Journal of Phytonanotechnology and Pharmaceutical Sciences 3(2): 1-7, 2023

Online ISSN:2583-0376

http://jpps.ukaazpublications.com

DOI: http://dx.doi.org/10.54085/jpps.2023.3.2.1

Journal of Phytonanotechnology and Pharmaceutical Sciences

Review Article : Open Access

Nanomedicines from natural sources for effective therapy in the management of immunomodulatory activity

Sneha Nawale*, Swathi Naraparaju◆ and Akhila Thotakuri*****

**Department of Pharmacognosy, Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad-500090, Telangana, India*

***Department of Pharmaceutical Chemistry, Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad-500090, Telangana, India*

****Department of Pharmacology, Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad-500090, Telangana, India*

Article Info

Article history

Received 19 April 2023

Revised 23 May 2023

Accepted 24 May 2023

Published Online 30 June 2023

Keywords

Immune response

Carbon nanotubes

Graphene oxide adjuvant therapy

Chitosan

Cancer immunotherapy

Smart nanoparticles

Abstract

Immune responses are corrective interactions of the innate immune cells and the acquired immune system. Presently, more interest was shifted towards the development of the immune system against toxicity over exposure to noxious chemicals, drugs, environmental pollutants and other factors such as stress, malnutrition, genetic variability, lifestyles, environmental pollutants and chemotherapy exposure which alters immune responses. Immunotherapy has emerged as a valuable tool for the prevention and therapy of a number of ailments, such as inflammation, cancer and autoimmune diseases. Traditional medicinal plants have been extensively explored for immunomodulatory potential with the use of nanosystems that can enhance the therapeutic effects and concurrently overcome many obstacles of phytocompounds, such as poor water solubility and bioavailability. This review highlights a few recent advances in nanotechnology utilizing natural sources for immunostimulation.

1. Introduction

The immune system is a remarkable network of biological processes that protects the organism against diseases. It is also a defense system within the body and also outside the body of all the vertebrates, protecting from invading foreign bodies (Sneha Anarthe *et al*., 2016). The transformation of the immune system provides the outcome involving the changes in responses such as induction, expression, amplification, inhibition or alteration of any part or in any stage of the immune response. So, immunomodulation encloses all the therapeutic alterations aimed at modifying immune responses. Immunomodulators act as controllers for the immune system and its effect inside and outside the body (Sneha Anarthe *et al*., 2017). There are two types of immunomodulators based on their effects or mode of action: immunosuppressants and immunostimulants. The inherent applications of immunomodulation in clinical practice include the re-creation of immunodeficiency (AIDS treatment) and conquering regular or excessive immune function (autoimmune disorders treatment). Immunological adjuvants containing the specific immunomodulators with antigens are administered to boost the immune response to the vaccine constituents (Dacoba *et al.,* 2017).

Several barriers protect organisms from infection, including mechanical, chemical and biological barriers. But, the recent inventions in nanotechnology have played a major role in the intervention of new methods in immunomodulation which is growing exponentially (Figure 1). Nanotechnology governs the invasion between pathogens and immune cells. The immune cells take up the nanocarriers of the nanotechnology and modulate their responses. Further, coupling nanocarriers with targeting moieties can favor their preferential access to specific immune cells and their populations. The flexibility in nanotechnology offers boosting of the desired aspect of immunomodulation in which (I) the immune system is activated to produce an immune response against a specific antigen, or (II) the induction of immune tolerance against antigens and immune active drugs (Figure 2). The scope of nanotechnology to implicate divergent responses arises from its creativity, gained through amalgamation and cautious selection of its molecular components and physicochemical properties of the nanosystems (Sengupta *et al.,* 2022).

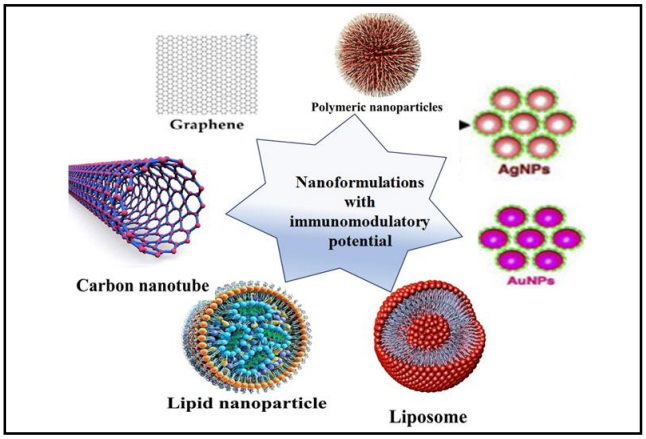

Figure 1: Various types of nanoformulations used as immunomodulators.

Corresponding author: Dr. N. Swathi

Associate Professor, Department of Pharmaceutical Chemistry, Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad-500090, Telangana, India

