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Review

Anti-inflammatory mechanism of various metal and metal oxide nanoparticles synthesized using plant extracts: A review

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ABSTRACT

Multiple types of inflammations caused by foreign pathogens or chemicals and mutations that upregulate inflammation enhancers kindle the need of developing new vectors for the treatment of inflammation. Nanoparticles have been used in various fields ranging from the food industry, cosmetic industry and agricultural industry to devices like sensors, solar cells, and batteries. Nanoparticles have been used in the medical and research fields due to their high penetration power even inside cells and have the excellent ligand-binding properties due to their high surface area to volume ratio. Mechanistic study of anti-inflammatory activities of various metal and metal oxide nanoparticles like silver, gold, zinc oxide, titanium dioxide, and selenium have been discussed in the following literature review. The present study focuses on the differential uptake of nanoparticles into cells and the anti-inflammatory mechanism adopted by the nanoparticles synthesized by green routes. It also gives a concise literature review of the various green sources used for the synthesis of nanoparticles and the mechanism of action of each nanoparticle.

1. Introduction

Nanoparticles (NPs) are known to exhibit superior physical, chemical, mechanical, thermal and biological properties as compared to the bulk materials. Some of these important to the biological and research fields are their anti-microbial, anti-inflammatory, anti-oxidant and anti-angiogenic properties. They also exhibit better catalytic activities [1,2]. Nanoparticles have a wide range of applications especially in the biomedical field which includes use in drug delivery systems, implants, and prosthetics, in-vitro diagnostics, bio-imaging devices, optoelectronic devices as well as sensors [3]. Nanoparticles have been extensively used in these fields due to their high stability, solubility, multi-functionality, bio-compatibility, adhesive properties, and therapeutic properties. The current trend is the development of nanoparticles which have better therapeutic properties as well as being environment-friendly [4,5]. Synthesis of nanoparticles using organic sources excludes the need of employing toxic chemicals as reducing and capping agents and also provides an environment-friendly and cost-effective method of nanoparticle synthesis. Nanoparticles have been synthesized using various organic sources like plant, bacteria, fungus, yeast, and viruses [6]. Plant-mediated 'green' synthesis of nanoparticles is accounted as one of the most preferred options for nanoparticle synthesis since it usually requires a neutral pH and also takes place at ambient temperatures [7]. Non-steroidal Anti-inflammatory Drugs (NSAIDs) is a class of drugs that reduces and helps prevents blood clots. They do so by blocking cyclooxygenases (COX) which are involved in the synthesis of prostaglandins which in turn are mediators [8]. However, some patients administered with NSAIDs have been reported to develop gastrointestinal tract complications, cardiovascular complications, and peptic ulcers. Several risk factors are also associated with NSAID administration including the history of heart diseases and ulcers and age factors [9]. Nanoparticles have a better penetrating capacity in epithelial cells and inflammatory cells which leads to better effectiveness and better persistence in the treatment. They also have a better selectivity of target sites such as inflammatory cells or tissues [10]. Anti-gastric ulcer properties have also been reported of silver nanoparticles [11] and solid lipid nanoparticles [12] and anti-peptic ulcer properties of chitosan nanoparticles [13]. Nanoparticles have also been reported to have been used in the treatment of cardiovascular disorders [14,15]. The following review literature also explains the anti-inflammatory mechanisms adopted by some nanoparticles. It also lists the different nanoparticles synthesized using plant extracts having different shapes and sizes which possess anti-inflammatory properties.

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1.1. Inflammation

Inflammation is a localized physical condition in which the inflamed part of the body develops swelling, redness, pain, etc. in response to an infection or injury. It is considered to be the backbone of pathology. It is the beneficial host response that ultimately leads to reinstatement of cellular homeostasis and tissue structure and function. Infections, wounds and tissue damages cannot heal without an inflammatory response. This response is mediated by two main components of the host's defense mechanisms: innate and adaptive immune response. The innate immune response is the primary host response to any foreign material which then is acted upon by granulocytes, phagocytes and other cells which are a part of the adaptive immune response. The adaptive immunity is characterized by specificity and helps in the elimination of pathogens in the later phase as well as the generation of immunological memory. However, sometimes the inflammatory response persists longer than necessary which causes more harm than benefit [16,17]. Since more blood has to be supplied to the damaged region, the small branches of arteries expand while supplying blood. During, there is an excess blood flow through dilated vessels which causes the heat sensation and the redness due to the increased number of erythrocytes in that particular area. There is also an increased infiltration of phagocytic cells into that area which causes the swelling, thereby, resulting in pain. There is also a temporary loss of function and/or sensation in that area. Chemicals that stimulate nerve endings are also released in the particular area, making it more sensitive. This is contradictory to of internal organs example lungs, where there are no sensory nerve endings nearby and therefore, there is little or no pain during [18]. Inflammation is usually initiated within minutes in a host with a functional innate immune system on contact with foreign stimuli. Innate immunity is the major contributor to inflammation and therefore, immune cells such as macrophages, mast cells, neutrophils, and dendritic cells as well as non-immune cells such as endothelial cells and fibroblasts also contribute to the inflammatory processes. Inflammatory pathways and target tissues vary depending on the nature of the stimulus. The duration of inflammation varies depending on the amount of damage caused by the infection and prolonged inflammation leads to systemic effects. These effects are mediated by excessive cytokines and coagulation factors production which in turn, induce hepatocytes to facilitate production of prostaglandins and acute phase proteins like C-reactive protein which act on the central nervous system, causing pain, fatigue, and fever [19,20]. Inflammation is classified into two types: acute inflammation which is less severe and confined only to a particular area and chronic inflammation which occurs due to failure to eliminate or destroy the pathogen responsible for causing the acute inflammation. It then turns into an auto-immune disorder that attacks normal, healthy host-cells resulting in a disease. Chronic inflammation can also eventually lead to rheumatoid arthritis and in some cases, cancers as well [21]. Both acute and chronic inflammation is characterized by the systemic production of TNF-α from macrophages which then activates the central innate immune response, particularly microglial cells. Where the microglial cells are already activated by chronic neuro degradative changes, an acute inflammation, in that case, causes an exaggerated innate immune response which causes the release of cytotoxic inflammatory mediators that aggravates neurodegeneration. Inflammatory mediators escalate advancement of inflammation through modification of vascular endothelial permeability (vasodilation), extravasation of neutrophils and excess plasma containing complement factors and antibodies to the site of inflammation [22]. NF-κB and COX-2 pathways are some of the paramount mechanisms involved in upregulation of inflammation.

