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Immunomodulation of nanoparticles: Unveiling immunosuppressive and anti-inflammatory properties

Tayyaba Asghar [1], Yasir Nawaz [1], Arslan Muhammad Ali Khan [2], Faisal Hafeez [2], Muhammad Shehroz Zafar [2], Muhammad Tjammal Rehman [2], Asif Ali [3], Dilawar Hussain [3], Muhammad Ammar Azam [4], Hasnain Idrees [2], Muhammad Usama [5]

[1] *University of Veterinary and Animal Sciences, Lahore, Pakistan*
[2] *University of Agriculture, Faisalabad, Pakistan*
[3] *University of Layyah, Layyah, Pakistan*
[4] *PMAS Arid Agriculture University, Rawalpindi, Pakistan*
[5] *Qaid I azam University, Islamabad, Pakistan*

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* *Corresponding author:*
Arslan Muhammad Ali Khan
Email: arslanrajpootkhan374@gmail.com

Reviewed by:
Muhammad Mohsin
University Medical College, Shantou, China
Arsalan Said
Abdul Wali Khan University, Mardan, KPK, Pakistan

Abstract

Interactions between nanoparticles and eukaryotic cells are nearly inevitable once they gain entry into the cell. Such accidental interactions between immune cells and nanoparticles may trigger a destructive chemical response and increase the risk for autoimmune diseases, tumors, and infections. Nanoparticles can also interface with biologic systems and elicit allergic or inflammatory responses, thereby activating the complement system. Nanoparticles have been known to stimulate the immune system either as haptens or adjuvants. The effects have also been known to be immunosuppressive. This review article summarizes some of the *in vivo* and *in vitro* studies carried out to show how nanoparticles stimulate or suppress the immune system in animals. Further research should, therefore, focus on the impact that the physical and chemical properties of nanoparticles have on their performance within the biological system to ensure safe usage of the particles. These qualities may interrupt the experimental process and have a greater influence on the interaction between nanoparticles and immune systems.

1. Introduction

Nanoparticles (NPs), generally, fall within the size range of 1 to 100 nm (Ijaz et al. 2020; Shah et al. 2021; Khan et al. 2022). They possess specific characteristics due to their small size, shape, charge, and high surface area-to-volume (A/v) ratio (Ramakoti et al. 2023). Artificial or synthesized NPs have industrial applications in agriculture, livestock, poultry, electronic gadgetry, energy, and medicine (Raha and Ahmaruzzaman 2022; Kausar et al. 2023). Most of the methods, such as chemical fusion, physical vapour transport (PVT), and material synthesis (MS) are used to produce artificial NPs (Nene et al. 2021). Nps are used as drugs to treat different disease conditions in animals and humans (Sadiq et al. 2023). They are highly effective against bacterial (Singh et al. 2020), fungal (Mba and Nweze 2020), parasitic (Bajwa et al. 2022), and viral infections (Hamidzade et al. 2024).

The immune system is a defense system of the body that recognizes foreign material, kills it, and saves the body from any harm caused by the material (Lin et al. 2020). It is well-recognized that a variety of inflammatory diseases, as well as benign and malignant cancers, are caused by aberrant immune systems (Sriharikrishnaa et al. 2023). Immune reactions can be divided into two categories based on the time of response (Breloer and Linnemann 2024). First is innate immunity which is acquired from birth and consists of predesigned tissue proteins that can instantly defend the living organism against the pathogen, and hence is called the first line of defense (Garcia et al. 2021). Different complementary systems, antibodies, peptides, lysozyme, C reactive protein, etc. have been induced once the foreign body passes the first line of defense (Liu et al. 2022). Next, a variety of cells including mast cells, neutrophils, basophils, dendritic cells, and macrophages form the second line of defense (Harvanova et al. 2023). If the foreign body passes the body's defenses and enters into the spleen, lymph nodes, thymus, tissues, and lymph nodes, then the third line of defense is the adaptive immune response (Kiboneka 2021). Unlike innate immunity, adaptive immunity

requires specific antigen stimulation and develops approximately four days following a foreign invasion. Cell-mediated immunity primarily involves cytotoxic T cells that can recognize afflicted cells and induce cell death (Dileepan et al. 2023).