E-mail: swathi8006@grcp.ac.in

Tel.: +91-98490 59163

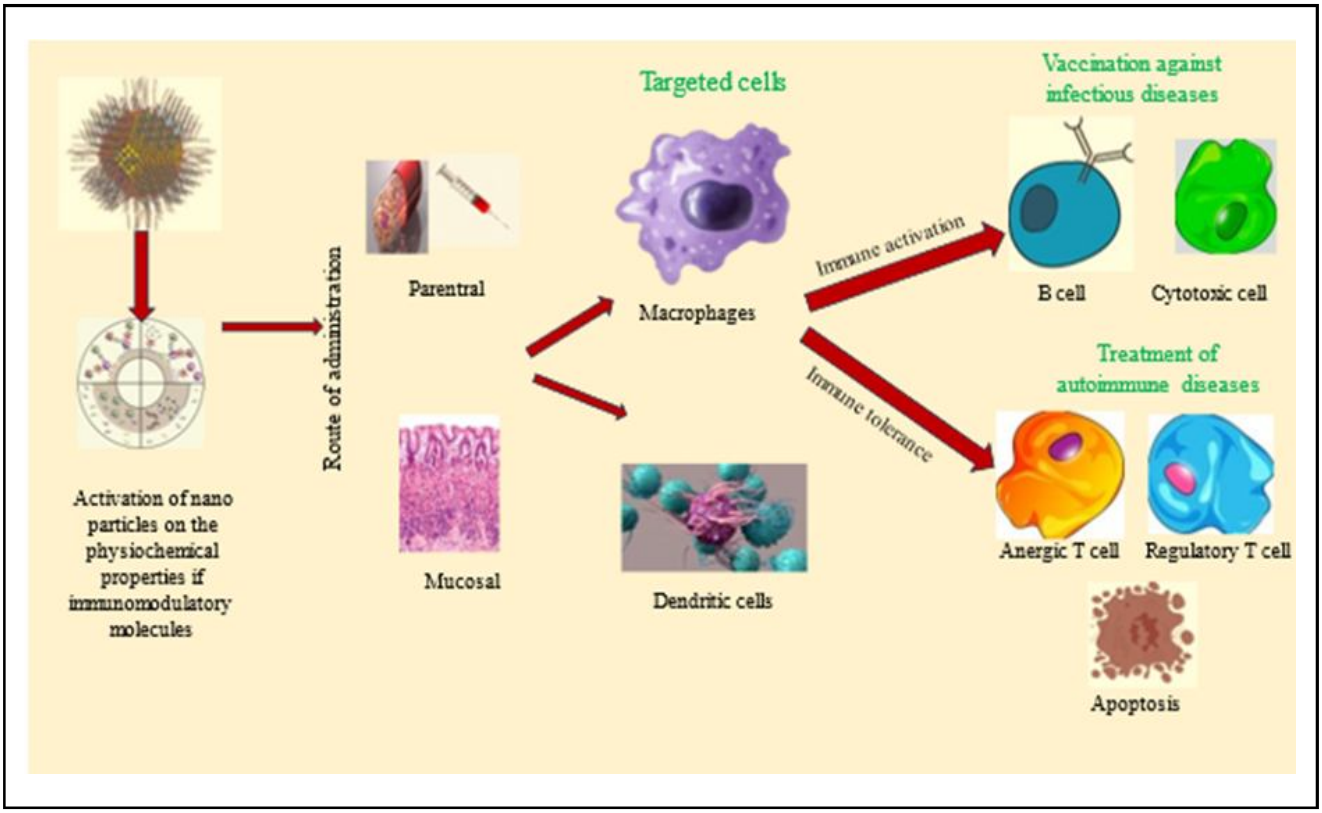

Figure 2: Mechanism for activation of immune cells by nanoformulation.

2. Nanoformulations with immunomodulatory potential

2.1 Functionalized carbon nanotubes

The influence of carbon nanotubes on the immune system has been of interest in the last decade (Alina Andersen *et al*., 2012; Hélène Dumortier, 2013; Marco Orecchioni *et al*., 2014; Elidamar Nunes de Carvalho Lima *et al*., 2021). Graphene sheet composed of carbon atoms is rolled up to from a cylinder-like structure to make carbon nanotubes (CNTs). These acting as support materials have various properties, such as a unique hollow structure and a peculiar surface area with chemical stability. CNTs are also beneficial for various antigen-delivery applications.

The use of CNTs in life sciences is limited due to difficulty in manipulation as they have poor aqueous solubility. To make use of CNTs beneficial for the scientific world, several strategies are currently being used. The most important among them utilizes the non-covalent and covalent functionalization of CNTs (Tasis *et al*., 2006). The modifications involve various chemical substances, such as surfactants, copolymers, nucleic acids, proteins, peptides and drugs are used to enhance their solubility, dispersibility, and biocompatibility. Microarray technology utilizing human immune cells was employed to track the transcriptomic change induced by four such types of functionalized CNTs (*f*-CNTs) (Mario Pescatori *et al*., 2013). Both adaptive and innate immune responses were investigated in Jurkat cells (T lymphocyte cell line) and THP1 (monocytic cell line), respectively. Real-time PCR of selected genes was utilized to validate the data. ELISA technique was utilized to assess the levels of IL6, IL10, IL1β and TNFα by THP1 and primary monocytes to achieve protein level confirmation and results corroborating with gene expression data.

The functioning of CNT compositions as modular vaccines was also documented (Tarek Fahmy *et al*., 2017). They were found to be effective as artificial antigen-presenting cells, thereby suggesting their probable role in *ex vivo* or *in vivo* activation of T cellsfor adoptive or active immunotherapy.

Researchers have identified the potential of CNTs with a support material Lentinan (β-1,6-branches on β-1, 3-glucohexaose), extracted from the mushroom *Lentinula edodes*. Clinically, it has been used as an immunostimulatory agent in various countries like Japan and China. The lentinan-bonded multi-walled carbon nanotubes (MWCNTs) were evaluated for their ability to boost immune response *in vitro*. The results showed that MWCNSTs carry sufficient amounts of antigen by penetrating into dendritic cells. In addition, the immune reaction (*in vivo* and *in vitro*) of MWCNTs is compared with C-MWCNTs, (31.8 µg/ml), L-MWCNTs (35 µg/ml), and lentinan (3.2 µg/ml). Significant improvement in the accumulation of antigens and enhancement of cellular and humoral immunity was observed as a result of L-MWCNTs treatment (Jie Xing *et al*., 2016).

