RESEARCH ARTICLE

Biomaterial Based Nanocarriers for Delivering Immunomodulatory Agents

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ABSTRACT

When a natural or synthetic material is used to replace a living structure or becomes a part of a biomedical device, it is termed as a biomaterial. The utility of biomaterials has expanded to areas of tissue, blood, biological fluids etc. Replacement and repair of skeletal parts is one of the major areas of application of biomaterials. This review article focuses its attention on the use of biopolymers based nanocarriers for delivering immunomodulatory agents. The role of biopolymers is to modulate, suppress and stimulate innate or adaptive immune system. Based on the data available, nanoparticles can direct the immune system by improving cellular uptake efficiency and modulating the immune system. Nutrients and trace elements such as Se, Mg, etc., can boost the immune system. Plant derived immunomodulators are known and nanosystems find applications as a carrier system for immunomodulatory drugs. This review details the various nanocarriers and the factors affecting the immunomodulation of nanoparticles.

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INTRODUCTION

When a natural or synthetic material is used to replace a living structure or become a part of a biomedical device such that it can interact with the biological system it is termed as a biomaterial. In another sense, it is a non-viable material that can treat, replace and augment tissues, organs and body functions [1]. The utility of biomaterials can be further expanded to areas of tissue, blood, biological fluids, used in prosthetics, diagnostics, and therapeutics and also for energy storage applications. A primary requirement though is that it should not adversely affect the organism and its components [2, 3]. Replacement and repair of skeletal parts such as knee, hip, joints, elbow, vertebrae, and teeth are one of the prominent applications of biomaterials, which till recently was through non-biological materials. Combining the areas of medicine, engineering, and material science, the use of biomaterials has expanded to include materials of natural origin and use in immune system modulation [4]. Through this effort, biomaterial research has spread to management of diseases including regenerative medicine [5].

A vast range of materials covering broad areas of synthetic or natural origin, in solid or liquid forms are today used as biomaterials. Researchers have employed metals, polymers, ceramics, composites, proteins, cells, tissues, and several other materials as bioinert, bioresorbable and bioactive materials [6]. Biomaterials are today permitted for use in a vast number of ways in the bio medical industry [7]. Polymer based biomaterials is a larger class of biomaterials that can be tuned to chemical, physical, surface properties and made as biomimetic materials. Polymers can be biodegradable and non-biodegradable [8]. Classical examples of non-biodegradables include polyethylene (high and low density), polyethylene terephthalate, polypropylene, polystyrene and so on [9]. The biologically derived (or natural) polymers and synthetic polymers are both extensively considered

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as biodegradable polymeric biomaterials. Some examples of naturally-derived polymers are collagen, albumin, cellulose, agarose, alginate, chitosan, heparin, dextran, hyaluronic acid, etc. [10]. The advanced class of biomaterials is called smart materials. The first "smart material" (i.e., environmentally responsive) polymeric material was probably a pH-sensitive, artificial muscle-like, swelling– de swelling hydrogel developed in 1950 by Kuhn et al. [5, 11]. Stimuli-responsive materials are advanced class of biomaterials, which changes their physical and chemical properties according to its environment. This kind of polymeric biomaterials are referred as stimuli-responsive polymers, or it can also be known as smart or intelligent polymers.

The immune system of human body defends the integrity of the body against external invaders or pathogens and internal factors [12] by relying on diversity, resilience to generate, maintain and resolve responses during an injury, infection or disease [13]. Immune system can be adaptive or innate and are first signs of response to an infection or danger. It is known that myeloid cells, dendritic cells and macrophages can induce and regulate immune responses [14] and the cells responsible for innate responses are phagocytes, dendritic cells, mast cells, basophils, eosinophils, NK cells as well as lymphoid cells (innate). Innate, adaptive systems can integrate signals to transfer information relating to conservation of immunity and nonspecific actions for suppressing immune response or providing immunity [13]. The pathogen like microbes can be phagocytosized by phagocytes (neutrophils and macrophages) where it engulfs and kill them through bactericidal pathways and thus create a first-line defense [15]. This innate immunity activates when cells recognize pathogen-associated molecular pattern (PAMP) molecules through their receptors. PAMP recognition triggers changes in gene expression, to release of chemokines, cytokines, and eventually for pathogen clearance in the body initiated by released cytokines that provide signals to the phagocytic cells (macrophages, neutrophils) [16, 17]. The other kind of immune system cells are adaptive immune cells that includes antigen-specific T cells, which activates and mediates proliferation via antigen presenting cells (APCs), and B cells that eventually differentiate into plasma cells to produce antibodies [18].

Biomaterials are engineered in such a way that it respond to various external and internal stimuli - pH, temperature, mechanical, electric or magnetic fields, and in the presence of different small molecules and biomolecules, etc. [19]. Triggering signals via signal molecules to the immune system such that an immune response is activated against a disease condition, or an unwanted self-antigen is one of the new areas of biomaterial usage incorporating these molecules works [20]. Today, a branch of biomaterials, viz., immunomodulatory biomaterials aim at active modulation of immune response over evasion/ suppression. The biomaterials carrying signalling molecules can create a desired activation state or phenotype within the host immune cells [21]. The class of immunomodulators actions are modulate, suppress, and stimulate innate or adaptive immune system. They are also called as immunoaugmentors and biological response modifiers.

Nanotechnology is an emerging and technologically developing field, with significance in medical field such as medical diagnostics. Nanostructures has great potential in various health care applications as biosensors, diagnostic tools, and it also act as a vehicle for targeted drug delivery [22, 23]. Nanoparticles (N.P.s) are engineered artificially at nanometer-length scale, with the size of 1–100 nm [24]. The potential benefits of N.P.s in biological application are categorised depending on their extensive properties including size/shape, hydrophobicity, and surface charge. Because of these properties, N.P.s can direct their immune system by improving cellular uptake efficiency and modulates the activity of immune system [25]. As nanomedicine, these nanoparticles can have active molecules that can be identified by immune system and inturn responsible for immunostimulation or immunosuppression according to the function of molecules incorporated. Immunomodulation effects rely mainly N.P.s on the role of it as carriers according to different applications. However, some nanoparticles are first recognized by the phagocytic cells (e.g., macrophages, neutrophils) and there is an interaction between nanoparticles and immune system that leads to immunomodulation or immunosuppression effects and therefore choice of nanocarriers play a significant role. They either promote inflammatory reactions, or increase the susceptibility of host to infectious and inflammatory diseases. Under such circumstances, N.P.s with immunosuppression effects could be used as therapeutic agents for inflammatory and autoimmune diseases.

Contrastingly, N.P.s modulates immune response against foreign particles that results in activation of immune system, so these particles can also be used as vaccines or vaccine adjuvants [26]. Site-specific delivery (drugs, genes and peptides, etc.), increase in stability, reduced side effect, these are the advantages of nanoparticles-based drug delivery system [27]. Nanoparticles are engineered or tailored for their immunomodulatory and immunostimulatory effect based on their ability to modulate innate or adaptive immune responses. The upcoming section will describe about the immune response and status on biopolymers and their immunomodulatory role.