Several inflammatory disorders are brought on by aberrant immune responses that induce either systemic or localized inflammation (Gusev and Zhuravleva 2022). Anti-inflammatory drugs are currently the cornerstone of care for conditions involving inflammation, and they may help achieve a balance between the immune system and the inflammatory response (Ribeiro et al. 2024; Sinibaldi 2024). Nevertheless, minimal cell specificity (Chen et al. 2022), general adverse reactions (Sonsupap et al. 2023), and inefficiency in overcoming biological barriers (Li et al. 2024) challenge the old drugs and move toward more effective alternatives (Hemrajani et al. 2022). Current research focuses on mixed substances that exhibit improved specificity and anti-inflammatory properties. This paper aims to provide an overview of the interaction of NPs with immune systems, including various chemicals linked to inflammation. This paper discusses many inflammations in which NPs are used to treat to provide recommendations for future research and the development of nanotools.

2. Interaction of NPs and Macrophages: Activation of innate immune response

Every macrophage originates from monocytes that are in circulation (Heo et al. 2019). Progenitor cells from the embryonic yolk sac were able to give birth to macrophages, even in the absence of hematopoietic stem cells (Ito et al. 2022). Furthermore, the study demonstrated that the majority of tissue-resident macrophages, including those seen in the dermis (Cao et al. 2024), liver (Wang et al. 2024), lungs (Langelage 2024), spleen (Sun et al. 2024), brain (Sun and Jiang 2024), and to a lesser extent, kidneys (Chew et al. 2024) originated from this embryonic stream. M1 and M2 macrophages are the two primary types, from which various M subtypes such as M2a, M2b, M2c, and M2d can be distinguished (Strizova et al. 2023). Membrane receptors, biological activities, signaling, and glycoprotein production profiles vary throughout macrophage subtypes. M2 subpopulations have different cytokine production profiles and functions and arise in response to distinct stimuli (Cutolo et al. 2022). Interleukin (IL-4 and 13) activated M2a cells, which are involved in the healing process, showed large quantities of mannose receptor C type 1 (MRC1), arginine1, and inflammatory zone proteins (de Brito Sousa et al. 2020). They produce pro-fibrotic, IL-10, and chemokine (CCL17, CCL18, and CCL22) (Wroblewska et al. 2023). M2b macrophages release growth factors, chemokines, and interleukins and regulate the immune system and inflammation (Zhang et al. 2012). M2c macrophages release IL-10, TGF-β, and CCL. M2b macrophages are also known as inactivated macrophages and undergo efferocytosis (Yousaf et al. 2023). The last subtype of macrophages called M2d is the main element of the tumor microenvironment (Basak et al. 2023).

Macrophages are commonly exposed to NPs through the oral or parenteral administration of NP based drugs or by inhalation of atmospheric NPs from a polluted environment, or internal generation of NPs as a result of metallic implant breakdown (Ferdous and Nemmar 2020). Moreover, after penetration through human body, NPs may also interact with macrophages and can provoke inflammatory response (Soni et al. 2024). The signaling proteins such as chemokines and cytokines are associate with the inflammatory response, which facilitate the molecular activities and interaction between macrophages (Tomlin and Piccinini 2018). The positively charged NPs generally have a greater potential of creating inflammation (Ajdary et al. 2018) and such strong interaction is due to the fact that the negatively charged sialic acid surface strongly interacts with the positively charged NPs (Ghosh et al. 2023). It is well known that macrophage cells recognize foreign antigens through their toll-like receptors (TLRs) (Chakraborty et al. 2023). Receptors will bind with the respective antigens, inducing the signal transduction and thus inflammatory response through (Soleiman-Meigooni et al. 2024). Logesh et al. (2023) have demonstrated increased expressions of TLR receptors and inflammatory cytokine productions in human macrophage cells treated with nontoxic doses of different metallic NPs. Titanium oxide (TiO_2) NPs produced pro-inflammatory mediators in human neutrophils e.g. the chemokine Growth factor-α, IL-8, and Interleukin (IL)-6 (Mohammapdour and Ghandehari 2022). These cytokines can stimulate immune cells and cause inflammation.

