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Review Article

Nanotechnology in food science: Functionality, applicability, and safety assessment

Xiaojia He [a,b], Huey-Min Hwang [a,*]

[a] Department of Biology, Jackson State University, Jackson, MS, USA
[b] Department of Marine Sciences, the University of Georgia, Athens, GA, USA

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ABSTRACT

Rapid development of nanotechnology is expected to transform many areas of food science and food industry with increasing investment and market share. In this article, current applications of nanotechnology in food systems are briefly reviewed. Functionality and applicability of food-related nanotechnology are highlighted in order to provide a comprehensive view on the development and safety assessment of nanotechnology in the food industry. While food nanotechnology offers great potential benefits, there are emerging concerns arising from its novel physicochemical properties. Therefore, the safety concerns and regulatory policies on its manufacturing, processing, packaging, and consumption are briefly addressed. At the end of this article, the perspectives of nanotechnology in active and intelligent packaging applications are highlighted.

1. Introduction

Nanotechnology has become one of the most promising technologies to revolutionize conventional food science and the food industry. Nanotechnology-assisted processing and packaging has proved its competence in food systems [1]. Different preparation technology could produce nanoparticles with different physical properties; thus, they could be used in food [2]. However, not only is the public perception regarding this new technology uncertain [3], but also the regulation agencies have not yet reached an agreement on worldwide-applicable rules [4,5]. Despite significant debate over the necessity of establishing new regulations for nanotechnology, United States Environmental Protection Agency, National Institute for Occupational Safety and Health, the Food and Drug Administration (FDA), the Health and Consumer Protection Directorate of the European Commission, International organizations such as the International Organization for Standardization and the Organization for Economic Cooperation and Development, as well as many regulatory bodies have issued multiple guidance documents with respect to the potential risks posed by nanomaterials.

- On August 5, 2015, U.S. FDA issued one final guidance document related to the use of nanotechnology in food for animals [6].
- On April 6, 2015, U.S. Environmental Protection Agency proposed one-time reporting and recordkeeping

* Corresponding author. Biology Department, Jackson State University, Box 18540, 1400 Lynch Street, Jackson, MS 39217, USA.
E-mail address: huey-min.hwang@jsums.edu (H.-M. Hwang).
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requirements under the Toxic Substances Control Act Section 8(a) [7].

- On June 24, 2014, U.S. FDA issued three final guidance documents related to the use of nanotechnology in regulated products, including cosmetics and food substances [8].
- In November 2007, The Working Party on Manufactured Nanomaterials of the Organization for Economic Cooperation and Development launched the Sponsorship Program for the Testing of Manufactured Nanomaterials (Testing Programme) [9].

The challenge remains for regulators that the lack of worldwide-accepted rules may ultimately fail to provide appropriate guidance in response to general public and occupational health risks associated with the manufacture, use, and disposal of nanomaterials.

Current scientific regulation of food nanotechnology is characterized by numerous uncertainties regarding risk characteristics. Functionality of food nanotechnology determines its range of applicability. Food nanotechnology can affect the bioavailability and nutritional value of food on the basis of its functions [10]. It is recognized that the biological properties (including toxicological effects) of nanomaterials are largely dependent on their physicochemical parameters [11–13]. In fact, the major links between nanotechnology and the food industry are enhancing food security, extending storage life, improving flavor and nutrient delivery, allowing pathogen/toxin/pesticide detection, and serving functional foods, as depicted in Figure 1. Achievements have been made in various areas of food systems, including foods and food packaging [14]. Most researches emphasize the regulation of nanotechnology in food packaging and processing [15]. Unfortunately, there is no comprehensive review on the potential risks associated with the functionality and applicability of food nanotechnology yet.

