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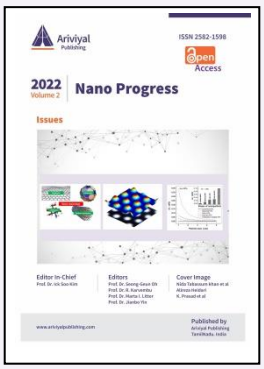

Therapeutic Targeting Strategies of "Nutrition-Inspired Nanomaterials": A Mini-Review

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Abstract: With the discovery of new functions of nutraceutical, "Nutrition-inspired nanomaterials," which are developed by incorporating the physical, chemical, and biological properties of individual nutraceutical as a foundation material, have the potential to significantly change the bio kinetics, intracellular accumulation, and physiological functions of Nano carriers for health purpose. This mini-review summarizes recent reports on "Nutrition- inspired nanomaterials" and describes their potential for the future.

Keywords: Ascorbic Acid; α-Tocopherol; Folate; Polyphenol; Vitamin; Drug Delivery System; Nano carrier

1. Introduction

Research of food and nutrition has been carried out for centuries, but modern nutritional science is considered to have begun with the first discovery of vitamins in early 1900s.[1] Since then, the individual functions of nutraceutical have been identified, and their effects on human health have been studied in various fields, such as cancer, dementia, obesity, lifestyle-related diseases, and life span. Since individual nutraceuticals have been synthesized chemically, they have been consumed not only through foods but also through supplements, and new physiological functions are still being discovered.[2,3]

With the development of nanotechnology, remarkable advances in Nano medicine, a technology that applies nanostructures to the medical and food industries, has been emerging. Among the Nano medicine, drug delivery systems, in which various modifications (aptamers, antibodies, cationic molecules, drugs, fluorescent dyes, polyethylene glycols, proteins, surfactants, etc.) are applied to the surface of nanostructures to make the encapsulated drug accumulate at the target site and reduce side effects or improve bioavailability, have been investigated worldwide as effective therapeutic technologies.[4,5] Compounds used as payloads in drug delivery systems are not limited to drugs. Drugs have the disadvantages of high cost and difficulty in obtaining them, but approaches are being made using commercially available and cost effective nutraceutical. The use of nutraceutical (such as carotenoids, curcumin, ferulic acid, polyphenols, vitamin B, vitamin E, etc.) as payloads in drug delivery systems has been studied to try to demonstrate their functions for various health purposes (such as anticancer, antioxidant, prevention of cognitive decline, enhancement of absorption).[6-11]

One of the topics that have begun to attract attention in recent years is "Nutrition-inspired nanomaterials," an approach to develop nano carriers with new functions by incorporating the physical, chemical, and biological properties of nutraceutical into materials, rather than using nutraceutical as payloads. Having the physical, chemical, and biological properties of the individual nutrients ensured in their matrix, nano carriers have potential to significantly modify the kinetics and cellular accumulation, as well as the originally physiological functions of the nutraceutical. Therefore, it might be potential to achieve therapeutic benefits that have been difficult to realize using the drug delivery system approach with a single drug as the payload. Because of the short history of this "Nutrition-inspired nanomaterials" research, there are not many reports on it, but there have been several reports on studies mainly using polyphenols and vitamins. This mini review summarizes recent reports on "Nutrition-inspired nanomaterials", characterizing the positioning of nutraceutical in the field of nano medicine and how nano medicine changes its behavior depending on moieties of nutraceutical, and discussing their prospects based on current evidence. The information provides a guideline for the development of new technologies in this research area.