WHAT IS IMMUNE RESPONSE?

The immune system responds to the antigens (usually proteins) or any toxic substances which invade human body. Antigens involves proteins and toxic substances like toxins, chemicals, drugs, or any other foreign particles and is present on the surface of the cells, viruses, fungi, or bacteria. These antigens in due course are recognized and destroyed by immune system. Protection of host from external threats is by immune cells that act as a biological network by maintaining homeostasis. Innate and adaptive immune system are the two main consequent factors of immune system. Innate immune response evokes a nonspecific inflammatory immune response and adaptive immune system provide specific immune response which involve antigen specific response and develops a abiding memory [24].

Innate immune response

Innate immune defense mechanism are present in the tissues like skin, mucosal linings of the respiratory and gastrointestinal (GI) tract and is also present at the interface which interact with the exterior environment. Innate immune system a non-specific defense system, according to its mechanism consists of various molecular and cellular components which come into contact with the external pathogens. The molecular component involves cytokines (interleukins, TNF, etc.) and cellular components (phagocytes and leukocytes) [28]. Neutrophils and APC as discussed earlier, identify PAMPs through PRRs to recognize the liable pathogens and after identification, the pathogen are engulfed by the cells, causing an inflammatory response [29]. Directing the host cell to identify between its and other inflammatory immune response requires an activated PRRs, and these PRRs are expressed on many receptors. By coping the interaction with these receptors they are responsible for the whole immunological responses [30].

Adaptive immune response

Adaptive immune responses are the reason for adequate immune response against infectious diseases. Unlike innate immune responses, the adaptive responses are particular to the pathogen that induced them [18]. Adaptive immune system consists of lymphocytes of stem cells that provide accurate and long-standing immune response to antigen or pathogens. They have a significant role in humoral immune response and dictate the cell-mediated immune responses [31]. Dendritic cells from lymph nodes exhibit non self antigens through major histocompatibility complex (MHC) recognised by T cells. T cells (CD8+) are activated by antigens (exogenous) present on MHC-I molecules whereas, T cells (CD4+) activated by MHC-II molecules and other T cells subgoups can be activated based on the antigens or co-modulation signals that included. The antigen specific receptors of lymphocytes are B cell and T cell receptor. These receptors develop during somatic gene recombination, is a novel feature and the role of both T and B cells has been extensively studied [25].

Role of immune response to nanoparticles

In today's interest and need, N.P.s and engineered nanomaterials (N.M.s) shows a great potential in regulating immune system. Interaction of N.P.s, and N.M.s with the immune system results in triggering the inflammation [32]. The N.P.s and N.M.s involved in nanomedical field (e.g drug delivery systems), when once inside the body are recognized and eliminated by immune system, especially macrophages. These N.M.s or N.P.s when properly engineered are involved in modulating immune system by escaping the immune surveillance [33]. Immunogenic properties of N.P.s when used as carriers of vaccines, helps to amplify the antigenic properties of conjugated poor antigens that does not elicit proper immune response. These antigenic properties of N.P.s/N.M.s can vary based on its size, and charge (surface) and can be used as adjuvants. Antigen loaded N.P.s induces Th1 (IFNγ) and Th2 cells (IL-4) based response on their recognition by the immune cells, and this activity of N.P.s also depends on its dimension of the nanostructure. To stimulate maturation of T cells, and B cells by N.P.s, it can done either directly or indirectly by surface receptors on T and B cells or APCs [34]. The classic properties of N.P.s includes its size, surface charge and immunogenicity that proves them to be used in or as nanomedicine and also as a vaccine delivery agent. Particularly non soluble N.P.s are more appropriate for controlled and sustained delivery of antigens and it also prevent vaccines from degradation [35].

BIOMATERIAL BASED IMMUNOMODULATORY AGENTS

Biomaterials has wide range of materials ranging from biodegradable molecular materials to asynthetic materials (artificially synthesized) [36]. Sometimes biomaterials involves the initiation of adverse immune reaction to the antigens, which results in inflammation, tissue degradation, impairment of healing, and fibrotic encapsulation or even destruction of medical devices [37]. The advantages being, in recent research in immunotherapy and vaccination fields revealed that it can modulate or activate the immune system in absence of stimulation signals and these properties of biomaterials in this areas trigger them to act as a carrier of molecules or as such stimulate the innate immune system pathways [38]. By enhancing the properties of biomaterials with various bioactive molecules, it can be used as the carriers to deliver modulating agents by easily eluding the immunological barriers. These materials also show valuable insight in other fields like regenerative medicine and tissue engineering. These can be explored to be used with carrier properties of vaccine or as adjuvants and immunotherapeutic carriers that can further modified to regulate immune response [39]. In the absence of immunostimulatory signals, some biomaterials have the ability to activate immune system and also their inflammatory pathways, the responses of biomaterials can be altererd by altering physiochemical properties [38]. To evaluate the immunomodulatory activity of polymers, it can be assessed by culturing dendritic cells in polymeric biomaterial films. The polymers involved in the study are synthetic (PLGA) and natural polymers (chitosan, HA, alginate, etc.), and these enhanced the markers present on the surface. For the maturation of dendritic cells (D.C.s), the markers involved are CD40 and MHC II complex proteins. These signals oversee antigen presentation to lymphocyte cells and recognise stimulatory markers [40]. Biomaterials can involve synthetic and natural materials like plant-derived materials, biopolymers, trace elements (selenium, zinc, etc.). These materials are involved in stimulating the immune responses.

Nutritional immunomodulators

A nutrient element which is essential to modulate immune system is fed with dietary supplement at higher levels than the established level to alter and modulate the immune responses. A large number of nutrients helps to boost the immune system and their effect is totally based on their amount and types involved in the diet, and these immunomodulators caused different turns in response of immune system [41]. The immune system to maintain homeostasis needs micronutrients and macromolecules. Some of the available trace elements like zinc, selenium, copper are considered as a required dietary supplement, which shows synergetic role and comes under micronutrients category and these are involved in modulating the responses of immune system [42].

Selenium

Selenium is a trace element also known to occur as as selenoproteins. It is involved in human dietary systems which shows a great importance in human health systems. The selenocysteine is the one present as the 21st amino acid of this protein. A proper enzymatic function of this is required to regulate immune system homeostasis. A major component of metabolic pathways and functioning of immune defense systems. Its antioxidant properties take part in a major role in modulating the functioning of immune systems. Chronic diseases like cancers, cardiovascular disease, and male fertility, increase risk of viral infections, decreased thyroid function, neurological disorders, and infalmatory disorders are caused by low level of selenium intake in short known as selenium deficiency [43, 44]. It is estimated that one billion population have insufficient intake of selenium. Recommended dietary allowance and daily intake levels, determine the sufficient amout of selenium intake per day and it is necessary for maximal plasma Glutathione Peroxidase (GPX) activity [45].