Mannose receptors are playing a key role in the identification of pathogens and presenting antigens. They are generously expressed on macrophages and dendritic cells. Haibo Feng *et al*. (2022) synthesized the mannose-modified carbon nanotubes (M-MWCNTs) and evaluated an antigen delivery system for *in vitro* and *in vivo* studies. Significant improvement in the dendritic cells maturation and elevated values of antigen-specific antibodies and cytokines *in vivo* in mice were observed. The results of the study indicated that M-MWCNTs activate humoral and cellular immune responses and thereby suggested their use as a powerful antigen-targeted delivery system (Haibo Feng *et al*., 2022).

Some of the undesirable effects of CNTs (including MWCNTs) such as immunotoxicity, inflammation, and oxidative effects were reversed by coupling CNTs with natural flavonoids. Quercetin, a natural flavonoid present in various vegetarian sources, is known for its antioxidant, anti-inflammatory and immunomodulatory profile. Its immuno-protective effect was investigated on pristine MWCNTs-induced immunotoxicity in mice at selected dose levels [0.5 mg/kg and 0.25 mg/kg body weight, intraperitoneally]. After the administration of quercetin (30 mg/kg BW, IP for 2 weeks) these detrimental effects were relieved, as indicated by decreased spleen weight, lipid peroxide malondialdehyde and enzymes levels as glutathione, superoxide dismutase, and catalase, reduced mRNA levels of inflammatory markers in the spleen, downregulated expression of immunomodulatory genes transforming growth factor-beta (TGFß), COX2, and IL10. Histopathological studies indicated decreased mononuclear cell infiltration, degenerative changes and lymphocytes depletion was restored in the spleen, along with the elevated levels of total leukocytes, lymphocytes, and neutrophils, elevated serum levels of IgM, IgG, and IgA, and antioxidant markers. The outcomes of the study indicated the potential of quercetin to reverse MWCNTs-induced oxidative, inflammatory and immunotoxic effects (Amira *et al*., 2022).

2.2 Graphene oxide-based adjuvant formulations

The immune effects of graphene oxide (GO) have been revealed through various literature. Its favorable features like biocompatibility, large surface area and exceptionally good adsorption capability encourage its use in vaccine and drug-delivery systems. But, inflammation at the site of injection and the development of oxidative stress limits its use. Carnosine is a dipeptide made up of amino acids α-alanine and histidine. The antioxidant properties of carnosine are well-documented (Vistoli *et al*., 2013). To take advantage of the immune properties of graphene oxide, it can be given in the form of adjuvant therapy. The ultrasmall graphene oxide covalently bonded with carnosine (GO-Car) was mixed with an antigen ovalbumin (OVA) and the resulting adjuvant formulation (OVA@GO-Car) was investigated in mice model. OVA-specific antibody response, lymphocyte proliferation efficiency, and $CD4^+$ T and $CD8^+$ T cell activation were promoted as a consequence of this treatment. The absence of allergic response, inflammatory redness/swelling, elevated surface temperatures, physiological anomalies of blood, and remarkable weight changes were noticed in the GO-Car adjuvant therapy. Further, it was observed that lung, muscle, kidney and spleen damage were reduced after modification with carnosine. The results of the study demonstrated GO-Car as a safe adjuvant and it can efficaciously reinforce humoral and innate immune responses to counter antigens *in vivo*. The graphene oxide adjuvant therapy with lentinan is also well-proven, as the latter has immunity-enhancing effects (Meng *et al*., 2016).

Zhenguang Liu and his team reported graphene oxide grafted lentinan (GO-LTN) as an adjuvant and tested its influence on the *in vitro* and *in vivo* immune response. The *in vitro* results of this formulation showed that it promoted antigen uptake in macrophages and also improved the efficiency of its application. A sustained and long-term immune response was observed by GO-LNT/OVA formulation over GO/OVA *in vivo* studies. Thus, the use of GO-LNT formulation as a safe and effective vaccine-delivery system was well demonstrated in this study (Zhenguang Liu *et al.*, 2020).

2.3 Gold nanoformulations

Nano size is playing a significant role in several domains due to physicochemical and electronic properties and its surface area to volume ratio. Isolation of *Bipolaris tetramera* KF934408 (phosphate solubilizing fungus) from rhizospheric soil utilized a nanotechnology tool. Gold (AuNPs) and silver nanoparticles (AgNPs) of this fungus was synthesized by using redox reactions. Both the gold (58.4 and 261.73 nm) and silver (54.78 nm to 73.49 nm) nanoparticles were characterized for shape and size and were further evaluated for their antibacterial and antifungal potential (Faria Fatima *et al*., 2015). The antimicrobial activity of AgNPs was proved to be signficant and moderate antimicrobial action with no antifungal activity was observed with AuNPs. Cytotoxicity studies performed using J774 and THP1 α cell lines disclosed that AuNPs were safe at both the test doses, while a dose-dependent potential was noticed for AgNPs. The outcomes of the study demonstrated that metal nanoparticles synthesized by the fungus can be employed as an economic and safe immunomodulatory delivery vehicle.

Macrophages and natural killer (NK) cells are one of the main components of the innate immune system. Decreased levels of pro-inflammatory cytokines are beneficial for several diseases, *viz.,* inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, *etc*. AuNPs of *Hypoxis hemerocallidea* extract were investigated to demonstrate its immunomodulatory activity. Various optical and spectroscopic techniques were utilized to confirm the AuNPs of *Hypoxis hemerocallidea* and its metabolite hypoxoside. The immunomodulatory effects of *H. hemerocallidea* extract and AuNPs (average size 26 ± 2 nm) proved that all four treatments decreased pro-inflammatory cytokine amounts in the macrophages, whereas the hypoxoside AuNPs reduced cytokine responses in NK cells (Abdulrahman *et al*., 2019).