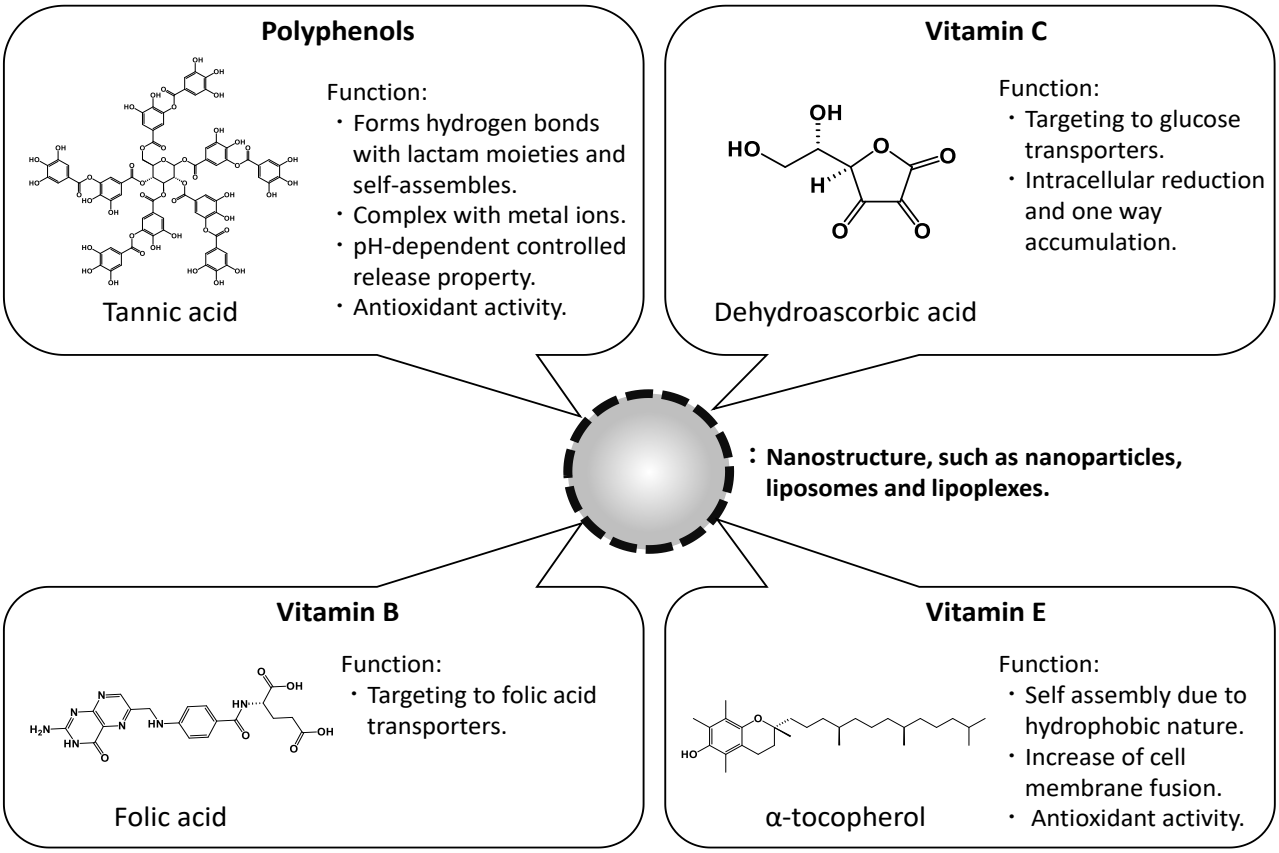

Fig. 1. Expected functions of moieties of nutraceuticals provided to nanomaterials, presented in this review.

2. Nanomaterials Containing Moiety of Polyphenol

Polyphenols are a general term for compounds that have two or more phenolic hydroxy groups in their molecules (Fig. 1, Polyphenols). Naturally occurring polyphenols are found mainly in plants and are broadly divided into flavonoids and non-flavonoids, which are further classified into anthocyanin, catechins, curcumin, quercetin, resveratrol, tannins, etc. depending on their chemical structure.[12] Polyvinylpyrrolidone (PVP), a polymer based on the polymerization of N-vinyl-2-pyrrolidone, is one of the most widely used polymers as a material for polyphenol based nano carriers.[13-15] This is because the formation of hydrogen bonds between the lactam moieties in PVP and the phenolic hydroxy groups of polyphenols promotes self-assembly and can build supramolecular structures such as gels and nanoparticles. In 2019, He et al. reported differences in the bonding between curcumin and three different materials (cyclodextrin, surfactant (poloxamer), and PVP).[16] In that report, phenolic hydroxy groups of the curcumin molecule were found to create multi-point hydrogen bonds with PVP. Furthermore, they orally administered a mixture of each of these three materials and curcumin to rats and reported that it was the group with the mixture of PVP and curcumin that the highest amount of absorbed curcumin. Their result may be due to the coexistence of PVP and curcumin, reducing curcumin degradation in the digestive system.