In this review, we mainly focus on the aspects of the functionality and applicability of food nanotechnology, and the current progress in their regulation and risk/safety assessment. In particular, some nanomaterials are toxic to animals and humans; they act as oxidant scavengers or antimicrobial agents [16,17]. Moreover, depending on their applications in processing and packaging, and as actual food ingredients, nanocomposites may have completely different consequences. Therefore, a clear view of the potential hazards associated with their functionality and applicability is urgently demanded for providing further guidance on the safety of food nanotechnology.

2. Functionality and applicability of food nanotechnology

2.1. *Protection against biological deterioration*

2.1.1. *Antimicrobials*

Microbial contamination has been leading to pathogenic infections and poor nutrition associated with weaning foods. Thus, dealing with bacterial deterioration is one of the most critical subjects in the production, processing, transport, and storing of food. Novel nanoantimicrobials have shown promising effects on safeguarding food deterioration, thereby extending the shelf life of food. A number of metal and metal oxide nanomaterials have long been suggested to be effective

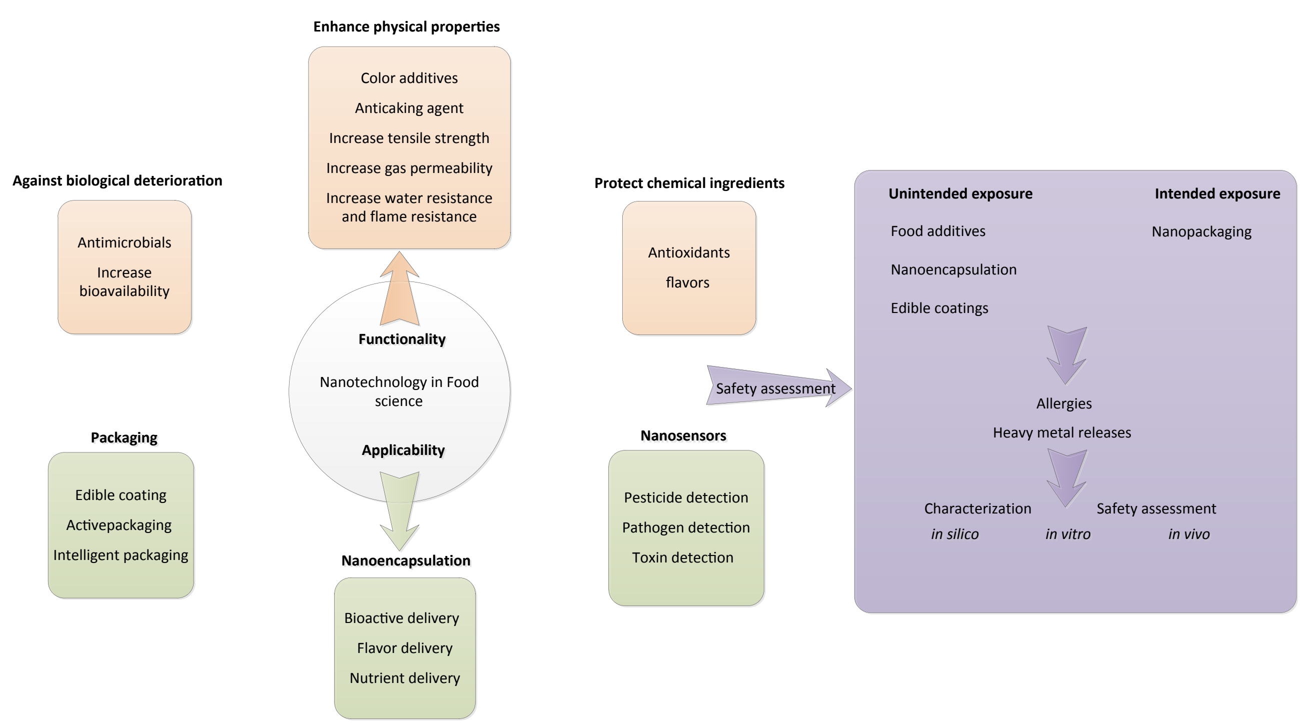

Figure 1 – Diagram showing the development of nanotechnology in food science/industry and its functionality, applicability, and safety assessments.

as antimicrobials. Their intrinsic physicochemical properties allow excessive formation of reactive oxygen species (ROS), leading to oxidative stress and subsequent cell damage [18,19]. Furthermore, the release of metal ions outside the cell, at the cell surface, or within the cell can alter cellular structure or function. Thus, metal/metal oxide-based nanocomposites have been utilized in food packaging and coating, or even as ingredients.

