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Nanoencapsulated nutraceuticals: Potential drug delivery systems for immune health

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Abstract

Nanotechnological products along with nutraceuticals are fast emerging as sought after products for good health. The enhancement in usage of these technological improvisations is mainly attributed to the better bioavailability, reduction in adverse reactions due to targeted delivery and over toxicity, sustained release requiring fewer doses/day and better sustainability. In current times especially after the pandemic, the emphasis on development of nanonutraceuticals, as supplements, and its consumption, to not only maintain health and immunity but also to treat a number of diseases, has taken a boost. The current review summarizes the utility of some nanonutraceuticals for health through strengthening immunity, which can further lead to healthy being from many disorders/diseases.



1. Introduction

The SARS-CoV2 infection initiated since November 2019, spread rapidly and in March 2020, WHO declared it as a pandemic. With widespread mortality, the world recognised the nonpareil role of immunity in maintaining good health. It has always been accepted that nutrition plays a significant role in strengthening immunity. Hereditary predispositions along with environment have also been known to influence immunity. Over-nutrition as in obesity as well as malnutrition, results in adversely affecting immunity leading to malfunctioning of innate as well as adaptive immune responses, thereby leading to a higher vulnerability to infection (Calder and Yaqoob, 2020). A positive correlation exists between nutrition and functionality of the immune system. A strong support to the immune system is provided by micronutrients as vitamins A, C and D ;

copper, magnesium, selenium, zinc, etc. (Gombart *et al.*, 2020; Maggini *et al.*, 2018).

Studies have recommended that foods rich in (a) antioxidants and vitamins, *e.g.*, vegetables and fresh fruits (Cena and Chieppa, 2020), nuts (Yahfoufi *et al.*, 2018), (b) omega-3 fatty acids (Seidelmann *et al.*, 2018), (c) micronutrients (Jampilek and Kralova, 2020), have a positive influence on the immune system. A new branch of science is nutraceuticals which is defined as foods and their derivatives, supplemented along with diet catering to important nutrients that support holistic wellness. These nutraceuticals use natural phytoconstituents with therapeutic effects and helps to maintain good health. As they are natural in origin, the adverse reactions are minimal and thus, the market for nutraceuticals has been growing exponentially in the past few decades.

The most convenient and desirable route of delivery of drugs or nutraceuticals or supplements is oral which has inherent issues especially low availability and first pass metabolism (Jampilek and Kralova, 2018, 2019). Nanoformulations are now evolving as the desired route for drug delivery, because it allows the targeted distribution of drugs to the selected tissues as well as controlled and sustained release, overcoming the undesired drug accumulation

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(Jampilek *et al.*, 2019). Further bioavailability of the drug is enhanced and drug resistance is overcome (Pentak *et al.*, 2016; Placha and Jampilek, 2019).

Amongst the nanotechnology based delivery systems developed and used in industries, as food, pharmacy as well as agriculture are micelles, liposomes, nanoemulsions/suspensions, solid lipid nanoparticles, lipid nanocapsules, lipid-polymer hybrid and nanostructured lipid carriers. For better bioavailability and to reduce adverse effects, natural and non-toxic biodegradable polymers as pectin, alginate, gums as xanthan, arabic, chitin, chitosan, gelatins, hyaluronic acid, cyclodextrins, *etc.*, are used (Jampilek and Kralova, 2018). This review presents a compilation of nutraceuticals formulated using nanotechnology with potential to strengthen immunity.

2. Some nanonutraceuticals

2.1 Vitamin C

Ascorbic acid is a potent antioxidant and is popular as 'scavenger molecule', as it has strong potential to scavenge free radicals generated during cell metabolism (Carita *et al.*, 2020; Moser *et al.*, 2016). Vitamin C is an immunomodulator and affects both innate (Franz *et al.*, 2011) and acquired immune responses (Molina *et al.*, 2014). Studies reveal that NK cells are activated, proliferation of lymphocytes is enhanced and chemotaxis is promoted and enhanced when vitamin C is supplemented in healthy subjects (Heuser and Vojdani, 1997). High vit. C dose also stimulates dendritic cells with boosted interleukin -12 secretion (Jeong *et al.*, 2011), as well as activation of T and B population (Woo *et al.*, 2010; Maeng *et al.*, 2009).