However, an in vivo study of sub-chronic accumulation in the spleen and thymus in humans and the immunotoxicity of TiO_2 particles (given intragastrically for 90 days) in the spleen showed the increase of several fibroblast growth factors, tyrosine phosphatase (TP) and kinases, monocyte chemotactic protein-1 (MCP-1), IL-13, and macrophage inflammatory proteins (MIP-1α, MIP-2), tyrosine phosphatase (TP) and kinases, and monocyte chemotactic protein-1 (MCP-1) (Brand et al. 2020; Chen et al. 2020). While the transmembrane protein (NKG2D, NKp46, and 2B4) expressions were lowered (Sung and Jang 2018). In one of the studies when metal oxide NPs were given to the mice, they increased the IL-1, tumor necrosis factors (TNF-α), and IL-6. Moreover, they noted a rise in the production of IgE (Park et al. 2014). In another study, the effects of Fe_3O_4 with Glu-Gingerol NPs were investigated using lung adenocarcinoma (A549) and normal cell lines (Alkinani et al. 2024). The results showed antiproliferative effects on lung tissue where a malignant tumor was formed (Alkinani et al. 2024). Tulinska et al. (2020) performed an in vivo study to examine the inflammatory response of female mice pulmonary cells after administering an accurate dose of cadmium oxide NPs and observed an increased concentration of immune thymus and spleen cells, and making of inflammatory cytokines and chemokines.

3. Activation of adaptive immune response

The adaptive immune response is antigen-specific which requires time to attain its maximum ability, and commonly works to form an immune database (Raffie et al. 2022). It has specific responses to humoral and cellular antigens which are triggered by NPs. The adaptive immune system must produce antibodies against the NPs (Khan et al. 2023). NPs make

interaction with dendritic, B cells, and macrophages in blood (Wang et al. 2021). These cells engulf and digest the foreign antigens and are present on the surface of both B and T lymphocytes (Sharma et al. 2017). The cytokine environment and dendritic cells stimulate the T-cell response. Dendritic cells produce the cytokine environment when CD4+, T lymphocytes, neutrophils, and macrophages are drawn to the inflammatory site along with stromal cells (Rosales 2020). To induce T cell anergy (self-tolerance) in young dendritic cells, for instance, antigens are introduced to them without the production of co-stimulatory molecules. Foreign antigens activated and matured the dendritic cells, which activate Th1, Th2, or Th17 cells (Cheng et al. 2023). Strong inflammatory mediators, Th17 cells, are important in the emergence of autoimmune disorders. Th1 cells further control inflammatory responses and facilitate cellular immunity. Conversely, Th2 cells drive B cell development to create immunoglobulin (Ig) G and IgE, hence increasing humoral immunity (Gowthaman et al. 2020). They also induce the proliferation of master cells and eosinophils. The innate and adaptive immune systems are linked cellularly via dendritic cells (DCs) in the thymus-dependent pathway (TD) route (Pondman et al. 2023). Through their TLRs, immature DCs engage with and ingest NPs, which triggers DC maturation toward APC.