Silver nanoparticles and nanocomposites are one of the most widely used nanomaterials, as antimicrobials, in the food industry. A dozen silver-containing zeolites or other substances have been approved by the U.S. FDA for use as food contact materials for the purpose of disinfection [20]. Silver nanoparticles likely serve as a source of Ag^{+} ions, binding to membrane proteins, forming pits, causing other morphological changes [21], and catalyzing the generation of ROS in bacterial cells, subsequently leading to cell death through oxidative stress [22]. Nevertheless, multiple latest research studies suggested that silver nanocomposites are safe for food packaging, with no detectable or insignificant levels of silver nanoparticles that are released and migrated from impregnated containers into real food samples and food simulants [23,24].

Nanocomposites offer added stability, which is important for sustaining antimicrobial activity and reducing the likelihood of migration of metal ions into stored foods. Polymers are largely engineered to form nanocomposites with metal/metal oxide nanomaterials for food application. Among these polymers, low-density polyethylene (LDPE), gelatin, isotactic polypropylene, and polylactic acid are most widely used as part of nanocomposites. For instance, Ag/LDPE [25,26], CuO/LDPE [26], TiO_2/LDPE [27], and ZnO/LDPE [26,28], are reported to be used in food applications. In addition, ZnO/gelatin [29–31], Ag/OMt–LDPE [32], Ag/poly(3-hydroxybutyrate-co-18 mol%-3-hydroxyvalerate) [33], ZnO/polycarbonate [34], ZnO/isotactic polypropylene [35], ZnO/polylactic acid [36,37], and ZnO/graphene oxide/polylactic acid [38], are targeted specifically for food packaging applications. Earlier, chitosan, polystyrene, polyvinylprolidone, and poly(vinyl chloride) have also been reported as nanocomposite films that bind to Cu or ZnO nanomaterials to inactivate food pathogens [39–41].

2.1.2. *Increasing bioavailability*

The use of nanomaterials as delivery systems to improve the bioavailability of bioactive compounds as nutritional supplements has been reviewed in some studies [42,43]. Bioactives, such as coenzyme Q10 (CoQ10) [44], vitamins [44], iron [45], calcium [46], curcumin [47], etc., have been widely tested in nanodelivery systems. Nanodelivery vehicles such as association colloids (e.g., casein micelles) [48], lipid-based nanoencapsulators/nanocarriers [49], nanoemulsions [50], biopolymeric nanoparticles [51], nanolaminates [52], and nanofibers [53,54] are largely developed.

Generally, nanodelivery systems can increase the bioavailability of bioactives in various ways. It is noteworthy that the bioavailability of bioactive compounds can be evaluated quantitatively using the following equation and as illustrated in Figure 2:

$$BA = B^{*} \times A^{*} \times T^{*}$$

where BA is the oral bioavailability of bioactive compounds, B^{*} is bioaccessibility, A^{*} is absorption, and T^{*} is molecular transformation [43,55]. Thus, in order to maximize the bioavailability of bioactives, one can improve the bioaccessibility and absorption, and alter the molecular structure that might have occurred during digestion. By altering particle size, solubility can be improved through an increase of the surface area-to-volume ratio, leading to an increase in bioaccessibility. For instance, CoQ10 is lipophilic and has very low bioavailability due to its poor water solubility [56]. A novel lipid-free nano-CoQ10 system modified with different surfactants was formulated to improve the solubility and bioavailability of CoQ10 by oral administration [57]. In addition, gastrointestinal permeability can be enhanced by selecting appropriate formulation surfactants [49]. This can lead to an increase in absorption as well as bioaccessibility. For instance, hydrochloric acid has been used as a surfactant for the preparation of soy protein-stabilized acidic oil-in-water green tea catechin nanoemulsions, resulting in increased permeability [58]. Moreover, surface-modified nanodelivery systems have been developed to control their interactions with biologic milieu and therefore their biodistribution. In fact, it is possible to modify the nanodelivery systems by chemical grafting of hydrophilic molecules. Among them poly(ethylene glycol) is the most known hydrophilic molecule [59]. By doing so, molecular transformation can be controlled in order to provide maximum bioaccessibility and absorption.