Selenium status shows a major impact on the cellular components of immune system. This can respond infectious diseases and other diseases and accordingly modulate our immune system and prepare our immune system. The tissue systems such as liver, spleen, and lymph nodes contain a notable amount of selenium and when the levels are as per standards, it shows a beneficial effect [44]. To increase T cell proliferation response in experimental animal models, lymphokine-activated killer cell activity, NK cells activity can be stimulated by giving selenium as a supplementation leading to delayed-type hypersensitivity response. Human (adult) requires supplementation of around 100 μg/day selenium to improve plasma level concentration, which inturn improves GPX (cytosolic and phospholipid) activity. Its aslo tends to increase other type of host immune responses (IFN-γ production, total percentage of T cells specially helper T cells) [46]. When deficiency of selenium, it leads to the progression of viral diseases by and rising the virulence of infectious agents. These viral pathogens cause cardiomyopathies during the infections that lead to secondary complications. An epidemological study indicated that by consuming 100 - 200 μg selenium (example - selenomethionine) daily for two years, it lowers the cause of cancers in large intestine, prostate, breast and lungs due to immunomodulatory roles [47]. A vast number of epidemiological, experimental, and clinical studies has proved the protective role of selenium against malignant tumors [48].

Zinc

Zinc is one of the trace elements and is an essential component for all organisms. In immune system, the immune cells require sufficient amount of zinc for differentiation, and proliferation of cells [49]. The sensitivity of the cells to pathogens (viruses like HIV) is increased majorly due to lack of zinc in human body. The pathological or diseased conditions such as diarrhea, renal deficiency and gastrointestinal diseases were caused based on the depletion of the elements. Other than this, *Acrodermatitis enteropathica* is the most well-known example of zinc deficiency in humans. This disease is classified under inheritable disease (autosomal recessive) leading to thymic atrophy, and sensitivity to other pathogens (like bacteria, fungi and virus) based infections [50]. The homeostasis of zinc is controlled by transporters of the zinc like metallothioneins, that can be regulated by storage and distribution of zinc and it also behave as signalling molecules, which transduce various signalling cascades according to their external stimuli [51]. Recently, an evidence on zinc has disclosed receptor expression was regulated by NF-κB and receptor is specifically responsible for maintaining natural immune defences [52]. Reports indicated that the zinc transporters and its targeting and release zinc from receptors plays a very crucial role in normal sustainence else can be linked to diseases [53]. The nonspecific killing of normal cells by natutal killer cells are generally promoted by deficient zinc and this effect is prevented in zinc deficient patients by depletion of this natural killer cell lysis activity [54]. According to immunomodulatory effects, supplementation of zinc can modulate the T cells based immune reactions in peripheral blood mononuclear cells and is mediated by production of cytokines (indirect effect) by immune cells. T cells stimulation, and suppression is based on concentrations of zinc, where zinc reduce the levels of IL-1 and these directly stimulates the T cell function via involving a IL-1 receptor kinase 1 [55]. Immunomodulatory effect of zinc for potential supportive treatment strategy for COVID-19 is stated as a hypothetical statement that "Supplementation of Zinc may provide a favorable potential impact in treatment of COVID-19" since it possess an immunomodulatory effect, which is evidenced through several mechanisms [56].

Magnesium

Magnesium is the most important element that has been considered as efficient for various biomedical remedies due to its advanced properties like mechanical strength, biocompatibility, biodegradability, and osteogenic ability, etc [57]. These cations are involved in the cellular systems modulation or aid in proliferation for stimulating inflammatory or immune respone, because of its most important anti-inflammatory properties [58]. Magnesium play crucially as a cofactor for immunoglobulins production/ adherence of immune cells/ antibody-dependent cytolysis/ binding between IgM and lymphocytes/ macrophage response to lymphokines or as adherence of T and B cells in immune responses [57]. Magnesium supplementation stabilizes the nucleic acids (DNA replication and repair). In a study, magnesium apparently decreased the DNA damage and also maintained its integrity [59]. Lei Sun et al., in 2020 investigated on anti-inflammatory effects of magnesium and found that it reduced the proliferation of leukemia cells and its derived macrophages which is an essential factor for cell function, but it did not affect the apoptosis of cells. The M1 and M2 subtype markers expressions were down regulated or upregulated, and pro-inflammatory or anti-inflammatory cytokines were secreted based on the exposure of macrophages to Mg2+. As per the results, magnesium can convert macrophages from one phenotype to other (M0-M2) and biological effects of magnesium micron sized particles on inflammatory cells was likely because of its prompt NF-κB activation as well as reduction [60].

Plant derived immunomodulators

Naturally derived products, active molecules, or plants and their extracts potentially has immunomodulatory effect and are being studied to supplement many therapies also as vaccine adjuvants including chemotherapy [61]. Some of the nutraceuticals are made up of plants derived compounds. Due to their multiple and pleiotropic effects, these products were widely studied as immunomodulating agents [62]. Since ancient times, several medicinal plants and phytochemicals are familiar because of their potentiality to stimulate the immune responses [63]. The most common plant derived pharmaceuticals are cochicine, morphine, quinine, atropine, pilocarpine, or theophylline, which are still required in current therapeutic applications [64]. Immunomodulatory role of components from various plant sources have been studied and analysed that provide a base in the form of prevention for clinical applications in various clinical practices [62].

Polyphenols

Plant derived phenolic compounds mainly invokes the nonspecific immune responses by increasing the phagocytic activity of immune cells especially by proliferating macrophages and neutrophils. These compounds exhibit advanced preventive and protective effects in cardiovascular diseases, diabetes, and cancer attributed to antioxidant, and anti-inflammatory effects [65]. Other characteristics attributed to phenolic compounds are antimicrobial, antithrombogenic, antithrombic and anti atherogenic, vasodilatory and cardio protective effects [66]. The major advantage of these compounds greatly lies on their antioxidant activity [67]. The dietary polyphenols such as phenolic acids, flavonoids, flavanones, stilbenes, and lignans are the major groups of plant polyphenols and their advanced and details in maintaining human health is studied. Flavonoids are composed of benzophenone structure with aromatic rings with hydroxyl groups connected by carbon bridge that gives the antioxidant property to these compounds [68]. Other than flavonoids, the secondary metabolites like phenolic acids of plants and even fungi can be extracted for wide range of applications [69]. Phenols are bioactive substances significantly improves the phagocytic activity of natural killer, through the activation of various mechanisms such as inflammation and mucosal immune activity, and also induce the proliferation of splenic T cells present [70].

Epigallocatechin gallate (ECCG)

EGCG is an active form of tea catechins. Physiological properties of EGCG includes, antioxidant and immunomodulatory activities, which usually involve in attacking the pathogens [71]. It can also activate the alveolar macrophages and in a study, it was shown to act against *L. pneumophila* via activating of cytokines which was secreted effectively [72]. Pae etal., (2013) provided a detailed review on EGCG and its immunomodulatory role with details on the mechanism [73]. EGCG inhibit the migration of monocytes which persuaded by chemokines, and these adhered to fibronectin in monocyte cell lines. So, it is concluded that this is related to the mechanism which direct EGCG to inhibit immune or inflammation related antherogenesis [78]. It is also reported that T cells (regulatory) play a vital role in development of immunity in murine model [74]. Recent studies in primary human T cells have indicated the immunomodulatory effects of EGCG and via suppression of cytokine secretion [75]. Recently, EGCG was shown to be useful in the treatment of atopic dermatitis in mouse model [76]. 3-chymotrypsin-like protease which is vital for the replication of viruses like coronavirus is shown to have high affinity for EGCG and to inhibit the enzyme with a concentration shown to be as low as 0.87 μM [77].