1.2. Anti-inflammatory properties of NPs

NPs have emerged as a potential anti-inflammatory agent in the past few decades. Since NPs have a large surface area to volume ratio, they are better at blocking inflammation-enhancers like cytokines and inflammation-assisting enzymes when compared to their bulk counterparts. Several metal and metal oxide NPs have been reported to be endowed with anti-inflammatory properties like silver [23], gold [24], selenium [25], copper [26], nickel [27], zinc oxide [28], zinc peroxide [29], magnesium oxide [30], cerium oxide [31], iron oxide [32] and titanium dioxide [33]. This literature review clearly demonstrates the mechanism-based anti-inflammatory properties of the NPs.

1.3. Mechanism

Inflammation is the body's immediate response to an internal injury, infection, hormone imbalance, malfunction in the internal organs or external factors like an invasion by pathogenic microbes or a foreign particle. It can also be caused due to obesity, food sensitivities or contact with environmental toxins. Innate immune cells have antigen receptors which detect chemical signals from languishing cells and infectious agents and accordingly generate responses to it. Inflammation is caused by cellular and tissue damage resulting from an imbalance between the regulatory signals of the inflammatory process [34]. When tissues are injured or attacked by a pathogen, an inflammatory response is generated based on the pattern of the damage caused and this response leads to the recruitment of macrophages, killer cells and stem cells which help in tackling the response [35,36]. Macrophages play a key role in auto-regulating the inflammatory process. Macrophages are large, heterogeneous, mononucleated, phagocytic cells which are generated in the bone marrow and are found as mobile white blood cells (WBCs) called monocytes in the bloodstream [37]. These monocytes migrate to sites of infection in various tissues and from macrophages. Macrophages are of two types: pro-inflammatory M1 macrophages whose production promotes inflammation and M2 macrophages which are alternatively activated in response to anti-inflammatory reactions and induce the process of remodeling of affected tissues and organs. Macrophages initiate, regulate and maintain the inflammatory process by the transformation between these two phenotypes depending on the condition of the response [38,39]. During inflammation, macrophages engulf cellular and tissue debris through a process called phagocytosis and promote inflammation through the production of activation signals which activate macrophages. Some of these activation signals include extracellular matrix proteins, lipopolysaccharide (LPS) and cytokines like interleukins, interferons, chemokines, lymphokines and tumor necrosis growth factor [40]. Neutrophils respond to inflammation by migrating to the inflammatory site and producing pro-inflammatory mediators which attract macrophages to the site.

1.4. Protein corona formation by metal nanoparticles

Metal NPs enter into the body through nasal, oral or dermal routes. Because of their small size, they can easily cross most biological barriers like mucous linings and reach even the sense organs. As soon as the metal NPs are into the body, they enter into the circulatory system [41]. Blood in the circulatory system is composed of cellular components and plasma which is made up of water and plasma proteins. The NPs inexorably interact with the proteins in the blood plasma. This interaction leads to the formation of a protein corona surrounding the nanoparticle. immunoglobulin (IgG), immunoglobulin M (IgM) and fibrinogen are some common proteins detected on nearly all NPs [42]. According to studies, IgG and IgM are involved in the natural inflammatory process [43,44]. The formation and composition of this protein corona, as well as the protein binding patterns, are dependent upon the physical properties of the NPs like their surface charge, size, geometric shape, the extent of hydrophobicity of the NP, surface roughness and curvature, and also on the chemical composition of the NPs [45]. Serum proteins, though being less abundant in the blood plasma, have a high affinity to bind to the metal NPs. Therefore, serum proteins form a major part of the protein corona around the NPs. This protein corona

alters the external morphology of the NP giving it a biological identity. This identity determines the transport and interaction of the NP to various chemical responses [46].

1.5. Nanoparticle-cell interactions and uptake of NPs by cells

NPs enter the cell through pores in the cell membrane or through ion channels. This mode of ingression depends upon the size of the NP. NP uptake by cell takes place without membrane receptors but involves adhesive interactions due to electrostatic interactions, Van der Waals forces or steric interactions. Different cellular effects are triggered based on the localization of the NP in the cell which again, depends on its size [47]. At higher concentration levels, some small sized metal NPs are readily endocytosed by most cellular vesicles. Phagocytosis and macro-pinocytosis are carried out by macrophages and neutrophils [48]. When the protein-coated metal NPs interact with macrophages or neutrophils at sites of inflammation, evidently, it is the protein corona which surrounds the nanoparticles that comes into contact with the cell surface receptors first [49]. This protein corona composed majorly of serum proteins acts as a ligand for the receptors on the M2 macrophage. This activates the anti-inflammatory M2 macrophages. These macrophages have a crucial role in NP uptake. Results show that in the presence of serum proteins, M2 macrophages exhibit a higher and rapid NP uptake when compared to the M1 macrophages. A phagocytosis gene array study conducted in M1 and M2 cells shows that there is an astounding increase in expression levels of receptors for immunoglobulins and complement factors (primarily FCGR2B and CD36 receptors) in M2 macrophages when compared to M1 which says that M2-induced receptors bind to the protein corona. This infers that adsorption of serum proteins (particularly immunoglobulins and complement factors) plays a key role in enhancing NP uptake by M2 macrophages. [50]. Neutrophils form extracellular traps (NETs) around them in response to endogenous stimuli like uric acid or cholesterol and exogenous stimuli like pathogenic microbes or foreign particles. The formation of these NETs is called mitosis and is influenced by contact with pathogenic bacteria or fungi and well as responses of inflammatory stimuli. NET formation depends upon receptor-interacting protein kinase 3 (RIPK-3) enzymes as well as Reactive Oxygen Species (ROS) radicals [51]. ROS are highly unstable and reactive as they contain unpaired electrons in their outermost shells. They are formed by lipid peroxide formation causing membrane damage. This causes an increase in the surface area of the cell membrane resulting in more O_2 absorption on the surface and thus, more ROS production [52]. These NETs are composed primarily of DNA and anti-microbial proteins in which gold nanoparticles get trapped easily [53] (Fig. 1).

2. Review of literature

Synthesis of different metal and metal oxide nanoparticles using plant extracts has been clearly demonstrated in Table 1. Phytochemicals used for reduction of the nanoparticle and the inflammation models used for testing have also been mentioned. The assumed mechanism of anti-inflammatory action of each plant extract coated nanoparticle and the morphology of the synthesized nanoparticles is also mentioned.