2.2. *Protection against chemical ingredients*

2.2.1. *Antioxidants*

Although some metal/metal oxide nanomaterials are known to cause oxidative stress via formation of ROS [13,60,61], less reactive nanomaterials are developed to act as antioxidant carriers. Polymeric nanoparticles are suggested to be suitable for the encapsulation of bioactive compounds (e.g., flavonoids and vitamins) and to release them in acidic environments (i.e., stomach) [62]. Similarly, SiO_2–gallic acid nanoparticles as novel nanoantioxidants are developed and tested based on its scavenging capacity of 2,2-diphenyl-1-picrylhydrazyl radicals [63].

Furthermore, application of antioxidant treatments in association with edible coating is the most common way to control browning of fresh-cut fruits [64]. It is well known that browning of fresh-cut fruits is an undesirable effect brought by the conversion of phenolic compounds into dark colored pigments in the presence of O_2, during storage and marketing [65]. However, there are only a few applications of nanomaterials directly as antibrowning agents. Nano-ZnO-coated active packaging has been reported to be a viable alternative to common technologies for improving the shelf-life properties of “Fuji” apples as a fresh-cut product [66]. In their study, the activities of polyphenol oxidase and pyrogallol peroxidase were significantly decreased in fruits stored in nano-ZnO packaging. Moreover, the initial appearance of fresh-cut Fuji