Vitamin encapsulated within liposomes in *ex vivo* studies showed higher antioxidant activity with reduction of malondialdehyde level in comparison to free vitamin C. The release of vitamin C from liposomes was almost 90% within 2 h (Parhizkar *et al.*, 2018). Co-encapsulation with folic acid in fatty acid co-loaded liposomes showed good stability and higher encapsulation efficiency with higher antioxidant activity than liposomes loaded with individual vitamins (Jiao *et al.*, 2019). Use of nanotechnology has shown to enhance vitamin C delivery along with improved intracellular Fenton reaction-based oxidative stress and found to be useful for Ferroptosis therapy (Pal and Jana, 2022). In combination with vitamin D and zinc, the immunomodulatory effects of vitamin C is boosted (Gautam and Santhiya, 2019). Vitamin C nanoparticles in conjugation with zinc oxide was found to improve the functioning of immune system of heat stressed broiler chickens (Bahrapour *et al.*, 2021).

2.2 Curcumin

Rhizomes of *Curcuma longa* (Gingiberaceae) has a yellow to orange natural dye termed curcumin, a derivative of 1,7-bis (4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione. Literature cites that in all forms of ancient medicines, curcumin has been used as antimicrobial (Manoharan *et al.*, 2020), anti-inflammatory (Fadus *et al.*, 2017) and antitumor (Hewlings and Kalman, 2017) as well as an antioxidant and hypolipemic (Zahedipour *et al.*, 2020). It is used for menstrual arrest, postpartum abdominal pain and GI disorders (Lopresti, 2018). For Alzheimer's, nanoformulations have shown prophylactic effect (Tsuda, 2018). Curcumin is known

to inhibit inflammation in animal models. It has been found to inhibit inflammatory signalling molecules as NF- κ B, JAKs/STATs and MAPKs (Kahkhaie *et al.*, 2019).

On nanoencapsulation of curcumin around zein, an increase in oral bioavailability was seen by Ipar *et al.* (2019). Curcumin nanoparticles were synthesised with surface-charged surfactants and its antimicrobial activity against *Listeria monocytogenes*, was evaluated. Highest antimicrobial activity was demonstrated with nanoparticles formed from positively charged surfactants (No *et al.*, 2017).

Treatment with curcumin nanoparticles has led to change of faecal fatty acid level towards short-chain ones and can be a therapeutic modality for IBD diseases (Ohno *et al.*, 2017). Curcumin nanoparticles were prepared by Manjili *et al.* (2016) using poly (caprolactone)-poly (ethylene glycol)-poly (caprolactone). These curcumin nanoparticles significantly inhibited proliferation of cells, induced apoptosis and boosted antitumor immunity. Adjuvant therapy with nanoformulations having curcumin-Meriva® has been found to suppress systemic inflammation in cases of solid tumors for patients under standard chemotherapy (Belcaro *et al.*, 2014).

2.3 Resveratrol

A natural polyphenolic antioxidant, resveratrol is derived from stilbene. It possesses antiplatelet, anticarcinogenic, antioxidant, anti-inflammatory, cardioprotective, and immunomodulatory activity (Mehrotra, 2020). Resveratrol is an immunomodulatory and induces lymphocyte proliferation, as well as stimulates natural killer cell cytotoxicity. Gianhecchi *et al.* (2020), have also suggested that resveratrol plays a regulatory role in apoptosis. Resveratrol can suppress the toll-like receptor (TLR) and pro-inflammatory genes expression.