Tulinska et al. (2022) demonstrated the proliferative response of T-lymphocytes of spleen cells of experimental mice when copper oxide NPs were inhaled. These NPs also increase the production of interleukins and cytokines but no significant effect on the production level of TNF-α was seen. Copper oxide NPs do also induce the pro-activation of Th1 and Th2 lymphocytes (Th1 and Th2), signifying adaptive immunity. Many studies have shown that NPs can also play the role of adjuvants. For instance, NPs of aluminum hydroxide, Al $(OH)_3$, and polymethylmethacrylate, and PMMA are adjuvants of the vaccine for the HIV-2 virus in mice for enhancing the extent of the antibody response (Garg and Dewangan 2020). Although the precise mechanism of how NPs function as adjuvants is unknown (Abusalah et al. 2023), recent studies indicate that they might activate APCs and enhance antigen uptake (Kaneko et al. 2021). It has also been noted that nano size particles can give a better humoral immune response compared to their micro sizes, even when using the same chemical composition (Gamucci et al. 2014). NPs can increase or decrease the responses of allergy. According to Chen et al. (2020), mast cell histamine release was directly induced by TiO_2 NPs. Mast cells have been linked to both inflammation and some harmful effects of NPs. There is mounting evidence that mast cells play a significant part in the biological processes that occur after being exposed to NPs. From the above studies, one can easily understand how NPs stimulate the immune system of the body but on the other hand, they are involved in immunosuppression.

4. Immunosuppression by NPs

Immunosuppression can reduce the body's resistance to infection and malignant cells (Togashi et al. 2019). But it can also help in the improvement of the treatments of autoimmune diseases and allergies. It also helps in decreasing the rejection of the body toward transplanted organs (Poudel et al. 2024). Many researchers have shown the immunostimulatory properties of nanoparticles (Lin et al. 2024; Mozafri et al. 2024) and a few studies described the immunosuppressive properties of NPs (Shen et al. 2012). For example, noble metal NPs, like gold and silver, might induce an immunosuppressive response (Zhao et al. 2022). Noble metal NPs react with both the innate and adaptive immune systems (Boraschi et al. 2023). The immunosuppression caused by Ag NPs has not been documented as extensively as that of Au NPs. It has been documented that the production of cytokines is stimulated by Ag NPs (Ninan et al. 2020). Zheng et al. (2024) showed that when Ag NPs are applied topically at a wound site cause modulation of cytokines. TGF-β1 levels were increased during the healing phase, although IL-6 mRNA expression was significantly reduced. Topical and systemic application reports of Ag NPs have also been received (Madawi et al. 2023; Zhao et al. 2024). It is crucial to remember that topical treatment of silver NPs demonstrated both a significant reduction in inflammatory cytokines and widespread inflammatory cell death. Numerous in vitro studies emphasizing the immunosuppressive characteristics of examined nanomaterials concentrate on a restricted range of cellular functions, primarily cytokine production and surface indicator expression (Stater et al. 2021; Dobrovolskaia 2022; Aljabali et al. 2023). The information is less to declare the immunosuppressive properties of Nps. For Example, these properties are not always present in NPs that produce anti-inflammatory TGF-β. TGF-β stops lymphocyte proliferation with the combination of specific cytokines. It also promotes the growth of some specific helper T cells, which cause inflammation in a range of autoimmune diseases (Zhang and Bevan 2012). Certain NPs can stimulate certain immunological functions (Pondman et al. 2023) while suppressing others (Muhammad et al. 2020). For example, silica oxide NPs increased the production of the pro-inflammatory cytokines TNF-α and IL-1β by lowering the expressive response of the innate immune receptor TLR9 and stopping immunological responses to CpG oligonucleotides (Liu et al. 2021). It has been proposed that the diverse responses seen are caused by the numerous paths through which nanoparticles enter cells and the numerous ways in which they disrupt the function of immune cells (Polo et al. 2017). According to other research, immunosuppressive medications can be delivered by NPs and the immunosuppressive effects of small-molecule medications can be avoided (Kiaie et al. 2023). Glucocorticoids were injected intravenously along with poly D,L-lactide-co-glycolide (PLGA) NPs into the inflammatory joints in a mouse model of arthritis (Mohanty et al. 2019). The inflammatory response was completely suppressed with PLGA NPs and the reason for the increased efficacy is regular release of steroids from the NPs.