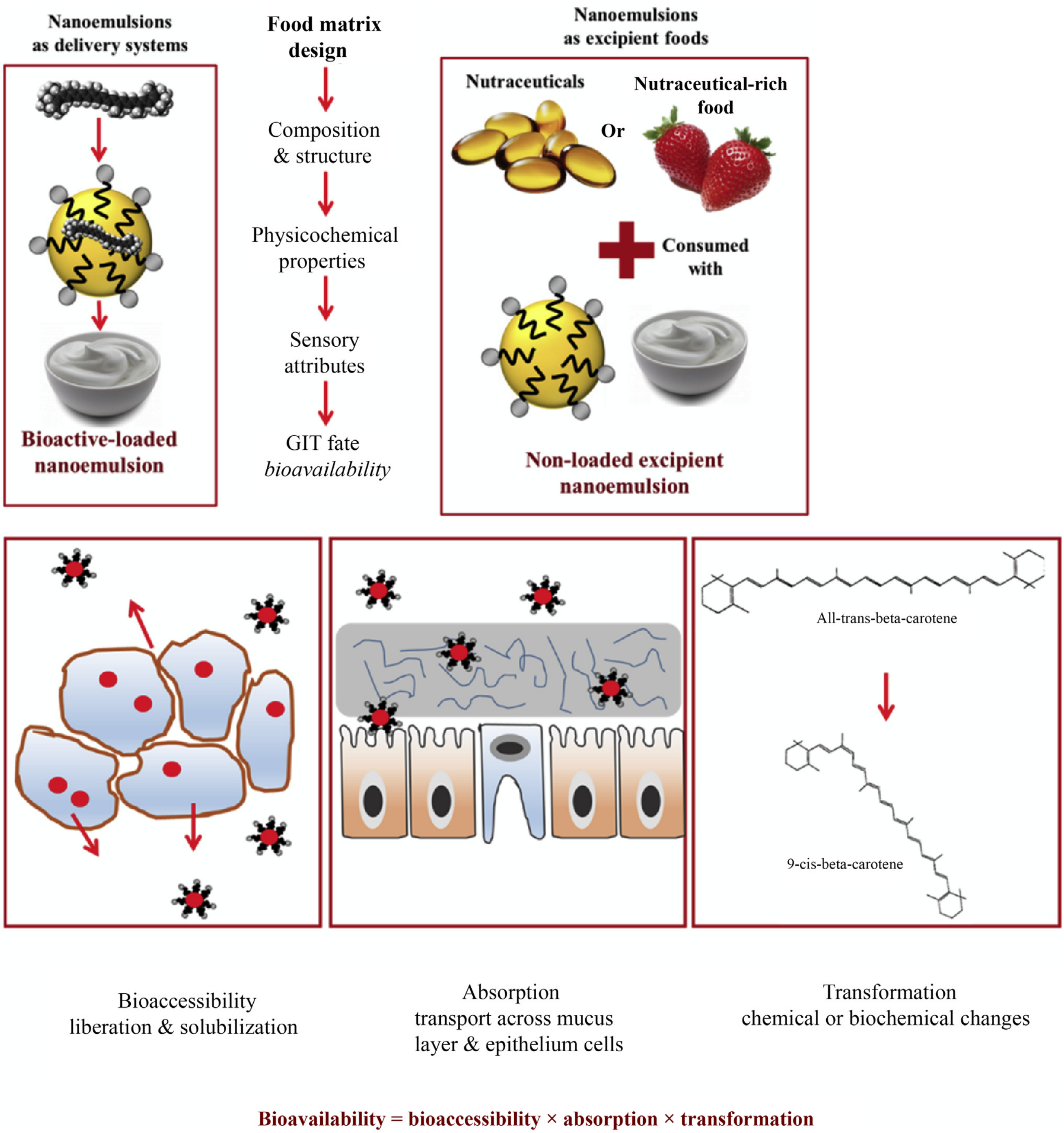

Figure 2 – Schematic diagram showing the delivery of bioactive components in food matrix. The overall oral bioavailability of bioactives is governed by three main factors: bioaccessibility, absorption, and transformation. GIT: gastro-intestinal tract. Reproduced with permission from "Excipient nanoemulsions for improving oral bioavailability of bioactives," by L. Salvia-Trujillo, O. Martín-Belloso, D.J. McClements, 2016, *Nanomaterials*, 6, p. 17 [43].

apples was retained, and the browning index was prevented in fresh-cut fruits stored in nano-ZnO packaging, which was only 23.9, much lower than that of the control group (31.7) on day 12. Zambrano-Zaragoza et al [67] also reported that treatment of fresh-cut *Red Delicious* apples with nanocapsules containing DL-α-tocopherol with a poly-ε-caprolactone biopolymer membrane significantly reduced the browning index.

2.2.2. *Flavors*

As one of most important parts of the food system, flavors deliver sensory perception of taste and smell to enhance the overall eating experience. Nanoencapsulation techniques have widely been used to improve flavor release and flavor retention, and to deliver culinary balance [68]. It has also been shown that SiO_2 nanomaterials can act as carriers of fragrances or flavors in food and nonfood products [69,70].

2.3. Enhancement of physical properties

2.3.1. Color additives

As required by law, food color additives are subjected to approval by the Office of Cosmetics and Colors in the Center for Food Safety and Applied Nutrition, the U.S. FDA, and must be used only in compliance with the approved uses, specifications, and restrictions. With the advent of nanotechnology, a wide range of nanoscale color additives are being studied and manufactured. Certain nanomaterial products have currently been approved for use as food color additives, which have a vital role in the psychological appeal of consumer products. The U.S. FDA approved TiO_2 as a food color additive with the stipulation that the additive should not to exceed 1% w/w [71] and now are exempted from certification [72]. Color additive mixtures for food use made with TiO_2 may also contain SiO_2 and/or Al_2O_3, as dispersing aids—not more than 2% total. However, the use of carbon black as a food color additive is no longer authorized [73].