3. Zinc oxide nanoparticles (ZnO NPs)

3.1. Blocking pro-inflammatory cytokines

Pro-inflammatory cytokines like IL-1, IL-1β, and TNF-α are involved in the up-regulation of inflammatory responses and their production leads to inflammation. They are known to promote differentiation and proliferation of mast cells. Active nuclear factor kappa B (NF-κB) switches on the expression of certain genes that keep affected cells proliferating, thereby, enhancing the inflammatory response [81]. The caspase-1 enzyme is an IL-1β converting enzyme which converts inactive cytokines like pro-IL-1β and pro-IL-18 to their active forms [82]. Mast cells are known to play important immunoregulatory roles in immune disorders by releasing various inflammatory mediators like histamines, chemokines, leukotrienes, and cytokines. They also induce allergic inflammatory responses by inducing IgE synthesis by B-lymphocytes [83]. ZnO NP blocks the caspase-1 enzyme in activated mast cells and also blocks NF-κB. Studies have demonstrated that ZnO NPs suppress LPS-induced NF-κB by upregulating A20 which is a negative regulator of NF-κB in RAW 264.7 macrophages. They are also proven to suppress the nuclear translocation of NF-κB and p65 (an NF-κB family protein) which was induced by LPS and also decrease cytosolic degradation of IκBα which is a cellular protein that inhibits NF-κB transcription [84]. This, in turn, suppresses Interleukin-1β (IL-1β) and Tumor Necrosis Factor α (TNF-α) production, both of which are pro-inflammatory cytokines. ZnO NPs also dose-dependently suppress malondialdehyde (MDA) production. MDA is a clear marker of oxidative stress; thus, it is inferred that ZnO NPs also help in reducing oxidative stress. They also decrease myeloperxidase levels which are majorly found in neutrophils, thereby, decreasing the neutrophil activity [85,86].

3.2. Inhibiting mast cell proliferation

ZnO NPs act against inflammation in a number of ways. They are known to decrease thymic stromal lymphopoietin (TSLP) production. TSLP is released by epithelial cells as a response to pathogenic microbes, external or internal injuries, trapped foreign particles as well as already present inflammatory cytokines. TSLP increases the production of Interleukin-13 (IL-13) which is a pro-inflammatory cytokine and a growth factor for mast cells, hence, causing proliferation of mast cells. According to studies, TSLP also increases T_H2 cytokine production along with Interleukin-1 (IL-1) and TNF-α in mast cells [87]. Activated mast cells are known to release inflammatory mediators like cytokines, histamines, and arachidonic acid metabolites that act on mucous glands and inflammatory cells [83]. ZnO NPs also inhibit proliferation of mast cells through p53 protein level regulation. Constant p53 activation is known to promote pro-tumorigenic inflammation by causing the release of High-Mobility Group Protein 1 (HMG-1). HMG-1 induces cytokine production and also promotes chemotaxis [88,89].

3.3. Suppressing LPS induced COX-2 expression

Lipopolysaccharide (LPS) is a component of the cell wall of gram-negative bacteria and activates macrophages to secrete secondary mediators like leukotrienes and pro-inflammatory cytokines like TNF-α and IL-1β [90]. COX-2 is strongly induced by growth factors and pro-inflammatory stimuli, particularly LPS. It is mediated by binding of inducible transcription factors to the COX-2 promoter. LPS induced cyclooxygenase 2 (COX-2) gene expression causes the release of inflammatory lipids and Prostaglandin E2 (PG-E2) which is an inflammation promoter. Research has shown that LPS- induced COX-2 expression is significantly lower in Tpl2 $^{-/-}$ macrophages. Tpl2 (Tumor Progression Locus 2) is a MAPK which is involved in conveying intra and extracellular stimuli to the effector proteins of cells. ZnO NP dose-dependently suppresses LPS induced activation of COX-2 in the macrophage cells; thereby, preventing the release of PG-E2 [91].

3.4. Suppressing iNOS expression

Inducible nitric oxide synthase (iNOS) is toxic to the cells as it promotes high synthesis of nitric oxide (NO). NO regulates specific immunity by regulating the functioning of host immune cells and also causes the destruction of local tissues and thus, becomes one of the direct causes of inflammation. NO is generated in high concentrations in some types of inflammation and these high levels of NO can induce

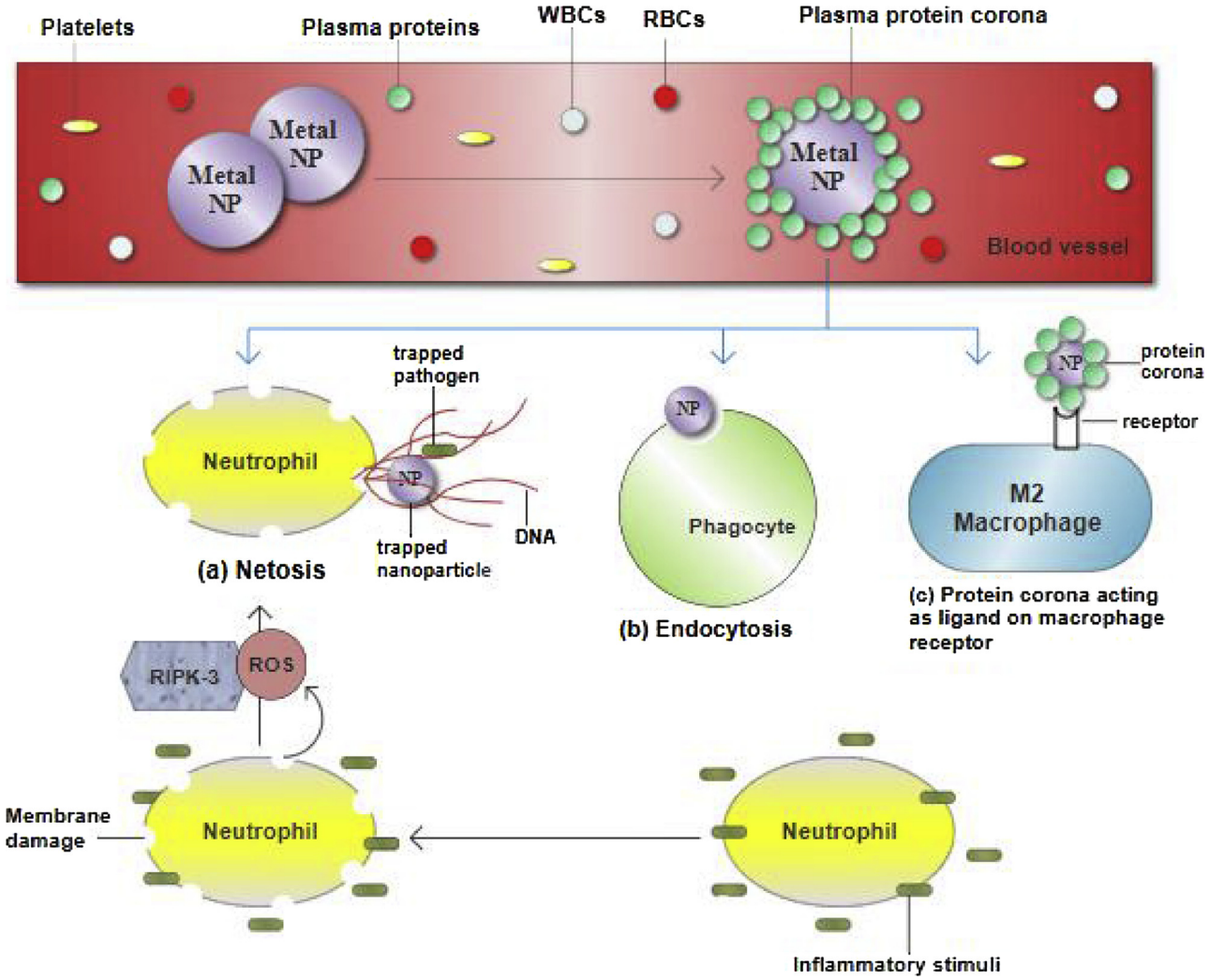

Fig. 1. Anti-inflammatory mechanism adopted by various nanoparticles.