The toxicity of chemicals to the T cells is one of the common modes of action for the induction of immunosuppression (Bou Zerdan et al. 2021). For instance, several immunosuppressive chemicals, like radiation, cadmium, tetrachlorodibenzo-p-dioxin, corticosteroids, and cadmium, act through their action on T cells, interfering with their proliferation and functions. The humoral response is the

process by which B cells identify foreign bodies in the blood (Mahmoud et al. 2023). It has been shown that iron oxide NPs follow the humoral immune response. Iron oxide NPs decreased the expression of TNF-α, IL-6, and interferon-γ and stopped macrophage and Th-cell activity. TNF-α and IL-6 are two cytokines that contribute to systemic inflammation (Shen et al. 2012). Moreover, the iron oxide NPs stopped the allergic reactions and altered the balance of the T helper cell (Deng et al. 2023). In a different animal model, microglia cells are treated with iron oxide NPs before being stimulated by an endotoxin which produces less IL-1β. IL-1β was attenuated by the iron oxide NPs through the inhibition of cytokine processing pathways (Shen et al. 2012). Other studies have demonstrated the immunosuppressive properties of NPs (Wang et al. 2022). On the other hand, existing immunosuppressive medications carry the risk of causing immunodeficiency, which can lead to greater cytotoxicity and genotoxicity to the active nanomaterial, as well as increased vulnerability to opportunistic infections and bone marrow deterioration (myelosuppression) (Hofer et al. 2022). Nonetheless, a few research projects have suggested using NPs to treat autoimmune disorders (He et al. 2023) and as a best agent for fruitful drug delivery (Paroha et al. 2023).

5. Anti-inflammatory properties of NPs

In the last few decades, NPs have gained attention as possible anti-inflammatory drugs (Mohsin et al. 2024). Many NPs have been used for this purpose because of their size, shape, and other peculiar properties. The mechanism of anti-inflammatory action of NPs is described below.

5.1 Anti-inflammatory mechanism

The body's initial reaction to intracellular damage, disease, hormone imbalance, internal organs, stimulus, or external causes such as a foreign particle or harmful bacterium invasion is inflammation (Gusev and Zhuravleva 2022). Inflammation can also result from environmental contaminants, food sensitivities, or obesity. Innate immune cells have antigen receptors that recognize chemicals from invading organisms and cells and produce an immune response (Boraschi et al. 2020). Tissue damage produces inflammation. It is also produced when foreign organisms invade the cells and this response stimulates the activity of immunity cells that help the body tackle these situations (Abaricia et al. 2021; Shanley et al. 2021). One important function of macrophages is to auto-regulate the inflammatory process. Macrophages are large, uninucleate, phagocytic, immunological, and formed in the bone marrow cells that circulate as mobile leukocytes. They are also referred to as monocytes in the bloodstream (Sanchez and Gustavo 2021). These monocytes go to infection sites and form macrophages in diverse organs. As mentioned above two important types of macrophages i.e. M2 and M1 take part in the anti-inflammatory reaction. Macrophages switch among these two phenotypes based on the state of the response, initiating, regulating, and maintaining the inflammatory process (Martin and Garcia 2021; Gupta and Sarangi 2023). In response to inflammation, neutrophils migrate to the site of inflammation,