Resveratrol is an effective antioxidant as it possesses ability to inhibit the eicosanoids production. These eicosanoids contribute anti-inflammatory properties and are beneficial in different autoimmune and for other chronic inflammatory diseases (Malaguarnera, 2019). Resveratrol niosomes have immense anti-inflammatory action. RES-loaded niosomal hydrogel was found to enhance the biological half-life, which is a challenge if resveratrol is given *via* conventional routes of drug delivery. In paw edema model, the anti-inflammatory activity was measured and it was found to reduce the edema and its therapeutic action lasted for longer time (Negi *et al.*, 2017).

2.4 Selenium

Selenoproteins the metalloprotein with selenium play a very important physiological functions and thus exemplifies the significance of this trace element (Zhang *et al.*, 2020). Literature cites that around 30 genes are present in human genome which transcribe and translate to produce selenoproteins which play a significant role as anti-inflammatory agents as well as antioxidants (Labunsky *et al.*, 2014). Rayman (2012) observed that in HIV, as the concentration of selenium supplementation was increased mortality rate reduced.

Nanoformulations of selenium are advantageous as the selenium is in zero oxidation state, thereby lowering the toxicity and enhancing the bioavailability though it is unstable as it easily transforms into an inactive form (Zhai *et al.*, 2017). Although, its stabilization can be achieved by encapsulation into suitable nanovehicles, for

example, chitosan (CS). Nanoformulations of selenium have potential immunomodulatory activity as they affect the functioning of granulocytes (Khabatova *et al.*, 2022). A study to assess the effects of selenium nanoparticles as feed additives for goldfish (*Carassius auratus*) was undertaken by Jahanbakhshi (2021). They found that the nanoparticles promoted growth, biochemical metabolic process, hepatic enzymes activities, and enhanced gene expression of ghrelin and IGF-1.

2.5 Zinc

Zinc as a mineral for maintaining immune health is significant as it is a component of thymulin, the thymus hormone associated with T-cell maturation and differentiation. It also stimulates the production of IL-12 by macrophages, and this cytokine further activates natural killer and T cytotoxic cells (Prasad, 2008). Thus, Zn deficiency affects immunity due to degeneration of thymus, by interfering with important cellular functions such as phagocytosis (Fukada *et al.*, 2019). Improved immunity against viruses as well as its antioxidant activity was observed with zinc supplementation as it maintains membrane integrity and prevents inflammation (Read *et al.*, 2019).

Zinc oxide quantum dot powder bound on ZnO polystyrene film as well as suspended in a poly vinyl prolidone gel, are very efficient as antimicrobial packaging against *Listeria monocytogenes*, *Salmonella enteritidis*, and *Escherichia coli* O157:H7 (Sun *et al.*, 2009).

Dietary supplementation of selenium and zinc oxide nanoparticles has been found to stimulate immunity and resist bacterial infection in *L. rohita*. Down regulation of serum lactate dehydrogenase and alkaline phosphatase with upregulation of SOD and acetylcholine esterase was found, thus increasing percentage survival (El-Katcha *et al.*, 2017).

3. Conclusion

Industrial revolution, information technology and associated improvisation of economy has led to a trend wherein lifestyle today has moved to being unhealthy, lacking physical exercise with an increase in consumption of fast foods. A balanced diet comprising of major nutrients, *viz.*, carbohydrates, proteins and lipids along with micronutrients as vitamins, antioxidants, and minerals in the amount needed is unarguable the key for maintaining homeostasis and functionality of the organism as a whole. Good health is at times synonymous to good immunity and in recent times the emphasis on these has increased.

Thus, the need of nutraceuticals to not only maintain health but also to enhance immunity has been escalated. These nutraceuticals however at times have poor bioavailability and poor stability and so the combination with nanotechnology has proved to be highly beneficial. Thus, nutraceuticals so termed as smartfoods, are seeing a makeover to nanonutraceuticals. However, it should also be considered that these nanonutraceuticals, still need to prove their utility to cure an already proven disease. Thus, in conclusion nanonutraceuticals surely can be the key to improve immunity, thereby contributing to holistic wellness as it is well said that 'A healthy mind stays in a healthy body'.

Conflict of interest

The author declares no conflicts of interest relevant to this article.

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