toxic chemical reactions in other host tissues. IFN-γ plus LPS caused a significant increase in iNOS expression which was greatly reduced on a co-treatment with ZnO NPs. ZnO NPs also significantly reduced NO production by IFN-γ plus LPS stimulated macrophages in a dose-dependent manner. [92,93] (Fig. 2).

4. Silver nanoparticles (Ag NPs)

4.1. Reducing VEGF levels

Similar to ZnO NPs, Ag NPs also act as an anti-inflammatory agent. They substantially decrease Vascular Endothelial Growth Factor (VEGF) levels. As per studies, VEGF produced by epithelial cells enhances antigen sensitization (development of antibodies in response to antigen), plays a key role in physiologic dysregulation, allows leakage of plasma proteins into extravascular spaces resulting in thickening of windpipe wall and also enhances T helper type-2 (T_H2) cell-mediated inflammation which secretes pro-inflammatory cytokines like IL-4, IL-5, IL-9 and IL-13. Excess antigen sensitization can lead to allergic reactions [94,95]. VEGF and IL-1β stimulate endothelial permeability via Src kinase pathway by phosphorylation of Src at Y419. Ag NPs directly block the Y419 phosphorylation in a dose-dependent fashion and inactivate the Src kinase pathway thereby, decreasing vascular endothelial permeability induced by VEGF and IL-1β. An increased vascular permeability is associated with elevated levels of cytokines and growth factors in inflammatory bowel disease. Ag NPs also block solute flux induced by VEGF and IL-1β and reduce VEGF-induced cell proliferation [96].

4.2. Decreasing (HIF)-1α expression

Ag NPs reduce expression of Hypoxia-Inducible Factor (HIF)-1α. (HIF)-1α mediates bacterial killing and controls pro-inflammatory gene expression. It also promotes neutrophil survival under anaerobic or minimal O_2 conditions [97]. According to studies, less O_2 causes elevation of TNF-α, IL-1α and IL-6 levels in macrophages and Kupffer cells. Inflammation-related adipokines are found to be at higher levels in hypoxic tissues [98]. HIF-1α binds to HRE (Hypoxia Response Element) DNA sequence and activates transcription of target pro-inflammatory genes. Ag NPs decrease the activity of the HRE reporter induced by HIF-1α in human breast cancer cell lines thus, inhibiting activation of the target genes. They also interfere with HIF-1α protein expression and induction of endogenous HIF-1α target genes like GLUT1 and VEGF-A. Both acute inflammatory stimuli and chronic inflammatory diseases are associated with lymphangiogenesis. Since HIF-1α and VEGF-A play a significant role in angiogenesis, Ag NPs are also inferred to reduce angiogenesis in vitro [99].

4.3. Preventing mucin hypersecretion

Hypersecretion of mucus glycoproteins (mucins), especially Muc5ac which leads to a decline in pulmonary function due to airway

Table 1
Anti-inflammatory mechanisms adopted by green synthesized NPs having different morphologies.