Phenolic hydroxy groups of polyphenols not only interact with macromolecules as described above, but also have the property of forming complexes with typical elements.[17,18] This property makes it possible to construct supramolecular structures that ensure more precise external stimulus responsiveness. Ejima et al. reported that the coordination complexes of epigallocatechin gallate and iron (III) showed pH-dependent changes (pH < 2, mono complex; 3< pH < 6, bis complex; 7 < pH, tris complex).[19] Tumor microenvironment is more acidic than the healthy environment.[20] Therefore, pH-dependent changes in polyphenol and typical element complexes are useful as a targeting strategy to cancer tissues. Reports of nanomaterials adapting this functionality include the following. Kim et al. prepared nanoparticles modified with tannic acid and iron (III) complexes on the surface of mesoporous silica.[21] When curcumin was encapsulated in these nanoparticles, the release of curcumin was inhibited at pH 7.4, while sustained curcumin release was observed below pH 6, which is considered tumor microenvironment. Chen et al. prepared nanoparticles modified with tannic acid and iron (III) complexes on the surface of curcumin.[22] These nanoparticles degraded during endocytosis of MCF-7 cells, elevating curcumin uptake and activating the apoptotic pathway. Furthermore, the study with the MCF-7 xenograft mouse model also confirmed that the tumor volume increase was suppressed. Another institute reported nanoparticles prepared by modifying the surface of a CaO_2 and PVP mixture with a complex of tannic acid and iron (III).[23] These nanoparticles generated hydrogen peroxide below pH 6 and was reported to inhibit tumor volume growth in a 4T1 xenograft mouse model.

The application of polyphenol and typical elements coordinating complexes in nano carriers has the potential to be used not only for the treatment of cancer but also other diseases. Yuan et al. prepared nanoparticles composed of PVP and iron (III)-curcumin complexes for the treatment of acute lung injury.[24] Results showed that both (pulmonary tissue and intravenous) routes of administration suppressed the inflammatory cytokine storms that generated in the mouse model of acute lung injury and showed almost no toxicity to the heart, liver, spleen, lungs, and kidneys. Among the research areas of "Nutrition-inspired nanomaterials," polyphenol-based nanomaterials have been the most studied among the various nutraceutical, with a relatively large number of research reports.

3. Nanomaterials Containing Moiety of Vitamin B

Vitamin B complex is a water soluble compound, rich in meat and dairy products, and is an important cofactor in enzymatic reactions in the body.[25] Among the vitamin B complex, folate is used as a targeting strategy for cancer tissues because folate receptors are overexpressed on the various cancer cells (Fig. 1, Vitamin B). It is known that the moiety of folic acid can be used as a complex with small molecule drugs or modifying the surface of nanoparticles to make them selective for cancer cells.[26,27] Alserihi et al. prepared nanoparticles of a blend of poly(D,L-lactide-co-glycolide)-poly(ethylene glycol) and poly(epsilon-caprolactone), modified to act as tumor targeting ligands with folic acid, in order to treat prostate cancer.[28] These nanoparticles incorporating epigallocatechin gallate were evaluated for their therapeutic effect on prostate cancer with 3D culture using PC3 and 22Rv1 (prostate-specific membrane antigen [PSMA]+) cells. As a result, the prepared nanoparticles showed a significant decrease in spheroid size in PSMA+ cells. This finding suggests that the ability of epigallocatechin gallate to bind to PSMA was more effective when encapsulated in nanoparticles.

Macrophages activated by inflammation is also known to express high levels of a cellular receptor called folate receptor.[29] Since folate receptors are not expressed on quiescent macrophages, the moiety of folic acid is selectively delivered to activated macrophages at the site of inflammation. Poh et al. prepared liposomes incorporating folate-conjugated poly ethylene glycol.[30] These radiolabeled liposomes showed bioimaging of inflammatory sites in atherosclerosis model mouse. Furthermore, encapsulation of betamethasone (used as an anti-inflammatory and immunosuppressive drug) in liposomes was found to be effective for the treatment of mouse model of ulcerative colitis.

In preclinical studies, bioimaging probes targeting folate receptors have been investigated in tumor imaging.[31] For the treatment of epithelial ovarian cancer, vintafolide (EC145), which is a folate conjugate of desacetylvinblastine monohydrazide, has proceeded to Phase II clinical trials.[32] On the other hand, there are concerns that folic acid itself promotes the formation of cancer cells, and that nanoparticles modified with folate receptor tend to accumulate in the breast of normal mice.[33] Further clarification of the details of such phenomena will be necessary to clarify the usefulness of targeting strategies of nano carriers with moiety of folate to folate receptors.