There were various reports on the biological activity profile of red algae-based AUNPs. Three kinds of AuNPs of red algae; namely, *Chondrus crispus* Stackhouse (CC), *Gelidium corneum* (Hudson) J.V. Lamouroux (GC), and *Porphyra linearis* Greville (PL) were screened for anti-inflammatory and immunomodulatory potential. The synergistic and antagonistic potential of CC-AuNPs, GC-AuNPs, and PL-AuNPs were measured. The results proved the significant potential of these NPs as immunotherapeutic agents (Rudtanatip *et al*., 2018; Abdala Díaz *et al*., 2019; Noelia González-Ballesteros *et al*., 2022).

Cancer immunotherapy is used to combat cancer by activating autoimmune responses. Adjuvants, cytokines and vaccines were designed and studied for immunomodulatory potential. Various limitations of cancer immunotherapy, such as uncontrolled immune responses, limited half-life, drug instability and rapid drug clearance have been overcome by loading immunomodulators with AuNPs. Gold nanoplatforms, *viz.,* nanocages, nanorods, nanoshells and nanospheres were extensively used in cancer immunotherapy. AuNPs are used as vehicles for delivering antigens and adjuvants to facilitate or activate the cytotoxic T lymphocytes and boost the immune system by killing tumor cells, which proved the utility of AuNPs as a cancer immunotherapeutic agent (Akshita *et al*., 2021).

The utility of AuNPs has been extended to vaccine preparation. They are used as adjuvant for designing effective vaccines by various researchers and prepared high-affinity antibodies to partial and complete antigens. Colloidal gold was conjugated with CpG oligodeoxynucleotides (ODNs) to study its immunological effects

further. The impact of various composites of AuNPs and CpG ODNs 1826 and shape and size of AuNPs on the immune response was also explored. In a study, mice were injected with BSA antigen conjugated with gold nanorods, nanoshells, nanospheres, and nanostars (Lev Dykman *et al*., 2018). Reduced levels of antibody titers are found to be in the sequence AuNPs-50 nm>AuNPs-15 nm> nanoshells> nanostars> nanorods> native BSA was observed. Results proved 50 and 15 nm gold nanospheres are good antigen carriers and can be adjuvant for immunization. Mice immunized with BSA-AuNPs and CpG-AuNPs conjugates have shown the highest levels of anti-BSA antibodies titer.

2.4 Silver nanoformulations

Omoniyi and his coworkers investigated silver nanoparticles (AgNPs) of *Labeo rohita* extract for its immunostimulatory potential. The work emphasized on the effect of growth, the immune genes expression levels, cellular ultrastructure, and infection risk from *Aeromonas hydrophila*. Fish of suitable average weight (30.1 ± 3.26 g) were fed for 56 days with diets and various doses of AgNPs inclusion levels (0, 10, 15 and 20 µg/kg). After the 56th day, growth, immunological and histological and protective immune response against *A. hydrophila* was screened. Immunological and oxidative parameters, SOD levels and catalase levels decreased with increased doses of AgNPs in the liver, and a decrease in catalase level in the gill. Gill, liver, kidney, and muscle of fish-fed diets combined with AgNPs, showed that levels of interleukin-8 and cyclooxygenase-2 were enhanced. These findings proved that a diet with AgNPs of the herbal extract (at 10 and 15 µg/kg) improved growth, health, and the protective immune response against *A. hydrophila* (Omoniyi Michael Popoola *et al*., 2023).

2.5 Chitosan nanoparticles

Chitosan is a linear polysaccharide in which acetylated (N-acetyl-D-glucosamine) and deacetylated (β-(1 $\rightarrow$ 4)-linked D-glucosamine) units are randomly arranged (Shahidi Fereidoon and Synowiecki Jozef, 1991). The basic amino moiety of the chitosan is protonated to make neutral solutions. This makes chitosan water-soluble and allows for its rapid binding with negatively charged surfaces (Dong Woog Lee *et al.,* 2013; Chanoong Lim *et al*., 2021).

The immune system restoration capacity of bioactive compounds was identified in various medicinal plants. But, their use is minimized because of their instability in the gastrointestinal tract. Chitosan-based nanoparticles (CNPs) of various drugs showed improved pharmacokinetic and pharmacodynamic profiles. The immunomodulatory activity of the chitosan-nanoparticles of leaves of *Ziziphus mauritiana* was determined (Bhatia *et al*., 2011). The immune system of Swiss albino mice was compromised by Hydrocortisone injection (10 mg/kg body weight, i.p.). Upon oral administration of *Ziziphus mauritiana* leaf extract loaded chitosan nanoparticles showed efficient immune restoratory ability in the mice.

The immunomodulatory efficiency of CNPs, gallic acid grafted chitosan nanoparticles (cGANPs) and chitooligosaccharides was studied in mice model. The immunosuppression in mice was achieved by the administration of intraperitoneal injection of cyclophosphamide (80 mg/kg body weight). A remarkable rise in the thymus and spleen indices when compared to control group, indicated reversal of immunosuppression by cGANPs treatment. This kind of reversal is not achieved by treating CNPs and chitooligosaccharides. The study also disclosed that both CNPs and cGANPs boosted cell mediated immunity *via* induction of Th 1 branch of the immune response and thus serve as better immune enhancers than chitooligosaccharides (Mudgal *et al.*, 2019).