Tannin

Tannins are active compounds, where its molecular weight, water solublity contribute to its potential role in biomedical applications. It is often present in plants as complex proteins, polysaccharides, or as alkaloids. Hydrolysable and condensed forms of these tannins participate in the immunomodulatory effects [78]. In a study, around 67 compounds related to tannins was screened for its immunomodulatory role against *Leishmania* that was infected to macrophage cells. The study further demonstrated its role in activating tumor necrosis factor, nitric oxide and interleukins by macrophages [79]. A possible role of silver nanoparticles coated with tannic acid for combating human dermal problems as a result of its immunomodulation activated by reactive oxygen species was suggested [80]. In an *in silico* study, binding affinity to covid-19 proteases was demonstrated [81].

Lignins

Lignins, structural components in the plant cell wall consists of three basic components with crosslinked polymers [82]. do Nascimento Santos *et al.* , (2020) [83] studied the lignin's immunomodulatory activity isolated from leaves of *Conocarpus erectus*. The lignin`s immunomodulatory activity on blood mononuclear cells as determined, and this led to elevation of the mitochondrial ROS levels and cytosolic Ca^{2+} in mononuclear cells. T lymphocytes and monocytes activation and stimulation produce nitric oxide, and cytokines which trigger response from T helper responses [83]. Lignin are generally carbohydrates molecules bonded to each other either by physically or chemically via a strong covalent linkage. Linkages between the complex molecules are ester or ether linkages, via phenylpropane subunits. Water soluble lignin with carbohydrate complexes are a class of compounds which is precipitated during digestion with polysaccharides and the sugars vary from that of bulk cellulose [84]. One example of lignin is lignosulfonic acid with no side effects even on tight junction protein expression and on maintaining epithelial integrity cells was reviewed [85]. Recently it was reported that nanoparticles of lignin was found to be good candidate to boost immune system when used as vaccine adjuvants by exhibiting long term immune responses [86].

Stilbenoids

Stilbenoids are non-flavonoid polyphenolic compounds called as phytoalexins. Also are metabolites (secondary) produced by plants to combat pathogens or stress factors. Stilbenoids occur as both monomers and oligomers and their bioactivities are largely studied. Resveratrol, pterostilbene, piceatannol, and oxyresveratrol are examples of monomers has two aromatic rings linked by transisomer**.** The transisomer is most common and stable in nature [87]. Mattio et al., in 2020 [88] provided a detailed review on the diverse antiviral activities of these compounds and its occurrence naturally and the many compounds that is semi synthesised based on these materials. A possible role of the adjuvant therapy due to the immune modulatory effect of resveratrol along with zinc is suggested [89]. Its ability to modulate tumor niche via triggering immune responses is a suggested mode to use it as adjuvant along with other therapies [90].

Saponins

Saponins are plant derived compounds present in various structural forms in plants and these can also be used as foods. These compounds are diverse, and it can be chemically divisible into triterpenoid or steroidal glucosides. These compounds are available in nature as a mixture of other related compounds, or it can be available commercially commonly used as an adjuvant and administered parenterally with vaccines for parasitic diseases [91]. In a study, spleen cells that were enriched with saponins resulted in the inactivation of antigen for rabies demonstrating its therapeutic immunomodulatory role [92]. In a recent study its immunomodulatory effect against a seasonal flu H3N2 was demonstrated via T helper cell response and not via cytokine production [93]. Involvement of saponin containing nanoparticles in trigerring cellular response has led to its use as a vaccine component which is under clinical trials [94].

Alkaloids

Alkaloids is one of the most efficient materials among the active substances of the plants and is therapeutically significant [95]. Alkaloids consists of a class of secondary plant metabolic compounds, contains nitrogen atoms which is responsible for therapeutic applications, usually these atoms are combined to form a cyclic structure [96]. Inhibition of inflammatory cascade by isoquinoline alkaloids has been suggested to reduce the need of antimicrobial growth promoters due to its anti-inflammatory property that can promote gut health [97]. It is also suggested that alkaloids can be safely delivered for the treatment of glaucoma with the help of nanoparticles [98].

Biopolymers

Biopolymers are the type of polymers that are available naturally or produced by living organisms and these are also called as polymeric biomolecules. Biopolymer extraction can be from plants, trees, sea weeds, algae, bacteria etc. Biopolymers can be classified based on their source, and structural properties into a) polynucleotides, b) polypeptides, and c) polysaccharides. Polynucleotides like DNA and RNA consist of 13 or more nucleotide monomers, and these are known as long chain polymers. Polypeptides, composed of amino acids (short chain polymers) and polysaccharides composed of polymers and carbohydrates, which are bonded to form polymeric carbohydrate structure [99]. Some examples of biopolymers are cellulose, chitosan, glucan, pectin, gum arabic, etc. involved in multiple biomedical applications because of their extraordinary properties like biodegradability, low toxicity, biocompatibility, etc., [100]. They have immunomodulatory effects by enhancing immune response due to its controlled release properties [101] as explained in the following sessions. Few examples of biopolymers for its immunomodulatory role under clinical trials is presented as in **Table 1**.

Glucan

Glucans are homopolymers made up of simple sugar glucose molecule. *Saccharomyces cerevisiae*, is the major source of glucan and it is also found in other biological sources like bacteria, fungi, and many other plants [101]. One class of glucans that stimulate the immune system are β- glucans, the structural residues which are linked by (β(1, 3)) glycosidic bonds attached to the glucose residues on the side chain by β(1, 6) linkages [102, 103]. Active constituents in mushrooms, oats, barley, yeast, bacteria, and algae are the major sources of β-glucans that aid in boosting immunity. It is also noteworthy to realise that they paly a major role in developing resistance strains of microbes [104]. Synthesised β- glucan an analog of lentinan unit, showed an increased levels of chemokines and interleukins suggesting its role in facilitating innate immunity [105]. Regulatory role of these in cellular and humoral immune responses is demonstrated recently in fish model [106]. Pogue et al., recently [107] suggested the potential of administering glucan so as to increase resistance to disease by non specific innate mechanism of defense. It is emphasized that β- glucans structure play an active role in immunomodulatory function [108]. The possibility of encapsulation anti-cancer drugs in β-glucan nanoparticles to induce innate immunity is demonstrated in a study by *in vitro* studies [109]. It is also suggested that coating nanoparticles with β- glucans can improve the biocompatibility of nanoparticles [110].