4. Nanomaterials Containing Moiety of Vitamin C

Vitamin C (ascorbic acid) is a water soluble compound found in fruits, vegetables, and meat, and is known to exhibit various physiological effects such as anticancer activity, activation of amino acid metabolism, and collagen synthesis (Fig. 1, Vitamin C).[34] Numerous cancer cells exhibit the Warburg effect, which increases glucose uptake and aerobic glycolysis.[35] Therefore, glucose transporters are overexpressed on their cell surfaces. Dehydroascorbic acid, an oxidized form of ascorbic acid, has been shown to specifically enter into the cell via a glucose transporter, then reduced in the cytoplasm and accumulates intracellular as ascorbic acid, and the amount of its intracellular uptake rate is depends on the levels of glucose transporter expression.[36,37] Since glucose transporters are localized at the blood-brain barrier, targeting of nano carriers to these transporters for brain transport is also investigated. Shao et al. prepared nano micelles with dehydroascorbic acid moieties conjugated to their surfaces.[38] The mechanisms of these nanoparticles are that the moiety of dehydroascorbic acid on the nano micelle allows it to be taken up via glucose transporter into cancer cells, and the intracellular glutathione reduces the moiety of dehydroascorbic acid to ascorbic acid, thereby achieving one way intracellular accumulation. Results of experiments using a U87 glioma mouse model showed that these nano micelles had targeting ability to glioma and also exhibited therapeutic effects when encapsulated paclitaxel. Furthermore, their group also reported in a subsequent study that these nano micelles, encapsulated with itraconazole, achieved an inhibitory effect in a mouse model of infection of the *Cryptococcus neoformans* into the central nervous system.[39] On the other hand, with respect to these reports, Puris et al. mentioned the lack of pharmacokinetic data for paclitaxel encapsulated in nano micelles and the study of intracerebral administration of itraconazole was conducted at only two time points (one and four hours) after intravenous administration to mice.[40] They commented that it is necessary to clarify that the efficacy increases with the degree of drug delivery to the target tissues.

5. Nanomaterials Containing Moiety of Vitamin E

Tocopherol is a fat-soluble compound found in nuts and vegetable oils, etc. and although there are many isomers, but only one type, α-tocopherol, is defined as vitamin E.[41] α-tocopherol is localized in cell membranes and is known to have various physiological effects, such as the cytoprotective properties against oxidative stress.[42] The hydrophobic nature of α-tocopherol have been applied to nano scale self-assembly and cell fusion properties (Figure 1, Vitamin E). Hamdi et al. prepared lipid-polymer hybrid nanoparticles coated with α-tocopherol on their surfaces.[43] These nanoparticles showed that the presence of moiety of α-tocopherol on the surface increased the hydrophobicity of the particles and dramatically increased their uptake by J774 cells. Muripiti et al. synthesized a conjugate of α-tocopherol and ascorbic acid.[44] These conjugates are amphiphilic molecules with hydrophobic α-tocopherol moieties and hydrophilic ascorbic acid moieties, so they form lipoplexes by self-assembling in water with DNA. They confirmed the efficiency of transfection of HepG2 cells with these lipoplexes, and found that the efficiency was

2.5 times higher than that of lipofectamine (commonly available transfection reagent). Furthermore, this nano carrier has moieties of α-tocopherol and ascorbic acid that also provide antioxidant activity, thus is expected to be used as a nano carrier with antioxidant activity. Their group later also synthesized a conjugate of α-tocopherol and arginine.[45] These lipoplexes formed by their amphiphilic molecules are expected to be an effective potential candidate for glioblastoma gene therapy because it is low toxicity to cells while stably retaining pDNA. Moreover, it showed high transit efficacy in an ex vivo model of the blood-brain barrier.

6. Conclusions

Throughout this review, it is clear that "Nutrition-inspired nanomaterials" are becoming a highly innovative approach to increasing the efficacy of nutrients and drugs and reducing their toxicity to healthy living cells. However, the findings of a survey of the literature have led to the development of new approaches that utilize the functions of nutraceutical, but there are still few research reports on this topic. In addition, the mechanistic implications of their targeting in vitro and in vivo remain unclear, and are found to be a significant limitation to the development of new technologies. More comprehensive pharmacokinetic studies on "Nutrition-inspired nanomaterials" would be necessary. Progress in this research area is expected to be further advanced in the near future.

Conflicts of Interest

The authors declare no conflict of interest.

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