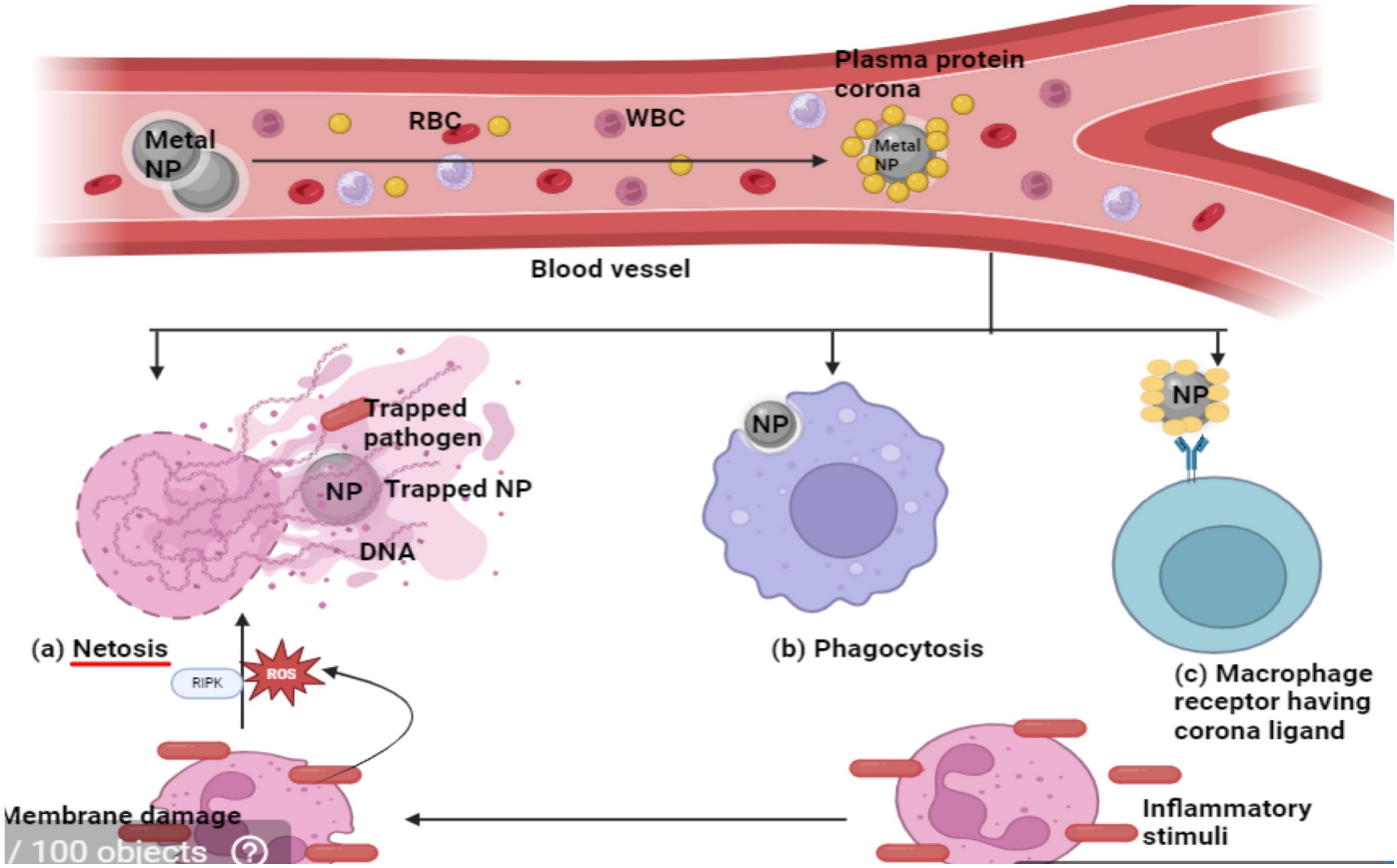

***Fig. 1**: Anti-inflammatory mechanism adopted by various NPs*

Table 1 Anti-inflammatory properties shown by various nanoparticles

Nanoparticle	Reducing agent	Size (nm)	Shape	Mechanism reported	Reference
Ag	*Acranythes aspera*	20-35	Cubical, rectangular, spherical	Inhibition of paw edema or swelling	(Vijayaraj and Vidhya 2016)
Ag	*Leucas aspera*	25-80	Clustered and irregular	Reduction in edema or swelling	(Kumaran et al. 2017)
Ag	*Dodonaea viscose*	60-90	Spherical	Albumin denaturation is inhibited	(Giridharan et al. 2014)
Ag	*Rosa indica*	23.52-60.83	Spherical	NO and superoxide production is attenuated	(Manikandan et al. 2015)
Ag	*Viburnum opulus*	10-50	Spherical	Cytokine production is decreased and edema is also reduced	(Moldovan et al. 2017)
Ag	*Pteristriparita sw*	32	hexagonal, rod-shaped	Reduction in edema	(Baskaran et al. 2016)
Ag	*Terminalia catappa*	10	Spherical	Enzyme inhibition	(El-Rafie and Hamed 2014)
Ag	*European black elderberry*	20-80	Spherical	The decrease in cytokine production, reduction in edema	(David et al. 2014)
Ag	*Calophyllum tomentosum*	-------	Spherical	Inhibition of albumin denaturation	(Govindappa et al. 2018)
Ag	*Piper nigrum*	40-100	Spherical and cuboidal	Cytokine production is decreased	(Mani et al. 2015)
Ag	*Dalbergia spinosa*	18	Spherical	Stabilize the membrane of the RBC	(Muniyappan and Nagarajan 2014)
Ag	*Black Pepper*	40-100	Cuboidal and spherical	Reduction in edema	(Mani et al. 2015)
Ag	*Salvia officinalis*	16	Spherical	COX-2 expression is suppressed	(Agarwal et al. 2019)