2.3.2. Anticaking agents

SiO_2 is used mainly to thicken pastes, as an anticaking agent to maintain flow properties in powdered products, and as a carrier of fragrances or flavors in food and nonfood products. It has widely been applied in food products and registered within the EU as a food additive (E551). Recent research showed that in powdered food materials containing E551, at least a part of the SiO_2 is in the nanosize range [69,70]. Moreover, findings also suggest that, upon consumption of foods containing E551, the gut epithelium is most likely exposed to nanosized SiO_2 [74,75].

2.3.3. Others

In addition to the abovementioned benefits, nanomaterials have also been constantly developed to enhance the physical and mechanical properties of packaging in terms of tensile strength, rigidity, gas permeability, water resistance, flame resistance, etc. Aimed at providing those aforementioned properties, polymer nanocomposites are the latest materials with a huge potential for application in the active food packaging industry [76]. Polymer nanocomposites with layered silicates were introduced in the 1990s [77,78]. As these new polymer nanomaterials are much stronger [79], more flame resistant [80], as well as having a potential role in UV-shielding applications [81], they are widely reported to have the potential to completely transform the food packaging industry [82]. Readers are encouraged to read the more extensive reviews listed in the reference section [83,84]. Notably, biodegradable polymer nanocomposites from renewable sources (biopolymers) are emerging as an alternative to synthetic plastic packaging materials, especially for use in short-term packaging and disposable applications [85,86].

3. Safety concerns

As the investigation into the application of nanotechnology in the food sector increases, the potential of nanotechnology in food science/industry also expands, and consequently so does the human exposure to these substances [87]. It is inevitable that human exposure to nanomaterials will increase in various ways, either intended or unintended. However, a few studies have focused on the potential toxicity of the presence of nanomaterials in foods, by analyzing food samples used in food additives/ingredients and food packaging. Little is known about the bioavailability, biodistribution, routes of nanomaterials, and the ultimate toxicity upon exposure to them. Most noticeably, nanomaterials, serving as food additives, come in direct contact with human organs. It may result in higher levels of exposure depending on their concentration in food and the amount of that food consumed. Increasing uses of nanomaterial substances in foods as flavor or color additives have attracted significant attention of public and government sectors [88]. A study on TiO_2 in sugar-coated chewing gum found that over 93% of TiO_2 in gum is of nanosize [89]. It is unexpectedly easy for TiO_2 to be released, be swallowed by a person chewing the gum, and be accumulated in the body gradually [89]. Similarly, the gut epithelium is most likely exposed to SiO_2 nanoparticles upon consumption of foods containing E551 [74,75].

In addition, nanoencapsulation also allows direct contact of nanomaterials with humans through oral intake. SiO_2 nanomaterials, one of the most used food nanomaterials, have been studied as carriers of fragrances or flavors in food products [69,70]. Lipid-based nanoencapsulation systems are also being developed to enhance the performance of antioxidants by improving their solubility and bioavailability [90], and entrap bioactives for targeted site-specific delivery and efficient absorption [91]. However, the safety of nanoencapsulation remains uninvestigated and calls for further risk assessment [92], particularly for long-term toxicity [88,93].

Nanoscale edible coatings have emerged as an attractive alternative to preserve food quality, extend storage life, and prevent microbial spoilage [94,95], allowing direct exposure of humans to nanomaterials. For instance, gelatin-based edible coatings containing cellulose nanocrystals [96], chitosan/nanosilica coatings [97], chitosan film with nano-SiO_2 [98], and alginate/lysozyme nanolaminate coatings have been reported to preserve the quality of fresh foods during extended storage [99]. In addition, another novel nanopacking method by blending polyethylene with nanopowder (nano-Ag, kaolin, anatase TiO_2, and rutile TiO_2) was also evaluated to assess its effect on preservation quality of strawberry fruits (*Fragaria ananassa* Duch. cv Fengxiang) [100]. However, none of them provided toxicological studies with respect to nanomaterial exposure.