Galih Pratiwi *et al*. (2019) reported the immunomodulatory activity of the Meniran herbal extract prepared as polymeric nanoparticles. The meniran extract (*Phyllanthus niruri*) prepared by maceration method using 70% ethanol was mixed with a chitosan and tripolyphosphate polymer solution to afford corresponding nanoparticles by the ionic gelation method. The preparation of nanoparticles was optimized by using simplex lattice design utilizing Design-Expert software and the optimal composition of the formulation was found to consist of chitosan 0.270 %, extract 0.626 %, and tripolyphosphate 0.074% with the desirability value of 0.841. The zeta potential and particle size of the resulting NPs were recorded using dynamic light scattering (DLS). Fourier transform infrared spectrophotometry-attenuated total reflectance (FTIR-ATR) was employed to study the interactions between components and scanning electron microscopy (SEM) was used for observing the morphology of the lyophilization. The immunomodulatory activity was tested by performing a latex assay method. When the phagocytosis index and phagocytic activity were evaluated, for NPs, they found to be differed significantly (p<0.05) when compared to unformulated extracts. Thus, the developed nanoparticles of the Meniran extract showed better immunomodulatory activity than that of the unformulated extract (Galih Pratiwi *et al*., 2019).

The dendritic cell (DC)-based (adoptive T cell transfer) strategies have been gaining importance in cancer immunotherapy. Elaborative *ex vivo* manipulations and administration of multiple injections limit the application of DC-based vaccination. Chitosan is an emerging choice for biological and its related fields considering its low toxicity, low immunogenicity, biocompatibility, and biodegradability (Qi *et al.*, 2006; Han *et al*., 2010; Noh *et al*., 2014; Kandra *et al*., 2015). Being positively charged species, chitosan makes electrostatic interactions with DCs. Thus, its use as a drug carrier in nanomedicine gained wide acceptance (He *et al*., 2010). Chitosan nanoparticles encapsulating ovalbumin as a model antigen by an ion complex phenomenon was developed by using poly I:C as the adjuvant (Han *et al*., 2010). These nanoparticles were targeted on Toll-like receptor 3 (TLR3) in endosomes by injecting them into tumor-bearing mice. When compared with controls, enhanced *in vivo* intracellular delivery of chitosan nanoparticles on DCs was observed (p<0.01). The results also indicated the promotion of DC maturation and unfolded the activity of antigen-specific cytotoxic $CD8^+$ T cells. Studies proved that the chitosan nanoparticles can be used as an immune response modulatory vaccine for active cancer immunotherapy without *ex vivo* manipulation (Han *et al*., 2010).

2.6 Smart (light-sensitive) polymeric nanoparticles

Light-responsive polymeric nanoparticles are gaining increasing attention, being non-invasive and highly selective in the clinical practice of cancer (Zhecheng Yu *et al*., 2023), which is more secure compared to chemotherapy, surgery, and radiotherapy (Wang *et al*., 2022). The deeper layers of tissues can be easily located with the use of near-infrared (NIR; λ 750-2000 nm) (Karimi *et al*., 2017). The antibody-photosensitizer conjugate will be analyzed with NIR, which shows less toxicity on surrounding healthy cells and is selectively lethal to targeted tumor cells (Activates anti-tumor immune action)

(Maruoka *et al*., 2020; Kobayashi and Choyke, 2019). By adopting this technique, targeted tumor cells can be killed with photosensitizer (Wei *et al*., 2022).

Components such as IR-780 exert photodynamic therapy effects by which they convert oxygen into cytotoxic RO species (Nakajima *et al*., 2021). Graphene oxide-iron oxide NPs are used for local heating or hyperthermia (Espinosa *et al*., 2016). In case damage signals are received by the sensor, then NIR-PIT will release tumor-specific antigens to cause immunogenic cell death (Kobayashi and Choyke, 2019). If a tumor-specific antigen causes the death of an immunogenic cell, the sensor will receive disturbing signals (Kobayashi and Choyke, 2019).

The utility of IR-780 and imatinib in cancer photo-immunotherapy was evaluated by preparing them as pH-sensitive hybrid nanoparticles (Ou *et al*., 2018). The core of these nanoparticles was embedded by poly-L-histidine and poly (ethylene glycol)-block-poly(L-glutamic acid) layers. This prevents degradation, and results in stimulus-responsive action with targeted locations exposed to NIR. NIR suppressed the growth of the tumor with apoptosis induction and tumor-associated antigen formation, against the treatment of B16/BL6 and MC-38 cancer mouse models.

A phase-transformation nanoparticle with multiple functions was synthesized with anti-PD1 antibody (aPD1), Fe_2O_3, perfluoropentane, PEG and Gly-Arg-Gly-Asp-Ser peptides. NPs of aPD1 showed an improved drug delivery when screened for B16F10-luc mouse model. Additionally, laser irradiation of Fe_2O_3 sensitizes dendritic cells to modify the tumor-specific effector T cell response followed by cell death and tumor-associated antigens also increased $CD8^+$ T cell infiltration in the tumor site (Zhang *et al*., 2019).