Sr. no.	Nano-particle	Reducing agent used	Precursor used	Nanoparticle characteristics	Inflammation model	Mechanism reported	References
1	Ag	Seed extract of *Acranythesaspera*	Ag nitrate	Size: 20–35 nm Shape: Cubical, rectangular, triangular and spherical Dispersion: Poly-dispersed	Carrageenan-induced albino rats	Inhibition of paw edema	[54]
2	Ag	*Leucasaspera* extract	Ag nitrate	Size: 25–80 nm Shape: Clustered and irregular	Carrageenan-induced paw edema model	Reduction in edema	[55]
3	Ag	*Dodonaeaviscosa* and *Capparisdeciduas* leaf extracts	Ag nitrate	Size: 60–90 nm Shape: Spherical	Bovine serum albumin	Inhibition of albumin denaturation	[56]
4	Ag	Petal extract of *Rosa indica*	Ag nitrate	Size: 23.52–60.83 nm Shape: Spherical	Rat peritoneal macrophages	Attenuate NO and superoxide production	[57]
5	Ag	*Viburnum opulus* fruit extract	–	Size: 10–50 nm Shape: Spherical	HaCaT cell line, Wistar rats	Decrease in cytokine production, reduction in edema	[58]
6	Ag	*Pteristriparita* Sw leaf extracts	Ag nitrate	Size: 32 nm Shape: Hexagonal, spherical and rod-shaped	Carrageenan-induced paw edema model	Reduction in edema	[59]
7	Ag	*Terminalia catappa*, *Terminalia mellueri*, *Terminalia bentazoe* and *Terminalia bellerica* leaf extracts	Ag nitrate	Size:10 nm(T. catappa), 10 nm(T. mellueri), 7 nm(T. bentazoe), 11 nm(T. bellerica) Shape: Spherical Dispersion: Mono dispersed	Carrageenan-induced paw edema model	Inhibition of the enzyme COX-2 leading to inhibition of prostaglandin synthesis	[60]
8	Ag	European black elderberry fruit extract	Ag nitrate	Size: 20–80 nm Shape: Spherical	HaCaT cells, carrageenan-induced paw edema in rats, psoriasis lesions in humans	The decrease in cytokine production, reduction in edema	[61]
9	Ag	Leaf extract of *Calophyllum tomentosum*	Ag nitrate	Shape: Spherical	Bovine albumin	Inhibition of albumin denaturation	[62]
10	Ag	Unripe fruit extract of *Piper nigrum*	Ag nitrate	Size: 40–100 nm Shape: Spherical and cuboidal Dispersion: Polydispersed	Human PBMC cells	The decrease in cytokine production	[63]
11	Ag	*Dalbergiaspinosa* leaf extract	Ag nitrate	Size: 18 nm Shape: Spherical	Human RBCs	RBC membrane stabilization	[64]
12	Ag	Black pepper extract	Ag nitrate	Size: 40–100 nm Shape: Cuboidal and spherical	Carrageenan-induced paw edema model	Reduction in edema	[65]
13	Ag	*Salvia officinalis* leaf extract	Ag nitrate	Size: 16 nm Shape: Spherical	MCF-7 cells	Suppress COX-2 expression	[66]
14	Ag	*Rosa damascena* leaf extract	Ag nitrate	Size: 60–80 nm Shape: Spherical	Wistar rat model	Reduction in edema	[67]
15	Ag	*Centratherum punctatum* Cass. leaf extract	Ag nitrate	Size: 50–100 nm Shape: Spherical	Bovine serum albumin	Protein denaturation inhibition, RBC membrane stabilization, proteinase inhibition	[68]
16	Ag	*Syzygium aromaticum* extract	Ag nitrate	–	Bovine serum albumin	Inhibition of protein denaturation, downregulation of cytokines	[69]
17	Ag	*Chamaemelum nobile* extract	Ag nitrate	Size: 24 nm Shape: Spherical	Carrageenan-induced paw edema in mice	The decrease in cytokine production	[70]
18	Au and Ag	Leaf extract of *Litchi chinensis*	$HAuCl_4$ and Ag nitrate	–	Carrageenan-induced paw edema model	Reduction in edema	[71]
19	Au and Ag	*Prunus domestica* gum extract	$HAuCl_4.3H_2O$and Ag nitrate	Size: 7–30 nm(Au) and 5–30 nm(Ag) Shape: Spherical	Carrageenan-induced paw edema model	Reduction in edema	[72]
20	Au and Ag	Fruit extract of *Prunus serrulata*		Size: 66 nm(Ag), 65 nm(Au) Shape: Spherical (Ag), hexagonal(Au) Dispersion: Monodispersed	LPS-induced RAW264.7 cell line	The decrease in pro-inflammatory cytokines and inflammatory mediators	[73]
21	Au	*Rubia cordifolia* fruit extract	$HAuCl_4$	Size: 5–20 nm Shape: Spherical Dispersion: Monodispersed	Rat peritoneal macrophages	Inhibition of LPS-induced NO release	[74]
22	ZnO	*Trianthema portulacastrum* Linn. leaf extract	Zn acetate	Size: 10–20 nm Shape: Spherical	Bovine albumin, human RBCs	Membrane stabilization, inhibition of albumin denaturation, proteinase inhibition	[75]
23	ZnO and Ag	*Heriteira fomes* and *Sonneratiaapetala* plant extracts	Zn chloride and Ag nitrate	Size: 50–400 nm(HF–AgNPs), 40–50 nm(HF-ZnONPs), 20–100 nm(SA-AgNPS), 400–500 nm (SA-ZnONPs) Dispersed	Bovine serum albumin	Inhibition of protein denaturation	[76]
24	ZnO	*Polygala tenuifolia* root extract	Zn nitrate	Size: 33.03–73.48 nm Shape: Spherical	LPS-stimulated RAW 264.7 macrophages	The decrease in pro-inflammatory cytokines	[77]
25	ZnO	*Andrographis paniculata* leaf extract	Zn nitrate hexahydrate	Size: 96–115 nm Shape: Spherical and hexagonal	Bovine serum albumin	Protein denaturation inhibition	[78]

(*continued on next page*)

Table 1 (*continued*)

Sr. no.	Nano-particle	Reducing agent used	Precursor used	Nanoparticle characteristics	Inflammation model	Mechanism reported	References
26	Se and Ag	*Spermacoce hispida* leaf extract	Selenious acid and Ag nitrate	Size: 120 nm(Ag) and 470 nm(Se) Shape: Rod-shaped	Bovine serum albumin	Protein denaturation inhibition	[79]
27	Se	*Ulva lactuca* polysaccharide	Sodium selenite	Size: 58–205 nm Shape: Spherical Dispersion: Mono dispersed	Acute colitis model in mice	Decrease in pro-inflammatory cytokines, protein from colonic inflammation damage	[80]

obstruction and chronic inflammation is dissuaded by Ag NPs in lung tissues [100]. Ag NPs also was shown to significantly decrease perivascular and peribronchial inflammation. Ovalbumin inhalation in mice models caused an increase in mucin hypersecretion in epithelial goblet cells of the lungs which was significantly reduced by administration of Ag NPs [101].

4.4. Suppressing pro-inflammatory cytokine production

Ag NPs suppress production of pro-inflammatory cytokines like IL-12 and TNF-α and also cause a reduction in COX-2 gene expression at higher concentrations [102] (Fig. 3).

5. Gold nanoparticles (Au NPs)

5.1. Reducing ROS production (oxygen radical scavenging)

Reactive Oxygen Species (ROS) are oxygen metabolites (OH^-, O_2^-, H_2O_2) which are in their partially reduced form and thus, have a strong oxidizing property. They are produced by NADPH oxidases present in phagocytes and are also produced as by-products of the Electron Transport Chain (ETC). They oxidize lipids and proteins in the cells and cause DNA damage. They are also known to oxidize tyrosine phosphatases which are cellular signaling proteins. This promotes endothelial dysfunction and causes membrane damage. Superoxide anion (O_2^-) combines with NO at specifically limited diffusion rates and this leads to the formation of Reactive Nitrogen Species (RNS). RNS induces nitrosative stress which promotes ROS production [103]. Au NPs are known to satiate ROS production in phagocytes, in a dose-dependent manner, thereby, acting as potential anti-inflammatory agents.

5.2. Decreasing LPS induced cytokine production

LPS increases the release of pro-inflammatory cytokines from splenocytes. Au NPs selectively inhibit production of some pro-inflammatory cytokines like IL-1β, IL-17, and TNF-α. They are known to the down-regulate proliferation of epithelial cells induced by IL-1β. They also reduce elevated levels of IL-12 production transposing the cellular immune response from T_H1 response (pro-inflammatory) to T_H2 response (anti-inflammatory).Au NPs significantly reduced the release of IL-17 and TNF-α triggered by LPS. Mechanistic study of the action of Au NPs on cytokines infers that IL-1β molecules aggregate around the Au NPs. These aggregates, therefore, reduce the number of IL-1β molecules available to interact with the interleukin cellular receptor which in turn subsequently reduces the biological activity of IL-1β [104,105].