In other cases, exposure may occur unintentionally via leaching from nanopackaging [101]. Nanoclay from food contact materials was found to migrate into food simulants [102]. It was observed that aluminum migrated into solutions both in dissolved form and as a part of nanoparticles, with a maximum migration value of 51.65 ng/cm^2 for the Aisaika bags and 24.14 ng/cm^2 for the Debbie Meyer bags [102].

Furthermore, it was found that migration of nanoclay from the multilayer film into food simulants increased with increasing contact time and temperature [103]. Moreover, inhalation of food packaging nanomaterials and their entrance through skin penetration is almost exclusively related to workers in the nanomaterial-producing industries [76]. Nevertheless, the number of tests on migration is still largely limited, and further investigation is needed before widely applying these materials.

It should be noted that the ultimate fate and toxicity of nanomaterials in foods and food packaging depend on physiochemical characteristics and dose [12,13]. Safe application of nanotechnology to the food industry requires thorough characterization and assessment *in silico* [104,105], *in vitro* [60], and *in vivo* [61]. Altogether, taking into consideration physical forces, osmotic concentration, pH, chemical factors, biological molecules, and commensal microbes, their absorption, distribution, metabolism, excretion, and ultimate toxicity could be quantified and evaluated for risk assessment [12,13,106,107].

Two major concerns, allergy and heavy metal release, of the adverse effects of nanomaterial exposure are briefly discussed in the following sections.

3.1. Allergies

Although nanotechnology is being developed to advance food-allergen management [108,109], one cannot ignore the fact that certain nanomaterials may promote allergic pulmonary inflammation [110–112]. A review of literature revealed promoted inflammatory response and increased ROS production to be common immune responses to nanomaterial exposure [112]. Literature indicates that SiO_2 nanoparticles can induce allergen-specific Th2-type allergic immune responses *in vivo*, as evident from a study of female BALB/c mice exposed to nanoparticles [110]. Intranasal exposure to ovalbumin (OVA) plus SiO_2 nanoparticles tended to induce a relatively high level of OVA-specific immunoglobulin (Ig) E, IgG, and IgG1 antibodies [110]. Exposure to Ag nanoparticles was also reported to be able to induce nanoparticle-specific immune responses [113].

Moreover, carbon nanomaterials are well known to cause allergic inflammation. It has been reported that single- and multiwalled carbon nanotubes increased lung inflammation and allergen-specific IgE levels in mice sensitized to OVA egg allergen [114]. Ryman-Rasmussen et al [115] also reported that multiwalled carbon nanotubes with preexisting inflammation would increase airway fibrosis in mice with allergic asthma. Furthermore, the research group of Lefebvre et al [116] found that carbon black nanoparticles with a smaller particle size, a higher specific surface area, and higher purity were associated with the direct adjuvant effect on Th2 cells in this genetically susceptible model of OVA allergy. They reported that coincubation of $OVA_{323-339}$ peptide with 12 μg/mL of 22 nm carbon black nanoparticles enhanced gene expression of *interleukin-4* (*IL-4*), *IL-10*, and *IL-13*, all allergy-associated Th2 cytokines. In addition, coincubation of $OVA_{323-339}$ peptide with 12 μg/mL of 9 nm carbon black nanoparticles significantly enhanced *IL-13* gene expression concurrent with the downregulation of the Th1-associated transcription factor *Stat4*.