2.7 Selenium nanoparticles

Antioxidant potential of yeast-derived selenium nanoparticles (Se-NPs) was reported using cyclophosphamide-induced rats. Selenium is effective for oxidative stress and infectious diseases by acting on glutathione peroxidase and selenoproteins. Even though, selenium is available in inorganic and organic forms, each one of them has limitations. The inorganic form of selenium is highly toxic and its high excretion in feces impacts the environment. The organic selenium is converted into selenols in the presence of thiols, which may lead to the propogation of RO species, leading to oxidative stress. Research interest has shifted towards the use of selenium nanoparticles as they offer greater bioavailability, low toxicity, more eco-friendly and economical over inorganic and organic selenium. Physical characterization (size, shape, stability) and Se-NPs structure was evaluated by using SEM, TEM, EDS, FTIR, XRD and XPS techniques. The antioxidant potential of Se-NPs was also evaluated by measuring levels of GSH-Px, MDA, SOD and AOC in the mice treated with 0.3-0.8 mg/kg of Se-NPs. Improved levels of antioxidant enzymes and decreased levels of MDA evidenced its antioxidant potential.The results showed that these yeast-derived Se-NPs act as immunostimulants by increasing the liver, spleen and kidney index (Ziqian Wu *et al*., 2021).

3. Conclusion

The application of nanotechnology in immunomodulation is in the developmental stages. There are certain limitations for secondary metabolites, *viz.,* solubility, pharmacokinetic properties and chemical stability, which can be overcome with nanotechnology-based delivery systems. Nano-based drug delivery will also help general health as well as autoimmune diseases. Limited nanoformulations, such as carbon nanotubes, graphenes, chitosan-based nanoformulations, gold and silver nanoparticles are formulated with various drugs from natural sources and screened for their immunomodulatory activity. The results proved that nanoformulation of herbals improved immunostimulant action and relieved the clinical symptoms of autoimmune disorders. Furthermore, multidisciplinary efforts are needed for exploring immunomodulation utilizing nanotechnology tools, especially from natural sources.

Acknowledgments

The authors are grateful to the Gokaraju Rangaraju Educational Society for providing the necessary facilities. The authors also sincerely thank the original researchers whose work was referred to in this review.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Abdala Díaz, R.T.; Casas Arrojo, V.; Arrojo Agudo, M.A.; Cárdenas, C.C.; Dobretsov, S.S. and Figueroa, F.L. (2019). Immunomodulatory and antioxidant activities of sulfated polysaccharides from *Laminaria ochroleuca*, *Porphyra umbilicalis*, and *Gelidium corneum*. Mar. Biotechnol., **21**:577.

Abdulrahman M, Elbagory.; Ahmed A, Hussein. and Mervin, Meyer. (2019). The *in vitro* immunomodulatory effects of gold nanoparticles synthesized from *Hypoxis hemerocallidea* aqueous extract and hypoxoside on macrophage and natural killer cells. International J. Nanomed., **14**:9007.

Akshita, Chauhan.; Tabassum, Khan. and Abdelwahab, Omri. (2021). Design and encapsulation of immunomodulators onto gold nanoparticles in cancer immunotherapy. Int. J. Mol. Sci., **22**(15):8037. doi: 10.3390/ijms22158037

Alina J, Andersen.; Peter P, Wibroe. and S Moein, Moghimi. (2012). Perspectives on carbon nanotube-mediated adverse immune effects. Adv. Drug Deliv. Rev., **64**(15):1700. doi: 10.1016/j.addr.2012.05.005

Amira A, Sallam.; Mona M, Ahmed.; Mohammed A, El-Magd.; Ahmed, Magdy.; Heba I, Ghamry.; Mohammad Y, Alshahrani. and Magdy F, Abou El-Fotoh. (2022). Quercetin-ameliorated, multi-walled carbon nanotubes-induced immunotoxic, inflammatory, and oxidative effects in mice, Molecules, **27**(7):2117. doi: 10.3390/molecules27072117

Bhatia, A.P.; Shard.; Dimple, Chopra. and Tulika, Mishra. (2011). Chitosan nanoparticles as carrier of immuno-restoratory plant extract: Synthesis, characterization and immunorestoratory efficacy. International J. Drug Deliv., **1**(2):381.

Chanoong, Lim.; Dong Soo, Hwang. and Dong Woog, Lee. (2021). Intermolecular interactions of chitosan: Degree of acetylation and molecular weight. Carbohydrate Polymers, **259**:117782. doi: https://doi.org/10.1016/j.carbpol.2021.117782

Dacoba, T.G.; Olivera, A.; Torres, D.; Crecente-Campo, J. and Alonso, M.J. (2017). Modulating the immune system through nanotechnology. Seminars Immunol., **34**:78.

Dong Woog Lee (2013). Strong adhesion and cohesion of chitosan in aqueous solutions. Langmuir, **29**(46):14222. doi:10.1021/la403124u.

Elidamar Nunes de Carvalho, Lima.; Ricardo Sobhie, Diaz.; João Francisco, Justo. and José Roberto Castilho, Piqueira. (2021). Advances and perspectives in the use of carbon nanotubes in vaccine development. Int. J. Nanomedicine, **16**:5411. doi: 10.2147/IJN.S314308

Espinosa, A.; Di Corato, R.; Kolosnjaj-Tabi, J.; Flaud, P.; Pellegrino, T. and Wilhelm, C. (2016). Duality of iron oxide nanoparticles in cancer therapy: Amplification of heating efficiency by magnetic hyperthermia and photothermal bimodal treatment. ACS Nano, **10**:2436.

Faria, Fatima.; Preeti, Bajpai.; Neelam, Pathak.; Sarika, Singh.; Shivam, Priya. and Smita Rastogi, Verma. (2015). Antimicrobial and immunomodulatory efficacy of extracellularly synthesized silver and gold nanoparticles by a novel phosphate solubilizing fungus *Bipolaris tetramera*. BMC Microbiology, **15**:52. doi: 10.1186/s12866-015-0391-y

Galih, Pratiwi.; Ronny, Martien. and Retno, Murwanti. (2019). Chitosan nanoparticles as a delivery system for polyphenols from Meniran extract (*Phyllanthus niruri L.*): Formulation, optimization, and immunomodulatory activity. International J. Appl. Pharmaceutics, **11**(2):50.

