory substance. Increased levels of TNF-α and decreased levels of GPx1 alongside upregulated NF-κB have been observed in macrophages cultured in a Se-deficient environment [55][56]. Se-glutathione, along with glutathione peroxidase, plays an important role in ROS and H_2O_2 neutralization. In a study, it was reported that nano selenium stimulated the expression of glutathione peroxidase, a Se-dependent enzyme, through selenophosphate formation, which is an essential part of selenocysteine-specific tRNA [57]. **Figure 2** explains the mechanism of nano selenium in response to ROS-induced OS and inflammation in detail.



(a)

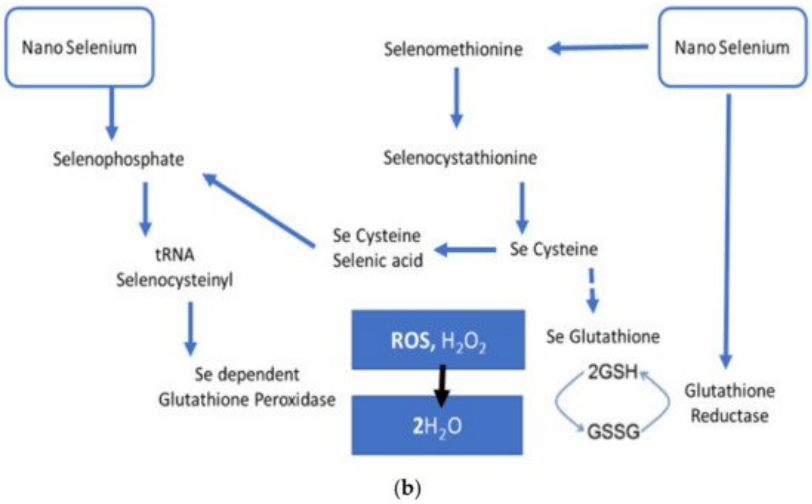


Figure 2. (**a**) Probable antioxidant mechanism of selenium nanoparticles. (**b**) Probable antioxidant mechanism of selenium nanoparticles.

6. Significance of Biogenic Nanoparticles

6.1. Potential of Plant-Derived SeNPs

Zingiber officinale (ginger)-derived SeNPs have been tested against aluminum chloride-induced hepatorenal toxicity in rats and provided significant antioxidant benefits through reduction in GSH, SOD, GPx, and malondialdehyde (MDA) levels [58]. Ginger-extract-made SeNPs have also been reported to have antioxidant-mediated anti-inflammatory properties and improved nicotine-induced renal inflammation-mediated impairment in rats [59]. Menon et al. also reported the antioxidant potential of *Zingiber officinale*-derived SeNPs through DPPH tests [60]. Given that long-term treatment using DMARDs and NSAIDs leads to renal and hepatic toxic damage in rheumatoid patients, [61][62] ginger-derived SeNPs can be a possible option to diminish the treatment-associated toxic effects in rheumatoid patients. Kameswari et al. reported on the potent free radical scavenging and anti-inflammatory potential of SeNPs derived from *Acalypha indica* extract [63]. Other SeNPs derived from plants have also showed significant antioxidant potential [64][65][66][67].

6.2. Potential of SeNPs from Bacteria

Lactococcus lactis NZ9000-derived SeNPs exhibited antioxidant and anti-inflammation effects in porcine intestinal epithelial cells (IPEC-J2) induced by H_2O_2 [68]. *Lactobacillus casei ATCC* 393-derived SeNPs showed antioxidant potential in H_2O_2-stimulated oxidative damage models of human colon mucosal epithelial cells (NCM460) and in diquat-induced intestinal barrier malfunction models in C57BL/6 mice [69][70][71]. Provided that a high risk of intestinal damage has been reported in rheumatoid patients due to possible influence of the underlying disease and long-term use of NSAIDs [72], *Lactococcus lactis NZ9000* and *Lactobacillus casei ATCC 393* SeNPs can be a suitable remedial option. *Cyanobacterial* strain-made SeNPs showed excellent antioxidant properties, among which Arthrospira indica SOSA-4-prepared SeNPs provided the best score for antioxidant potential as indicated through IC50, DPPH, and SOR testing [73].

6.3. Potential of SeNPs from Fungi

Ganoderma lucidum polysaccharide (SPS)-decorated SeNPs showed anti-inflammation effects in LPS-stimulated murine macrophages through the inhibition of NF-κB, JNK1/2, and p38 MAPKs signaling cascades [74]. *Ulva lactuca* polysaccharide (ULP)-coated SeNPs also showed anti-inflammation effects through the inhibition of NF-κB-mediated hyper inflammation in murine acute colitis models [75]. Given that ulcerative colitis (UC) and RA have a notable correlation [76], it can be proposed that ULP-SeNPs can be a potential therapeutic or combinational alternative for UC and RA remedial regimens.

6.4. Potential of SeNPs from Proteins

Proteins have been reported to be associated with SeNPs, however, the underlying functions and molecular mechanisms are still not known [77][78]. It was observed that intracellular organic matter on the proteins acts as capping agents, influencing the surface charge and stability of the SeNPs. Proteins enriched with charged amino acids can control the formation as well as stabilization of the SeNPs [79]. This protein-derived control of the size of NPs has countless applications for industrial-scale production [77]. Keratin and bovine serum albumin have been used to prepare SeNPs and tested in vitro and in vivo for their antioxidant potential in H9c2 cell lines [80].

7. Conclusions

SeNPs have vast applications from diagnostics to treatment of otherwise nondiagnosable and untreatable health-related contradictions. Se is an important trace element that plays an essential role in bodily functions in both healthy and diseased individuals. Biogenic SeNPs have shown exceptional potential to be used as a therapeutic alternative for RA due to their unique properties such as large surface area, nano size, surface charge and chemistry, solubility, and multifunctionality. SeNPs derived from biological methods are less toxic as well as more bioavailable than other organic and inorganic forms of Se. SeNPs can act as both pro-oxidants and antioxidants based on subsequent duration, dose, frequency, as well as oxidation state. SeNPs that have potent antioxidant and anti-inflammation effects can be used to diminish ROS, OS, and inflammation and in combination with present regimens to reduce associated complications linked to available treatment options. Comparisons of different studies included in the article showed that the antioxidant and anti-inflammatory activity is dependent on the size and concentration of the SeNPs. There are toxicity and dosage concerns about the use of SeNPs in a therapeutic role, but these can be overcome via preclinical studies in animal models. Thus, preclinical studies are the need of the hour before SeNP-based treatments can see the light of the day. SeNPs present a cost-effective alternative that can be derived in an ecobeneficial manner and prove a spectacular therapeutic agent if further research finds valuable information in the future. It is also of immense importance to translate these findings from bench to bedside with proper commercial regulations and market policies to innovate healthcare.

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