5.3. Modulating MAPK and PI3K pathways in Kuppfer cells and hepatic stellate cells

LPS binds to Toll-like Receptors (TLRs) present on the surface of monocytes and activates certain kinases which in turn activates the MAPK (Mitogen-Activated Protein Kinase) pathway. PI3K (Phosphatidyl Inositol 3-Kinase) pathway is involved in gene expression, cell proliferation, protein synthesis, and cytokine stimulation. The PI3K pathway downregulates LPS-induced TNF-α production and LPS-induced NF-κB activation in human monocytes. It is directly down-regulated by ROS generation [106,107]. MAPK pathway activates intracellular secondary messengers like Ca^{2+} and cyclic AMP (cAMP) and also co-ordinates G-coupled cell surface receptor-protein interactions. These result in the activation of transcription factors, leading to an alteration in gene expression [108]. Kuppfer cells (liver macrophages) are directly known to initiate and maintain inflammatory responses by carrying out phagocytosis of foreign particulates and releasing large amounts of chemokines and cytokines when activated [109]. Au NPs modulate various signaling pathways like MAPK pathway and PI3K

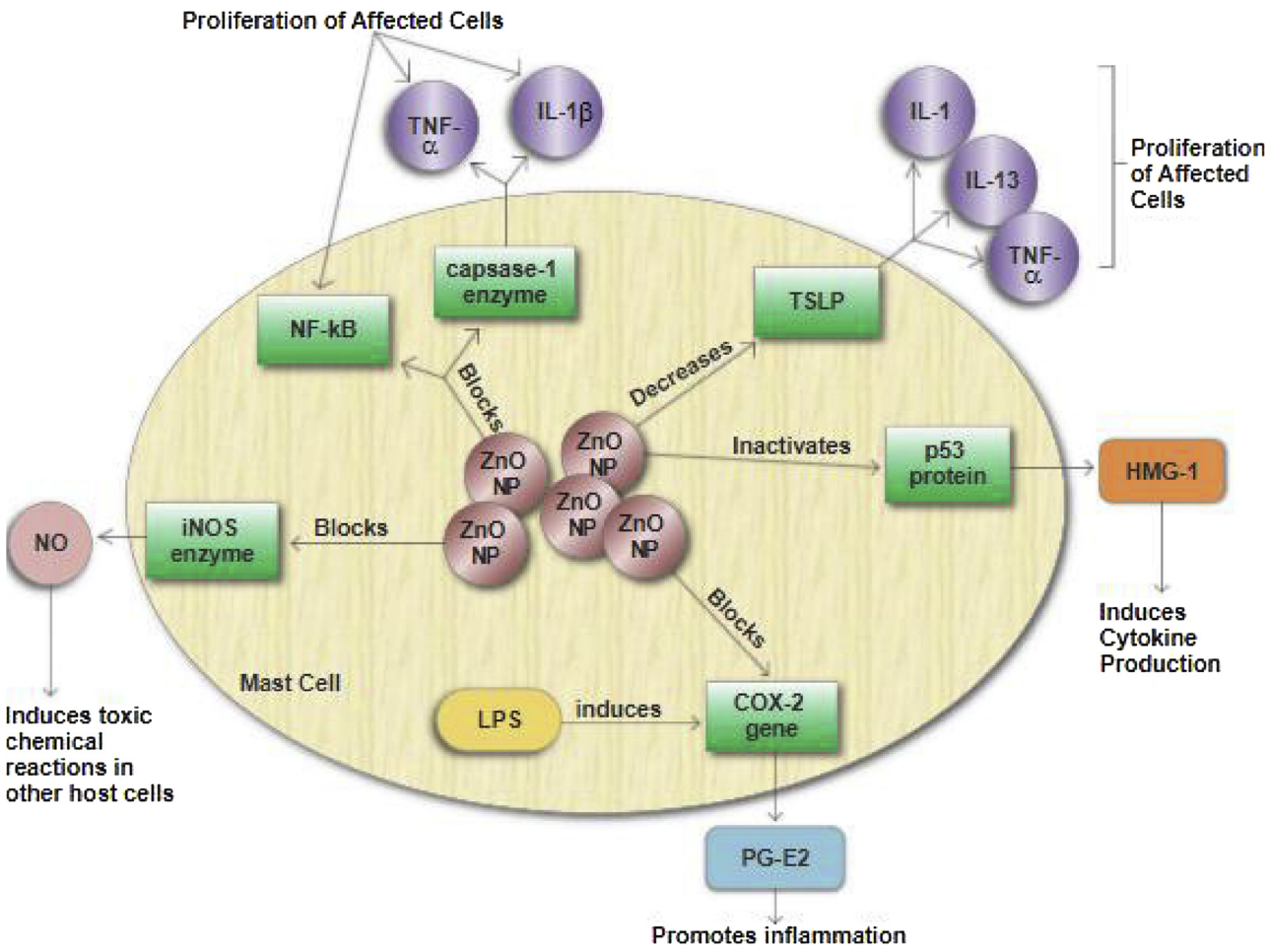

Fig. 2. Anti-inflammatory mechanism adopted by ZnO NP.

pathway, thereby, negatively regulating the production of pro-inflammatory cytokines in Kuppfer cells and hepatic stellate cells affecting their oxidative stress and cytokine profile [110] (Fig. 4).

6. Titanium dioxide nanoparticles (TiO_2 NPs)

6.1. Reducing platelet numbers

Platelets exhibit recognition receptors on their surfaces called Toll-like Receptors (TLRs) which get activated upon contact with foreign microbes or pathogens. TLRs enhance microbial trapping by the formation of NETs. Stimulation of TLR augments pro-inflammatory response of the platelet and P-selectin expression. P-selectin is an adhesion molecule. Hence, when a foreign pathogen enters the body, there is a rise in platelet levels. Neutrophils and monocytes produce PSG1 (P-selectin Glycol protein) which on interacting with P-selectin results in the formation of O_2^- (a type of ROS), resulting in oxidative stress in macrophages. According to studies, platelet counts in blood were found to be reduced after incubation of blood with TiO_2 NPs [111,112].

6.2. Increasing thrombin-antithrombin levels

Thrombin amplifies inflammation through downstream mediators or signaling via Protease-Activated Receptors (PARs). PAR activation leads to induction of P-selectin and cytokines like IL-6, IL-8, and TGF-β. P-selectin is a cell adhesion molecule which mediates aggregation of activated platelets on leukocytes. [113]. During an external or internal injury, prothrombin is released which is subsequently converted into its active form of thrombin for blood coagulation. Thrombin acts on platelets and fibrinogen and is inactivated in the plasma by antithrombin resulting in the formation of a thrombin-antithrombin (TAT) complex [114]. As per studies, TiO_2 NPs are known to increase TAT levels; i.e. more thrombin inactivation by antithrombin takes place, and subsequently, inflammation is reduced by suppressing the PAR pathway [112] (Fig. 5).

7. Selenium nanoparticles (Se NPs)

7.1. Inhibiting NF-κB pathway and PG-E2 expression

In its inactive state, NF-κB is complexed with IκB-α (I kappa B-α) which is an inhibitory protein. Pro-inflammatory mediators and LPS promote the release of NF-κB from this complex by bringing out phosphorylation of IκB-α. Due to phosphorylation, IκB-α loses its capacity to bind to NF-κB. NF-κB is an activator of pro-inflammatory cytokines involved in promoting the inflammatory response. Se NPs are known to inhibit the phosphorylation of IκB-α, thus, preventing the release of NF-κB. In addition, Se NPs also inhibit the expression of iNOS and COX-2 [80]. Se NPs assimilate into selenoproteins and increase their antioxidant activities resulting in a reduction in inflammatory responses. They are also known to inhibit PG-E2 which is an activator of pro-inflammatory cytokines like IL-6 and TNF-α.