Haibo, Feng.; Yangyang, Feng.; Lang, Lin.; Daiyan, Wu.; Qianqian, Liu.; Hangyu, Li.; Xinnan, Zhang.; Sheng, Li.; Feng, Tang.; Ziwei, Liu. and Linzi, Zhang. (2022). Mannose receptor-mediated carbon nanotubes as an antigen delivery system to enhance immune response both *in vitro* and *in vivo*. Int. J. Mol. Sci., **23**(8):4239. doi: 10.3390/ijms23084239

Han, H. D. (2010). Targeted gene silencing using RGD-labeled chitosan nanoparticles. Clin. Cancer Res., **16**:3910.

Hélène, Dumortier. (2013). When carbon nanotubes encounter the immune system: Desirable and undesirable effects. Adv. Drug Deliv. Rev., **65**(15):2120. doi: 10.1016/j.addr.2013.09.005

Jie, Xing.; Zhenguang, Liu.; Yifan, Huang.; Tao, Qin.; Ruonan, Bo.; Sisi, Zheng.; Li, Luo.; Yee, Huang.; Yale, Niu. and Deyun, Wang. (2016). Lentinan-modified carbon nanotubes as an antigen delivery system modulate immune response *in vitro* and *in vivo*. ACS Appl. Mater. Interfaces, **8**(30):19276.

Kandra, P. and Kalangi, H. P. (2015). Current understanding of synergistic interplay of chitosan nanoparticles and anticancer drugs: Merits and challenges. Appl. Microbiol. Biotechnol., **99**:2055.

Karimi, M.; Sahandi Zangabad, P.; Baghaee-Ravari, S.; Ghazadeh, M.; Mirshekari, H. and Hamblin, M.R. (2017). Smart nanostructures for cargo delivery: Uncaging and activating by light. J. Am. Chem. Soc., **139**:4584.

Kobayashi, H. and Choyke, P.L. (2019). Near-infrared photoimmunotherapy of cancer, Acc. Chem. Res., **52**:2332.

Lev A, Dykman.; Sergey A, Staroverov.; Alexander S, Fomin.; Vitaly A, Khanadeev.; Boris N, Khlebtsov. and Vladimir A, Bogatyrev. (2018). Gold nanoparticles as an adjuvant: Influence of size, shape, and technique of combination with CpG on antibody production. Int. Immunopharmacol., **54**:163. doi: 10.1016/j.intimp.2017.11.008

Marco, Orecchioni.; Davide, Bedognetti.; Francesco, Sgarrella.; Francesco M, Marincola.; Alberto, Bianco. and Lucia Gemma, Delogu.(2014). Impact of carbon nanotubes and graphene on immune cells. J. Transl. Med., **12**:138. doi: 10.1186/1479-5876-12-138

Mario, Pescatori.; Davide, Bedognetti.; Enrica, Venturelli.; Cécilia, Ménard-Moyon.; Camilla, Bernardini.; Elena, Muresu.; Andrea, Piana.; Giorgio, Maida.; Roberto, Manetti.; Francesco, Sgarrella. and Alberto, Bianco. and Lucia Gemma, Delogu. (2013). Functionalized carbon nanotubes as immunomodulator systems. Biomaterials, **34**(18):4395.

Maruoka, Y.; Furusawa, A.; Okada, R.; Inagaki, F.; Fujimura, D.; Wakiyama, H.; Kato, T.; Nagaya, T.; Choyke, P.L. and Kobayashi, H. (2020). Combined CD44- and CD25-targeted near-Infrared photoimmunotherapy selectively kills cancer and regulatory T cells in syngeneic mouse cancer models. Cancer Immunol., Res., **8**:345.

Meng, C.; Zhi, X.; Li, C.; Li, C.; Chen, Z.; Qiu, X.; Ding, C.; Ma, L.; Lu, H.; Chen, D.; Liu, G. and Cui. D. (2016). Graphene oxides decorated with carnosine as an adjuvant to modulate innate immune and improve adaptive immunity *in vivo*. ACS Nano, **10**(2):2203. doi: 10.1021/acsnano.5b06750

Mudgal, J.; Mudgal, P.P.; Kinra, M. and Raval, R. (2019). Immunomodulatory role of chitosan based nanoparticles and oligosaccharides in cyclophosphamide treated mice. Scand. J. Immunol., **89**:e12749. doi: org/10.1111/sji.12749

Nakajima, K.; Miyazaki, F.; Terada, K.; Takakura, H.; Suzuki, M. and Ogawa, M. (2021). Comparison of low-molecular-weight ligand and whole antibody in prostate-specific membrane antigen targeted near-Infrared photoimmunotherapy. Int. J. Pharm., **609**:121135.

Noelia, González-Ballesteros.; Lara, Diego-González.; Mariano, Lastra-Valdor.; Maria, Grimaldi.; Antonella, Cavazza.; Franca, Bigi.; Carmen Rodríguez-Argüelles, M. and Rosana, Simón-Vázquez. (2022). Immunomodulatory and antitumoral activity of gold nanoparticles synthesized by red algae aqueous extracts. Mar. Drugs, **20**:182. doi: 10.3390/md200301823

Noh, K. H. (2014). GM-CSF-loaded chitosan hydrogel as an immunoadjuvant enhances antigen-specific immune responses with reduced toxicity. BMC Immunol., **15**:48.