Gum arabica

Gum arabica (gummy exudate) is procured from branches, stems of *Acacia senegal* or from any related species. Its main components include sugars, rhamnose, arabinose, and galactose along with a complex arabinogalactan protein which makes it water soluble polysaccharides. Along with glucuronic acid, it also contains minerals such as calcium, magnesium, and potassium thus being included in the medical applications category [111]. Protective role of this in patients (covid-19) for its immunomodulatory [112] is under clinical trials (NCT04381871). It is interesting to note that selected glycoproteins of this biomaterial is investigated for its excellent adjuvant role in mice for a probale cancer immunotherapy [113]. A detailed review on its drug delivery and tissue regenerative role is recently discussed [114]. Its immunomodulatory role is primarily by its action on dendric cells [115].

Pectin

Pectin, a complex polysaccharide is abundantly present on the cell walls of plants or any other certain variety of fruits or their peel extracts and these polymers are generally branched sometimes linear with diverse biological activities, includes immunomodulation activity. These are the various fragments of pectin are homogalacturonan, rhamnogalacturonan, xylogalacturonan, and apiogalacturonan [116]. In female mice, pectin and modified pectin was shown to increase proinflammatory cytokines - tumor necrosis factor, interleukins, and interferon indicating its beneficial effects in immunotherapy [117]. In another *in vivo* study, pectin extracted induced lymphocytes from bone marrow and spleen and triggered interleukin -10 [118]. Much have been discussed especially about the role of papaya pectin in immunomodulation for the prevention of dengue [119] and the extent of ripening can aid pectin interaction with toll like receptors that results in the reduction of inflammation [120]. Reduction of systemic inflammation and the radical scavenging

Table 1. Few examples of bipolymer immunomodulators under clinical trials

Type Of Polymer	Study objective	Summary	Dose	Result
Gum Arabic **(NCT04381871)** [68]	Role as immunomodulatory agent in (COVID 19) patients	Study the immunomodulatory, and anti inflammatory role of Gum Arabic against COVID 19 seropositive patients. To compare the effectiveness of a gum Arabica can be determined by given to half of the participants against placebo	As given as a supplement of 30 gram per day for 4 weeks. 110 participants will involve in the study. Comparative studies are followed with pectin till phase 2 & 3.	At phase 1 the gum arabic tend to cause a change in the level of tumor necrosis factor, interleukins. The time frame of 4 weeks was followed. Increased the immune response.
Pectin (NCT00277147) [131]	Pectin- typhoid conjugate (Phase I clinical trial) vaccine	Vaccines derived from polysaccharide conjugates. It is demonstrated as an efficient compound could be used in young children at large endemic regions.	25 healthy particiants around 18 to 45 years old were injected with pectin conjugate and importantly immunoglobulinG antibody's reaction with pectin were analyzed.	64% of the participants obtained increase than 4 folds rise of anti- IgG.
β-glucan (NCT00403689) [132]	Outcome on insulin: its effects on sensitivity, and inflammatory markers of metabolic syndrome	β D glucan from baker's yeast were isolated and the inflammatory markers and sensitivity were look over by the investigators. Increased C- reactive protein factors in obese patients were taken as indicators.	1.5g of β-D-Glucan was administered orally each day. 12 participants were involved in the studies	β -D-glucan induced changes in inflammatory markers, (adipokines) and gut hormones. These changes were altered by gene expression in adipose tissues. This results in changes in the sensitivity of the insulin.
Chitosan (NCT01578070) [133]	Chitosan as adjuvant-based vaccine delivery	A chitosan-based formulation with a vaccine to *Haemophilus influenza* type b and its adjuvant property were observed and studied. Shown to enhance the immune responses.	Study was conducted as phase A and phase B. In Phase A, 10 subjects were studied. In phase B, a randomized and single blind with 5 groups (20 subjects/group) with varying doses with or without antibodies were assessed.	The efficacy in serum was evaluated by calculating the antibodies ELISpot analyses showed improved interferon responses

activities of pectin rich in hesperidin is considered as an approach to combat cytokine release in covid-19 patients [121, 122].

Chitosan

Chitin, one of the most abundant polymers (naturally available biopolymer) available on the earth and is deacetylated to form chitosan. its uses in medical applications is mainly based on their structural characteristics, presence of cationic groups like amine, and it has better physicochemical properties [123]. Chitosan is considered as biodegradable biopolymer along with its properties like biocompatibility, bioadhesivity, bioactivity and low solubility. Due of its properties it shows a vast range of applications it is one of the main biopolymer extensively researched [124]. Proinflammatory, and antiinflammatory growth factors, cytokines, and chemokines, are induced thus branding it in immunostimulatory activity [125]. In a study, herpes simplex virus mice treated with chitosan, proved its immunomodulatory and stimulatory role [126]. In a recent review, a triple approach to combat covid-19 by chitin and its derivative chitosan is suggested [127]. It is also suggested that the induction of cell based

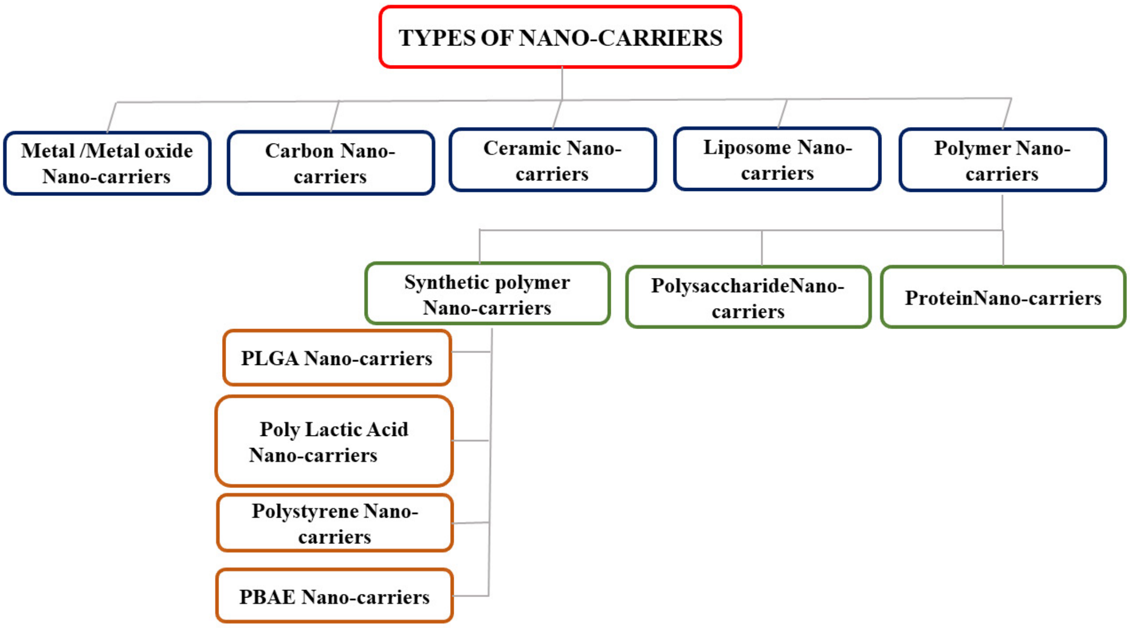

Fig. 1. Nanocarrier classes with immunomodulatory role.

immunity by chitosan is via stimulating T helper cells [128]. Chitosan nanoparticles is also shown to have boosted immune response and is shown to develop resistance against diseases [129] and is also suggested for its role as immunomodulatory response vaccine for cancer therapy [130].