3.2. Heavy metal release

Metal-based nanomaterials integrated with food contact polymers have been reported to enhance mechanical and barrier properties, prevent photodegradation of plastics, and serve as effective antimicrobials in the form of heavy metal ions [117]. It is well known that releases of heavy metals from nanomaterials are one of the major routes that lead to toxic outcomes [12,13]. Thus, one cannot ignore the possibility of the adverse effects of heavy metal releases into food simulants, particularly their long-term accumulation. Among metal-based nanomaterials, ZnO [118], Ag [119,120], and CuO [121] are three mostly reported metal-leaching nanomaterials. Most likely, the release of metal ions from those metallic nanomaterials is highly correlated to an increase of intracellular ROS level [118], further resulting in lipid peroxidation and DNA damage.

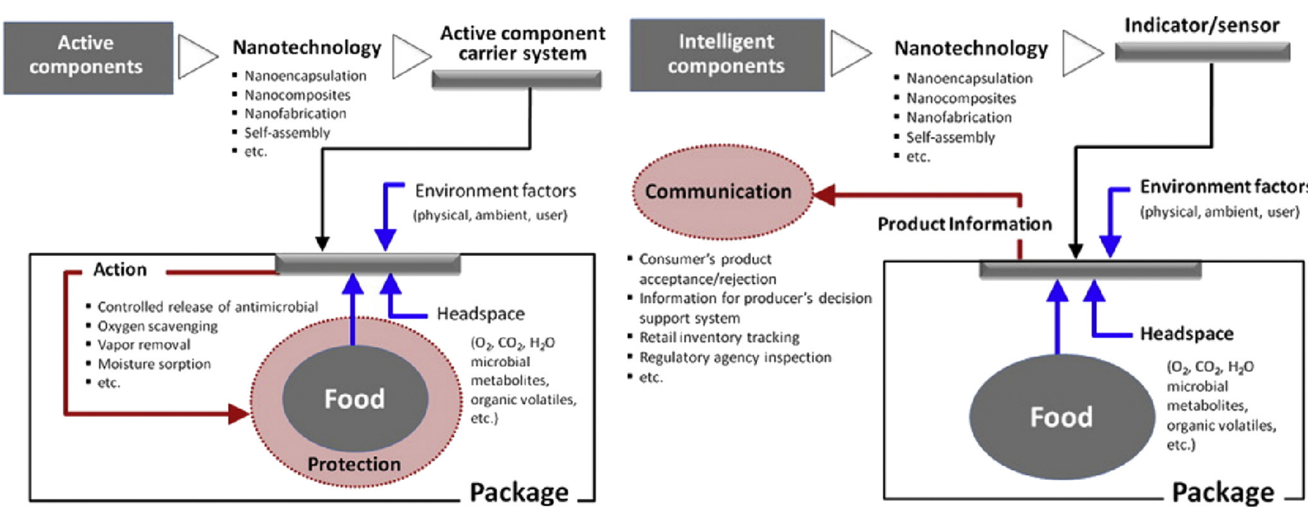

Figure 3 – Development of nanotechnology and its application in active and intelligent packaging. Reproduced with permission from "Nanotechnology development in food packaging: A review," by S.D.F. Mihindukulasuriya, L.T. Lim, 2014, *Trends Food Sci Technol, 40, p.* 149–67 [131].

4. Implication and perspectives

One should be cautious but not afraid, to embrace the development of nanotechnology and its application in food science and the food industry, along with its success in other various fields [12,122–124]. Although the fate and potential toxicity of nanomaterials are not fully understood at this time, it is evident that there have been significant advances in the application of novel nanotechnology in the food industry In addition to the benefits we discuss in this review, nanotechnology can also assist in the detection of pesticides [125], pathogens [126,127], and toxins [128], serving in the food quality tracking–tracing–monitoring chain. Furthermore, nanotechnology has the potential to transform our future food packaging materials, as part of an active and intelligent packaging system [129–131], as described in Figure 3. However, the challenges to develop a healthy and sustainable food industry remain even with the advent of nanotechnology. The associated health, safety, and environmental impacts should be addressed and regulated at the forefront. To be successful in the long run, proper education of the public is also paramount in the introduction and development of nanotechnology in food system.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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