Ag	*Rosa damascena*	60-80	Spherical	Edema was reduced	(Ahmad et al. 2015)
Ag	*Centratherum punctatum*	50-100	Spherical	Denaturation of the protein is inhibited, membrane of RBC is stabilized	(Krithika et al. 2016)
Ag	*Syzygium aromaticum*	——-	———	Downregulation of cytokines, Inhibition of protein denaturation	(Varghese et al. 2017)
Ag	*Chamaemelum nobile*	24	Spherical	Cytokine production is reduced	(Erjaee et al. 2017)
Au/ Ag	*Litchi chinensis*	——-	———	Reduction in edema	(Murad et al. 2018)
Au/Ag	*Prunus domestica*	7-30 Au, 3-30 Ag	Spherical (Ag), Hexagonal (Au)	The decrease in Pro-inflammatory cytokines and inflammatory mediators	(Islam et al. 2017)
Au/Ag	*Prunus serrulata*	66 Ag, 65 Au	Hexagonal Au, Spherical Ag	LPS-induced NO release was inhibited	(Singh et al. 2018)
Ag	*Acranythes aspera*	20-35	Cubical, rectangular, spherical	Inhibition of paw edema or swelling	(Vijayaraj and Vidhya 2016)

release pro-inflammatory mediators, and draw macrophages (Daseke et al. 2021). Macrophages produce activation signals that trigger the phagocytosis of cellular and tissue debris (Wu and Lu 2019). This mechanism occurs both to initiate and sustain inflammation. Proteins, lipopolysaccharides (LPS), and cytokines such as interleukins, interferons, chemokines, lymphokines, and tumor necrosis growth factors are a few of these activation signals (Mir et al. 2023).

5.2 Anti-inflammatory Mechanism Induced by NPs

NPs can enter a cell via ion channels or holes in the cell membrane (Zhu et al. 2024). The size of the NP determines this