NANOCARRIER SYSTEMS

Nanocarriers (N.C.s) are colloidal compounds that act as drug carrier system due to their submicron particle size typically <500 nm. N.C.s are extensively studied for its use in drug delivery to improve efficacy of drug [134]. N.C.s has the potential ability to alter the basic properties and bioactivity of the drugs and have emerged as advantageous vehicles to interact with cells and organs of immune system [135], hence finds applications as a carrier system for immunomodulatory agents. These N.M.s has ability to target specific immune cells, and is being considered for cancer immunotherapy. For this immunomodulatory role, many different N.M.s with a unique physical, biological, and chemical trait that can be constructed/engineered/tailored according to the target needs for stimulating the immune system [136]. The micro and N.C.s provide great opportunities in modifying the immune system during transplant, autoimmune condition, infectious disease, and cancer condition, etc. N.M.s synthesised via bioroute have also achieved familiarity due to their biocompatibility, cytocompatiblity, nature friendly, superior bioactivity than in some instances chemically synthesized N.M.s that donot follow sustainable route of synthesis [137]. It is to be realised that nanocarriers has capability to modulate the immune response to generate a tolerogenic effect, based on their entirely conjugated signals [138]. Few nanocarrier classes (**Fig. 1**) and its immunomodulatory role is provided in this section.

Metal or metal oxide based nanocarriers

Metal nanoparticles are a type of nanoparticles derived from metals (Au, Ag, iron oxide, Cu, etc.) is used for biological and medical applications. The properties of nanomaterials such as a) size, b) charge, c) hydrophobicity, d) hydrophilicity, and e) the steric effects of nanoparticles aid them to interact with the immune system [139, 140]. Some examples of metal/metal oxide-based nanoparticles include nano silver, nano gold, and nano-metallic oxides. It should also be noted that the most widely manufactured nanomaterials of titanium dioxide is shown to induce immunotoxicity by invoking inflammation [141]. In an yet another interesting study, gold nanoparticles synthesised using a grass extract aided in the retainment of many active principles of the extract immobilised on nanoparticles and aiding in suppressing cytokines a proinflammatory agent from macrophages and natural killer cells [142].

Lipopolysaccharide a well known inflammatory causative agent was suppressed *in vivo* by gold nanoparticles carefully engineered with surface that is hydrophobic as well as zwitterionic demonstrated immunomodulatory effects [143]. Size based role of gold nanoparticles as antigen carriers as well as adjuvants was demonstrated in a study [144]. Another set of nanoparticles with excellent optical and antimicrobial properties is silver nanoparticles. In a study conducted in mice, cytokine release in cancer induced mice was found to be suppressed by silver nanoparticles [145]. In a recent study, silver nanoparticles is shown to decrease deleterious effect of coronavirus by reducing cytokine release, inhibition of viral entry and by its immunomodulation of host virus leading to its apoptosis [146]. In another study, copper and silver nanoparticles were found to impart toxicity to tumor cell lines, through its immunomodulatory role though its mechanism unclear [147]. Recent findings suggests that these metal nanoparticles are effective against coronavirus due to its anti-inflammatory and immunomodulatory role [148]. It is noted in the case of iron oxide nanoparticles immune stimulation as well as immunosuppression was observed, this is due to the size effect as well as the method of engineering nanoparticles with functionalities. It was also found to accumulate in stem cells or tumor specific cells thus providing an immunomodulatory effect in enhancing tumor eradication [149]. In a novel approach, hollow shaped iron oxide nanoparticles for nitric oxide release were prepared and was found to reprogram tumor associated macrophages [150]. In a recent study very small iron oxide nanoparticles was found to trigger apoptosis of undifferentiated hemopoietic stem cells and inflammation was mainly caused by macrophages of spleen suggesting size effect in immunomodulation [151].

Carbon based nanocarriers

Carbon nanotubes are considered as biomaterials, and this attracted ample attention due to their excellent properties. Low solubility, dispersion, toxicity of carbon nanotubes is an hindrance in its biological applications [152]. Accordingly functionalization of these can improve biocompatibility as well as modulate the immune cellular functions, either as a stimulating or suppressive response [33]. The antioxidant properties of carbon-based nanomaterials, is better than the dietary antioxidants and find applications in inflammatory diseases [153]. The role of carbon nanotubes in stimulating cell specific stimulation of immune system finds place in future to be used as immunotherapeutic agents [154]. Fadel et al ., [155] investigated in mice that the carbon nanotube along with a polymer as a composite has the ability to mimic as an antigen presenting cell (artificial) and aid in proliferation of T cells indicating its clinical applications. In another study, it was found that carbon nanotubes when functionalised did not affect lymphocytes but triggered proinflammatory cytokines [156].

Ceramic based nanocarriers

Ceramic nanoparticles also contain inorganic nanoparticles, besides metals, metal oxides, and metal sulphide N.P.s, and these are synthesized at different size, shape, with different pore size [157]. Basically, ceramic N.P.s can be classified into inert, resorbable ceramic N.P.s [158]. They can modulate immune system either defensive way or via stimulating inflammatory response, dose play a major player in immunomodulation and time of exposure also plays a major role [159] [160]. Immunomodulatory role of bioceramics aids in bone regeneration which is also considered as an alternative for bone grafts [161].

Liposome based nanocarriers

Liposomes are spheroidal vesicles formed from bilayer membranes of lipids and has ability to entrap and encapsulate both hydrophobic as well as hydrophilic agents protecting the molecule from enzymatic degradation. Advantageous of liposomes for drug delivery systems includes – a) stealthness, b) biocompatibility, c) high drug loading efficiency, d) increased stability in biological systems, and e) controlled release kinetics properties, and many drugs are based on these is available in the market [162]. Once such example is liposomal formulation of amptothericin [163]. Liposomes can be made as cationic liposomes, anionic liposomes or neutral liposomes depending upon the type of phospholipid involved [164, 165]. Although pharmacological profiles of drugs lodaded in liposomes have therapeutic profiles, it is unfortunate that the drugs actually reach mononuclear phagocytic system [166]. Detailed review by Zahednezhad et al., provides insight on various aspects of its interaction with the immune system is discussed [167]. Although there are several concerns, liposomes are considered as a predominant choice of biomaterial related to immunotherapeutic nanosystems in cancer due to its negligible toxicity [213].