8. Pharmacokinetics of nanoparticles

Nanoparticles can be incorporated into the body by dermal penetration, ingestion or inhalation. The absorption and solubility of nanoparticles depend upon its size, surface charge, concentration and pH

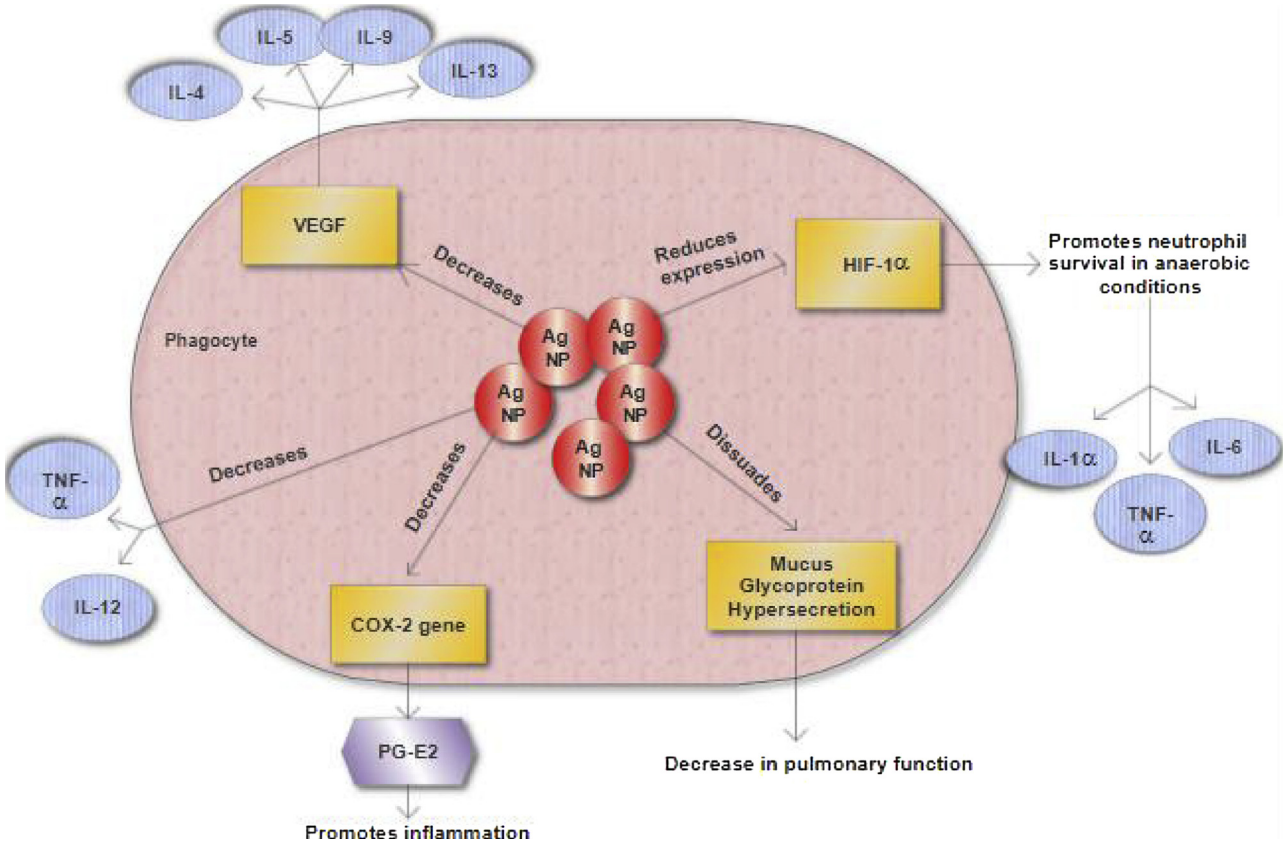

Fig. 3. Anti-inflammatory mechanism adopted by Ag NP.

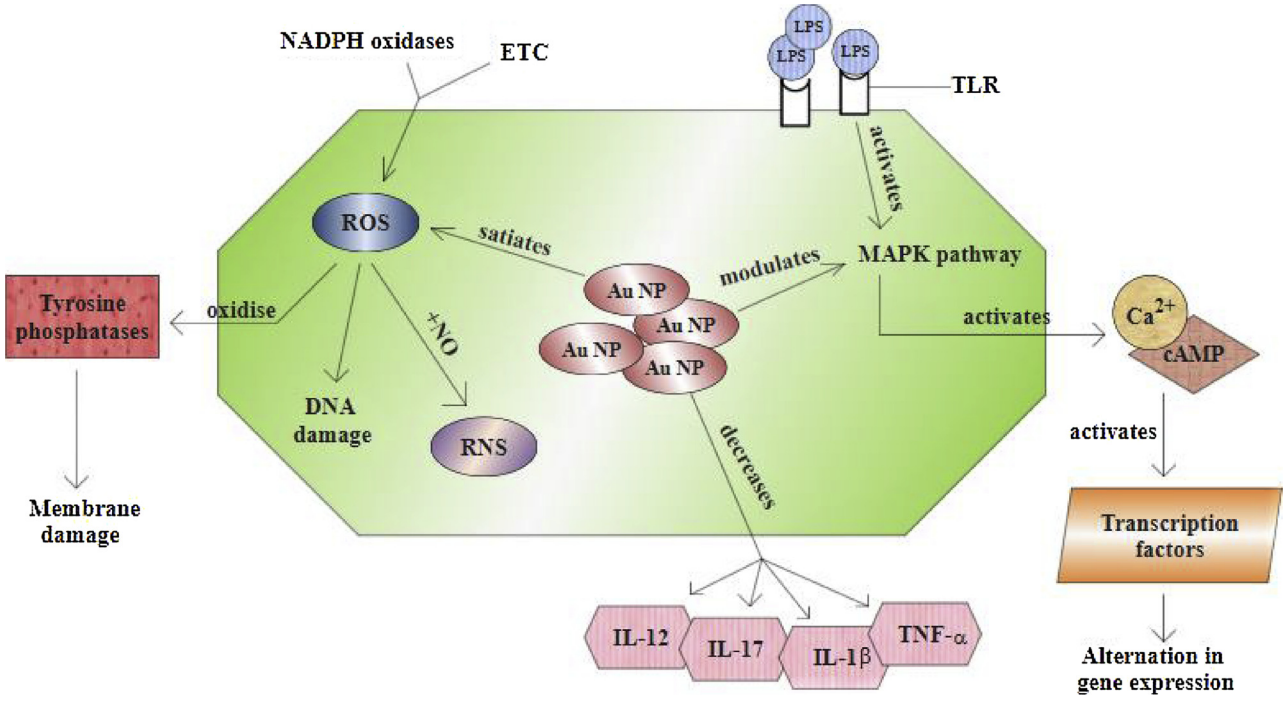

Fig. 4. Anti-inflammatory mechanism adopted by Au NP.