Omoniyi Michael, Popoola.; Bijay Kumar, Behera. and Vikash, Kumar. (2023). Dietary silver nanoparticles as immunostimulant on rohu (*Labeo rohita*): Effects on the growth, cellular ultrastructure, immune-gene expression, and survival against *Aeromonas hydrophila*. Fish and Shellfish Immunol. Rep., **4**:100080. doi:10.1016/j.fsirep.2022.100080

Ou, W.; Jiang, L.; Thapa, R.K.; Soe, Z.C.; Poudel, K.; Chang, J.H.; Ku, S.K.; Choi, H.G.; Yong, C.S. and Kim, J.O. (2018). Combination of NIR therapy and regulatory T cell modulation using layer-by-layer hybrid nanoparticles for effective cancer photoimmunotherapy. Theranostics, **8**:4574.

Qi, L. and Xu, Z. (2006). *In vivo* antitumor activity of chitosan nanoparticles. Bioorg. Med. Chem. Lett., **16**:4243.

Rudtanatip, T.; Lynche, S.A.; Wongprasert, K. and Culloty, S.C. (2018). Assessment of the effects of sulfated polysaccharides extracted from the red seaweed Irish *Moss Chondrus* crispus on the immune-stimulant activity in Mussels mytilus spp. Fish Shellfish Immunol., **75**:284.

Sengupta, S.; Bhattacharya, G.; Shaw, S.; Hans, M. and Devadas, S. (2022). Immunomodulation in autoimmune disorders. Immunomodulators and Human Health, pp:303. Doi: https://doi.org/10.1007/978-981-16-6379-6_10

Shahidi, Fereidoon. and Synowiecki, Jozef. (1991). Isolation and characterization of nutrients and value-added products from snow crab (*Chionoecetes opilio*) and shrimp (*Pandalus borealis*) processing discards. J. Agric. Food Chem., **39**(8):1527. doi:10.1021/jf00008a032

Sneha J, Anarthe.; Aleeti, Pravalika.; Enishetty, Malavika. and Ganga Raju, M. (2016). Assessment of immunomodulatory activity of *Ficus benghalensis* Linn. aerial roots. Int. J. PharmTech Res., **9**(1):153.

Sneha J, Anarthe.; Spoorthisudha, P. M.; Swetha and Ganga Raju, M. (2017). *In vitro* and *in vivo* screening of *Clitoria ternatea* (Linn.) for immunomodulatory activity. Int. J. ChemTech Res., **10**(1):116.

Tasis, D.N.; Tagmatarchis, A. and Bianco, M. Prato. (2006). Chemistry of carbon nanotubes. Chem. Rev., **106**:1105.

Tarek M, Fahmy.; Lisa D, Pfefferle. and Gary L, Haller. (2017). Carbon nanotubes compositions and methods of use thereof. US 9,737,593 B2, US Patent and Trademark Office, https://www.freepatentsonline.com/9737593.pdf

Vistoli, G.; De Maddis, D.; Cipak, A.; Zarkovic, N.; Carini, M. and Aldini, G. (2013). Advanced glycoxidation and lipoxidation end products (AGEs and ALEs): An overview of their mechanisms of formation. Free Radic. Res., **47**(1):3. doi:10.3109/10715762.2013.815348

Wang, F.; Duan, H.; Xu, W.; Sheng, G.; Sun, Z. and Chu, H. (2022). Light-activated nanomaterials for tumor immunotherapy. Front. Chem., 10:1031811.

Wei, X.; Song, M.; Jiang, G.; Liang, M.; Chen, C.; Yang, Z. and Zou, L. (2022). Progress in advanced nanotherapeutics for enhanced photodynamic immunotherapy of tumor. Theranostics, **12**:5272.

Zhang, N.; Song, J.; Liu, Y.; Liu, M.; Zhang, L.; Sheng, D.; Deng, L.; Yi, H.; Wu, M. and Zheng, Y. (2019). Photothermal therapy mediated by phase-transformation nanoparticles facilitates delivery of anti-PD1 antibody and synergizes with antitumor immunotherapy for melanoma. J. Control. Release, **306**:15.

Zhecheng, Yu.; Xingyue, Shen.; Han, Yu.; Haohong, Tu.; Chuda, Chittasupho. and Yunqi, Zhao. (2023). Smart polymeric nanoparticles in cancer immunotherapy. Pharmaceutics, **15**(3):775. doi:10.3390/pharmaceutics15030775

Zhenguang, Liu.; Jin, He.; Tianyu, Zhu.; Cong, Hu.; Ruonan, Bo.; Adelijiang, Wusiman.; Yuanliang, Hu. and Deyun, Wang. (2020). Lentinan-functionalized graphene oxide is an effective antigen delivery system that modulates innate immunity and improves adaptive immunity. ACS Appl. Mater. Interfaces, **12**(35):39014. doi: 10.1021/acsami.0c12078

Ziqian, Wu.; Yanli, Ren.; Yuejuan, Liang.; Liting, Huang.; Yuanting, Yang.; Ayesha, Zafar.; Murtaza, Hasan.; Fujie, Yang. and Xugang, Shu. (2021). Synthesis, characterization, immune regulation, and antioxidative assessment of yeast-derived selenium nanoparticles in cyclophosphamide induced rats. ACS Omega, **6**(38): 24585.

Citation **Sneha Nawale, Swathi Naraparaju, Akhila Thotakuri (2023). Nanomedicines from natural sources for effective therapy in the management of immunomodulatory activity. J. Phytonanotech. Pharmaceut. Sci., 3(2):1-7. http://dx.doi.org/10.54085/jpps.2023.3.2.1**