Polymer based nanocarriers

Polymeric nanoparticles are synthesized artificially through various biological sources. These nanosized spherical particles size are scaled as 10 to 500 nm. It can either be synthetic, natural or a composite material (natural and synthetic materials), the major characteristics of the polymeric N.P.s are biodegradability, solubility, biocompatibility, but the copolymers encompass low water solubility. These advantages impart them as a potential candidate for carrying therapeutic agents as a carrier for drug delivery (targeted). Drug loading capacity, encapsulation efficiency and releasing ratio can be tuned by modifying the polymeric carriers [168]. Polymers can be classified into a) synthetic, and b) biodegradable nanoparticles. Example of synthetic polymers or artificially synthesized polymers are polyesters, and polyaminoacids are natural proteins or polysaccharides. Some of the examples of biodegradable or biocompatible polymers are PLGA, chitosan and other plant derived polysaccharides (pectin, glucan, cellulose, gum exudates). These polysaccharides have been extensively studied, its properties identified and structural characteristics decoded and is recommended immunotherapy [169]. Polymeric nanoparticles also has ability to produce or modulate immunocellular responses and exhibit high potential in cancer and other infectious diseases as immunotherapy [170].

Synthetic Polymer Nanocarriers

These can be synthesized chemically, and novel properties is attributed to chemical composition that is engineered. They are tuned for sustained release of drugs/agents at the target cells, tissues, or organs by their stimuli responsiveness properties [171]. These novel properties of polymeric nanoparticles determine their functions based on their structural and functional characteristics (like degree of polymerization, and groups present) and majorly the size and shape of the poymer depends on the methods of synthesis [172]. Their involvement in modulating immune system as a vaccine or vaccine adjuvants or as development of immunotherapeutic moiety for diseases has been investigated widely.

PLGA (Poly D, L-lactic co-glycolic acid) Nanocarriers

PLGA nanoparticles are safe, stable, and biodegradable drug carriers. PLGA nanoparticles as a polymeric drug delivery systems helps to decrease transplant rejection by controlling systemic effects [173], and therefore is an important carrier approved by FDA [174]. Honey loaded cationic PLGA polymeric nanoparticles known for its immuno-adjuvant activity by T helper cells immune response, also stimulated interferons, interleulins and TNFα by activating macrophages [175]. Adjuvant activity of these polymers with antigens/polysachharide entrapped for H9N2 vaccines in chicken resulted in humoral as well as cellular immune responses [176]. Curcumin loaded PLGA nanoparticles modulated cell-mediated immune response at varying concentrations of 5 or 10 mg/kg and these nanoparticulate system significantly enhanced humoral immune response [177]. Recently Maleki et al., [178] have reported the possibility of co loading paclitaxel and etoposide on mPEG-PLGA nanoparticles. The co-loading of two drugs enables to overcome pharmacokinetic and physiological limitations of individually loaded drugs and enhancement of therapeutic efficacy in the treatment of intracranial glioblastoma. It is also today possible to prepare electrospun fibers and optimize their preparation using artificial neural networks model [179]. Many studies suggest PLGA based nanoparticles for use as drug delivery/carrier system for delivering antigens with good stability.

Poly lactic acid nanocarriers

Polylactic acid based nanoparticles (PLA-NPs) has a great potential in maintaining therapeutic levels of drugs used in nanomedicines by sustained release of drug molecules at different time intervals [180]. In a study conducted in rats, tetanus vaccine antigen was encapsulated in these nanoparticles coated with polyethyene glycol as a nasal vaccine delivery vehichles that exhibited prolonged immune response with high load of antibodies [181]. Anionic nanoparticles of PLA were prepared containing DNA or protein antigen and was tested against animal models against HIV protein. High levels of interferon gamma produced in animals indicate the role of surface charge in vaccine development using nanoparticles [182]. In an interesting study, inhalable PLA along with PLGA nanoparticles were prepared with the surface of nanoparticles carrying hepatitis B surface antigen that indicated a continuous release of this antigen for nearly 42 days which makes it a potential candidate for vaccine development [183].

Polystyrene nanocarriers

Polystyrene is an aromatic polymer which can be prepared by polymerization of monomers of styrene. It is one of the most enormously used types of plastic. It is used in medical devices such as laboratory equipments due to its inertness, biocompatibility, and hydrophobicity, for biological applications it can easily undergo oxidation and provide a surface for the cells to grow [184]. These nanoparticles were found to target immune system in marine organisms [185]. An *ex vivo* research revealed a surge in cytokine release, suggesting its immunomodulatory role with a significant damage to DNA in human blood [186]

Poly (α-amino ester) nanocarriers

Poly (α-amino ester), a novel class of synthetic polymers, are cationic polymers has pH-dependent solubility and hydrophobic polymer [187]. Wang et al., designed pH responsive co-polymers of these nanoparticles along with interleukin -2 as a cargo and found that they could specifically release the payload in the tumor microenvironment [188]. In another study, it was found that curcumin encapsulated in these nanocarriers did not register any burst release of curcumin and the release of it was consistent for 48 hours [189].

Polysaccharide nanocarriers

Biopolymeric nanoparticles possess multiple application in nanobased delivery (drug) systems and can be administred as drugs or vaccines. The presence of biologically active materials as nanoparticles enhances its activity by specific targeting and delivery at targeted sites. Although they are reported to be less immunogenic [190], when it comes to therapeutic applications they can increase immune response by the controlled release of cargo is involved in modulating the immune system [191]. Zwitterionic polysaccharides can also interact with T cells to produce interleukin 2. Detailed discussion on the polysaccharides from microbes and plant is presented recently by Sindhu etal., [192]. Polysaccarides based nanomedicine can also efficiently carry and deliver adjuvants, cytokines, nucleic acids, and as well as intrinsically modify immune system and can be used in cancer immunotherapy [193]. It should also be noted that polysaccharides can be capped on the nanoparticles like silver can exhibit immunomodulatory properties against resistant strains of bacteria which helps in healing process of wound [194]. Polysaccharide mediated engineering of nanovaccine is the most researched topic for a better design vaccines with adjuvats [195].

Protein nanocarriers

Amphiphilic nature of protein nanocarriers makes it one of the attractive candidates as nanocarriers as it can associate with drug as well as solvent [196]. Bio-nano interface of protein along with components of immune system is a well researched topic [197]. Polymers like polyethylene glycol has gained attention because of its stealth effects is largely attributed to adsorption of protein on surface of these nanoparticles [198]. Leukocyte associated immunoglobulin like receptor an immune receptor interacts with collagen and understanding this binding is suggested in the design of collagen based biomaterials for immunomodulation [199]. Recently, cell membrane based nanoparticles that are classified as biomimetic materials is gaining significant attention for use as nanocarriers due to its rich composition of biomacromolecules especially protein which efficiently acts as a communicator for the bio-nanointerface interaction which can positively contribute to immune based therapy [199]. Few examples are presented as in **Table 2**.

ROLE OF NANOCARRIERS IN IMMUNOMODULATION

The interaction of nanosystems with immune system results in altering activity of the immune cells of immune system either by activating or supressing the activity of the cells. The N.P.s have large surface area and strong oxidative property than normal or bulk particles, which can interact with cells which are majorly responsible for modulation or suppression in immune cells [200]. Nanoparticles that can trigger inflammatory responses via release of cytokine or chemokine or even oxidative stress is tapped for killing tumor cells [201, 202]. Components involved in immunomodulaton by nanoparticles [203-205] is presented (**Fig.2**).