[115]. Studies have shown that the concentration of nanoparticles in blood plasma increases during 24 h in a dose-dependent manner. Nanoparticles were primarily distributed to the liver, lung, and kidney within 72 h of administration. Small-sized nanoparticles are eliminated through urine itself while the other nanoparticles of a relatively larger size are eliminated through the fecal and biliary routes [116]. Toxicology study of nanoparticles on animals and in-vitro cells give rise to the possibility of the adverse effects on the immune system like lung disorders, reduction in cell viability, oxidative-stress related disorders and excessive glutathione (anti-oxidant) depletion as a mechanism of

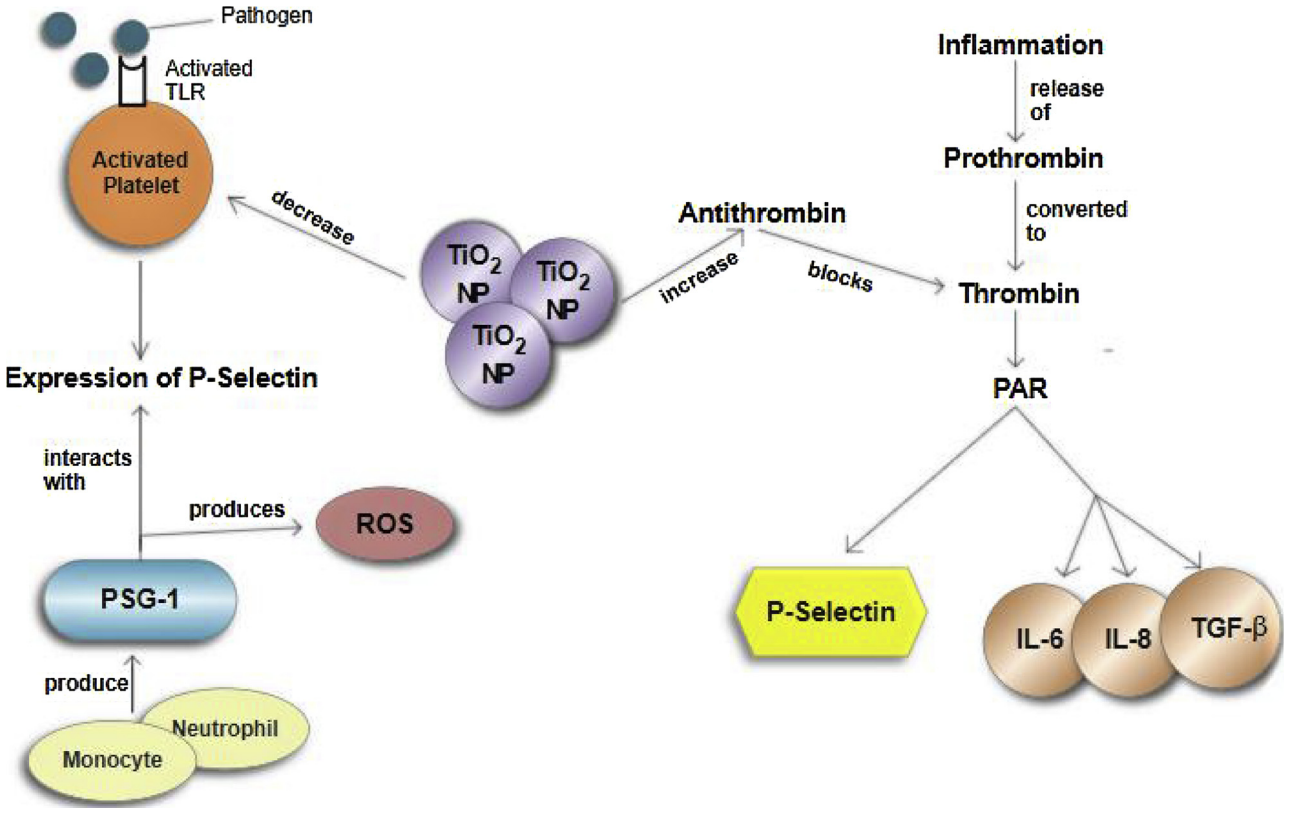

Fig. 5. Anti-inflammatory mechanism adopted by TiO_2 NP.

cytotoxicity. Some nanoparticles also showed a dose-dependent nuclear protein aggregation and thus, interference with gene expression. Nanoparticles at higher concentrations get accumulated in the liver and spleen causing liver damage. They also cause a disturbance in the respective metal ion homeostasis in cells. However, the doses needed to produce these effects are relatively high [117,118]. Therefore, the size and most importantly, the concentration of nanoparticles that are to be administered needs to be optimized depending on the level of inflammation, area of target and route of administration. According to research, cytotoxicity of nanoparticles can also be reduced by surface coating with ethylenediamine tetramethylene phosphonic acid (EDTMP). This significantly reduced oxidative stress induced by a higher concentration of nanoparticles [119].

9. Conclusion

The present study presents a notable and concise report on the anti-inflammatory mechanisms adopted by various nanoparticles like silver, gold, zinc oxide, titanium dioxide and selenium. Nanoparticles tend to form a protein corona around themselves which enhances their uptake by phagocyte cells. Different nanoparticle-cell interactions and mechanisms adopted by the nanoparticle for entering cells have been discussed. Some of the general mechanisms involved in the anti-inflammatory activity are blocking pro-inflammatory cytokines, ROS scavenging mechanisms and inhibiting the NF-κB and COX-2 pathways. Blocking pro-inflammatory cytokines is considered as one of the important mechanisms since cytokines are enhancers of immune response and this mechanism is adopted by nearly all nanoparticles. A review literature emphasizing the different green sources of various nanoparticle synthesis, different morphologies of the nanoparticles, inflammation models used for carrying out the experiment and assumed mechanism of action of each nanoparticle has been discussed in the tabular column. Nanoparticle-mediated toxicity issues have also been discussed which depend on their size, shape, concentration of administration and surface defects. Anti-inflammatory mechanism of the different nanoparticles can be applicable for drug designing and targeting as well as in the food and cosmetic industry and can also offer a probable solution for the treatment of various kinds of inflammation with minimal side-effects.

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