infiltration mode. Without the need for membrane receptors, NP is taken up by cells through sticky contacts brought on by steric, van der Waals, or electrostatic forces (Dogra et al. 2019). Depending on where the NP is located within the cell, which again relies on its size, different cellular actions are activated. Certain small-sized metal NPs are easily endocytosed by the majority of cellular vesicles at greater concentration levels (Xu et al. 2023). Macrophages and neutrophils perform phagocytosis and micropinocytosis. The protein corona that envelops the protein-coated metal nanoparticles gets into proximity to the cell surface receptors during interactions between the NPs and neutrophils or macrophages in inflammatory areas (Kyriakides et al. 2021). This protein corona is constituted by serum proteins and acts as a ligand for the M2 macrophage receptors, hence inducing anti-inflammation (Tuli et al. 2023). The studies indicate that M2 macrophages absorb NP at a higher rate than M1 macrophages in the presence of serum proteins (Andrade et al. 2020). According to an investigation using phagocytosis gene arrays in M1 and M2 cells, in M2 macrophages, an extraordinary upregulation of receptors of immunoglobulins and complement factors occurs (Mariotton et al. 2021). This presumably implies that the receptors induced by M2 attach themselves to the protein corona. This also goes on to imply that improvement in NP absorption by M2 macrophages is totally dependent upon the adsorption of serum proteins, especially immunoglobulins and complement components. Following an exogenous stimuli (infectious organisms and foreign particles) and internal stimuli (uric acid and cholesterol), neutrophils surround these targets with extracellular traps NETs (Bonaventura et al. 2018). For the development of NETs, ROS radicals are needed as well as a group of protein kinase 3 enzymes (Stojkov et al. 2022). Because ROS have unpaired electrons in their outermost shells, they are extremely erratic and reactive. They are formed by lipid peroxide inside the cell, which damages membranes. This results in an increase in the cell membrane's surface area, which increases the O_2 absorption and, consequently, the formation of ROS. Gold NPs are readily entangled in these NETs (Saafane and Girard 2022; Vanharen et al. 2023).

A study has been done in which the anti-inflammatory response of NPs is checked to treat type 1 diabetes (T1D) in mice. The study showed that if polyethylene glycol (PEG)-PLGA loaded with insulin is given orally it reduces hyperglycemia. In T1D patients, oral PLGA NPs containing TGF-β and al-trans retinoic acid produced therapeutic regulatory T cells. It has recently been revealed that the therapeutic capabilities of bile acid ursodeoxycholic acid (pUDCA), which is well-known for its anti-inflammatory and immunomodulatory actions, was significantly improved by NP polymerization (Horwitz et al. 2021). Furthermore, insulin may be administered orally with pUDCA NPs without intestinal breakdown. These NPs were quickly and completely absorbed by intestinal macrophages and monocytes, which have high levels of bile acid TGR5 receptor expression. Their differentiation into M2 anti-inflammatory macrophages is the outcome of this interaction, which has significant therapeutic ramifications (Horwitz et al. 2021). Rapamycin-containing pUDCA NPs reduced hyperglycemia caused by cyclophosphamide. Insulin-containing pUDCA NPs reduced blood glucose, reduced inflammation, and improved survival in hyperglycemic NOD mice. The ratio of CD4 Tregs to cytotoxic CD8 cells in draining lymph node tissue was reversed in both models, indicating a shift in immunogenic dendritic cells to tolerogenic ones. Therefore, it appears that pUDCA NPs are a first-of-its-kind oral ingestible carrier with exceptional therapeutic capabilities that can be used to treat a range of inflammatory immune-mediated disorders (Passeri et al. 2021). Table 1. Illustrated some nanoparticles with their anti-inflammatory effects.

6. Conclusions

Nanoparticles possess various characteristics including immunosuppressive and anti-inflammatory properties and these properties are due to their physiochemical nature i.e. size, shape, charge, dose, and surface area. The present data suggest that nanoparticles not only exhibit the immuno-stimulant activity but also cause a decrease in immunity and have a significant role in reducing inflammation. However, data also suggested the interaction of nanoparticles with the macrophages to reduce inflammation and decrease the production of TNF-α and interleukins for immunity suppression. Furthermore, the anti-inflammatory properties also depend upon the route of administration of nanomaterials, i.e. inhalation, ingestion, and via skin. Future research should concentrate on understanding the processes of the same nanoparticles inducing immunostimulation and immunosuppression and figuring out what exactly sets off immunomodulatory effects. It is crucial to comprehend what causes a given nanoparticle to be immunostimulatory in one type and immunosuppressive in another. Scientists working on drug delivery formulations will benefit from this as they select suitable nanoparticle carriers, which will undoubtedly progress the quickly expanding field of nano immunotoxicology.

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