FACTORS AFFECTING IMMUNOMODULATION OF NANOPARTICLES

Immunomodulation by nanoparticles

Table. 2. Immunomodulatory effects of protein nanocarriers – Few examples

Type of protein nanocarriers	Drug/material	Study	Comparative analysis	Mechanism of action
Spider silk	Recombinant variant of spider silk proteins	Human blood	Different charged variants of protein used.	Biomolecular corona affected by the type of variant, based on charged groups and the extent of charged groups present [206].
Albumin with aluminium	Photosensitizer	Mice	Compared with iron albumin nanocarriers or free photosensitizer.	Induction of immune related response after phototherapy [207].
Silk fibroin on titanium surface	Peptide	Mesenchymal stem cells from rats and implantation to rats	Silk fibroin treaed group when compared to groups treated with only titanium implants showed higher experesson of macrophage receptor.	Inflammation regulation at injured site [208]
Collagen-Synthetic polymer	Hydroxyapatite	Mouse model with subcutaneous implantation of nanogel	compared with subcutaneous implantation of nanogel without hydroxyapatite	Moderate activation of immune system. Collagen stabilised nanogel [209].
Gelatin	Oligonucleotides	Mice	Compared to oligonucleotides treated mice	Increase in adaptive as well as innate immunity [210].
Zein	-	Mice	Different sized nanoparticles with different doses	Did not register any immunogenicity for different sized nanoparticles but dose mediated immunogenic response noted [211].

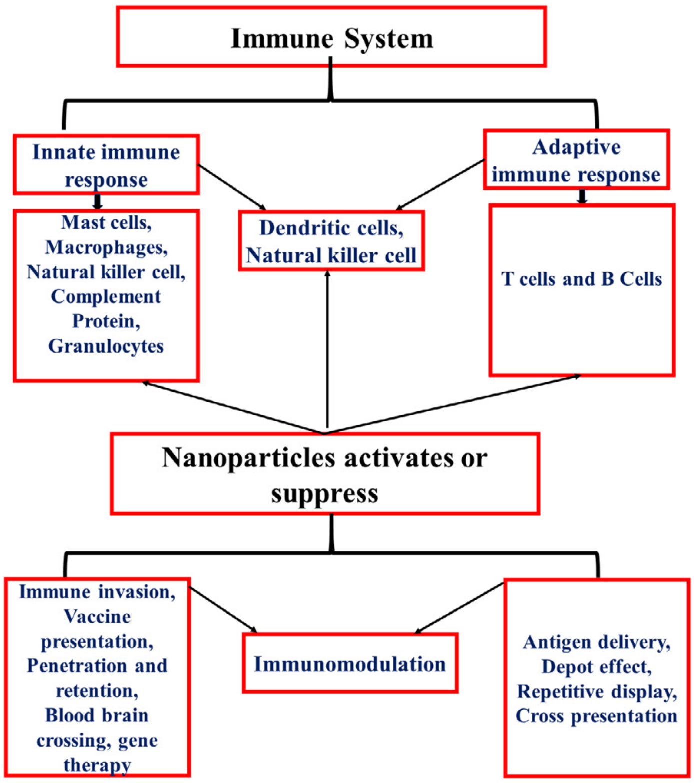

Fig. 2. Components of immune system and immunomodulatory role of nanoparticles

depends on fabrication/synthesis/preparation of nanoparticles methods that involves modification to improve the targeting of vaccine for example, nanoparticles to the dendritic cells. The nature of nanoparticles such as chemical signature, its size, water solubility, chemistry, shape, and protein-binding ability everything plays a role in eliciting immune response [212]. Few important characteristics of nanoparticles and their effect on immune response is discussed here.

Effect of size/shape, composition, and surface chemistry of nanocarriers on immune response

Nanoparticles primarily interact with antigen presenting cells dentritic cells which is mainly due to the physiochemical properties of nanoparticles [213]. For lymph node targeting around 20 – 40 nm sized particles were found to be ideal [214] and nanoparticles of similar size was found to be accumulated in dentritic cells [213]. Baranov et al., recently reviewed the role of surface properties, shape and size of nanoparticles in the uptake of pathogen, similarly nanoparticles too have a role in the T cell activation [215]. In a study, three different sized very small gold nanoparticles 5 nm, 15 nm and 30 nm were monitored in cell lines for uptake and it was found that 5 nm sized nanoparticles downregulated toll like receptor expression suggesting its role as adjuvants in cancer therapy [216]. In an interesting recent review the role of size, shape, sequence, stochiometry, and surface properties linked to immunostimulation was thoroughly discussed [217]. Flexible nanoparticles by way of using biomimetic nanoparticles can trigger specific immune responses which might pave way to alternative immunotherapies [218].

Route of exposure

Gold nanoparticles designed with aptamers that were specific to the dendritic cells registered an improved response in mice via T helper as well as T regulatory cells that was delivered under the tongue (sublingual) [219]. For instance, in the case of zein nanoparticles for a study conducted in mice, parenteral or subcutaneous or intramascular route showed different types of immune response and it was found that parenteral administration resulted in a long-term immune response and it was suggested that either functionalisation or reduction in the dose is required to eradicate undesired immunogenicity [220]. Chenthamara et al., provided a detailed review on the type of nanoparticles and the challenges associated with each nanoparticle with respect to the route of administration of them for drug delivery and care need to be taken in drug design based on the route of administration [221]. In a study, PLGA nanoparticles was encapsulated with an antigen and threitolceramide indicated that intravenous administration of nanoparticles was needed for invoking a proper anti tumor immune reaction [222]. Many nasal covid – 19 vaccines are under trials and results registered activation of mucosal response including inhibition of viral replication [223]. Hence, all the parameters and properties of nanoparticles need to be considered to take nanoparticles forward to clinical trials.

FDA approval of biomaterial immunomodulators

Emphasis is given for those biomaterials that are biodegradable and FDA approved [224]. Biomaterials are approved by FDA for specific properties like the case of PLGA for sustained release properties [225]. An FDA approved biomaterial as dental fillers, hyaluronic acid was second most popular choice of material among women as a cosmetic injection [226]. An interesting feature of a biomaterial like chitosan getting a nod as wound dressers is due to its biocompatible property [227]. Scaffolds based on collagen as biomaterial got approval from FDA as it can integrate well with native tissues for regenerative purpose. Research in this field is very vast such that the kind of architecture of collagen whether as hydrogels or as sheet is also looked at [228]. An extensive study on recent trends in biomedical use of biomaterials is presented in a recent review and the knowledge gap from the review is understanding the functionality of biomaterials can help in vascularization of new construct [229].

CONCLUSION

The manuscript describes the role of immunomodulators and how nanocarriers effectively enhance the activity of natural and synthetic immunomodulators. The significant advantages of each class of immunomodulators and the enhancement of activity through a range of nanocarriers is discussed. Way forward for clinical application of nanocarriers is to optimize the route of exposure and seeking necessary regulatory clearances through better understanding of characteristics of nanocarriers on immune response.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest

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