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Original

Application of metal oxide/metal nanoparticle-based antimicrobial films in food packaging: Potential use, risk factors, safety assessments and regulatory matters

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Abstract: Packaging is an important feature of our everyday life and it has a vital role in the food industry. A lot of work is being done for diversifying the role of packaging, including its use for increasing the storage time of food items. In this review, we discuss the role of commonly used metals and metal oxide nanoparticle-based antimicrobial agents as components of packaging material. The potential antimicrobial activity of zinc oxide and titanium dioxide is discussed in detail; and as for metals, we use silver and gold nanoparticles as role models to study their application in packaging. Also, the potential health hazards derived from the probable leaching of packaging nanomaterial to food are addressed. Furthermore, safety assessment and key routes for nanoparticle migration from packaging material to food are discussed. Finally, this paper addresses the regulations for nanoparticle application in food packing, by comparing and contrasting the major economies of the world.

Keywords: Nanoparticles, food-packaging, anti-microbial activity, regulations

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1. Introduction

At the present time of rapid economic development and globalization, the food industry has witnessed a massive change. The emergence of working couples and nuclear families has led to a leap in the growth of the packaged food/packed food industry. With growing awareness and increased buying capacity, consumers are willing to pay for ready-to-eat food products. It is important to note that the current trend in the food industry favors minimally processed foods with a feeling of freshness. The major challenges faced in food processing include surface dehydration, oxidation, contamination via processing environment as well as processing equipment like cutting boards, knives, working surfaces, etc. These factors put forth a need for the robust packaging system which not only plays a primary role of wrapping and transportation but also helps in extending the usable life and ensuring traceability of the products (Duncan, 2011; Llorens et al., 2012; Luo et al., 2021; Weiskopf et al., 2020). With these points in consideration, the application of nanotechnology in the food industry is slowly but steadily attracting research interest.

Among all the potential applications of nanoscience and technology, the most coveted area is food packaging. This is attributed to the fact that consumers, in general, have a greater need of novel materials for take-out food packaging rather than of the fortification of food with nanoparticles. The major roles of nanomaterials in food packaging are as follows:

a. They act as nano reinforcements and improve the mechanical and barrier properties of polymers used in packaging.
b. In packaging material, nanoparticles interact with food and its environment, thereby they act as smart and/or active packaging.

The properties induced by nanomaterials in food packaging systems are usually related to safety and stability of the content or are informative about the safety and stability of the content. (Hur et al., 2005). One important application of nanomaterials is antimicrobial packaging (Soysal et al., 2015) because they constitute a better alternative to the conventionally used chemical preservatives, which mainly include organic acids and their salts such as potassium sorbate, propionic acid, benzoic acid, ascorbic acid, citric acid, acetic acids, and alcohols, which are predominant because of their low prices and affordability (Mlalila et al., 2018).

According to Santiago-Silva et al., antimicrobial packaging interacts with packaged food or package headspace in order to reduce, retard, or even inhibit the growth of spoilage and pathogenic microorganisms (Santiago-Silva et al., 2009).

Though the exact mechanism of antibacterial action is yet to be comprehended, there are a few possible mechanistic pathways to achieve antimicrobial action (Dobrucka & Ankiel, 2019; Kim et al., 2007; Pandimurugan & Sankaranarayanan, 2021; Pulit et al., 2011; Rabea et al., 2003; Weir et al., 2008). These are summarized in Fig. 1.

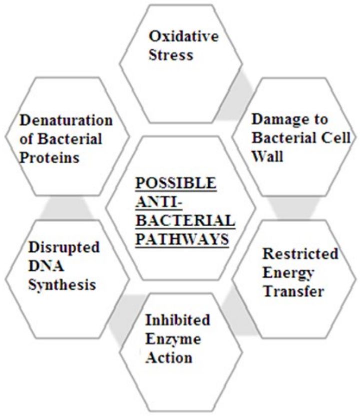

Figure 1. Different mechanistic pathways of antibacterial active packaging.

Several materials have been included in the polymer packaging to form composite materials. In this review article, we have discussed the use of metal oxides and metals in the food packaging industry. The commonly used metal oxide nanoparticles in food packaging are TiO_2, ZnO, Al_2O_3 and silica while common metals used include copper and silver. They have a potential to perform multiple functions including photocatalysis, antimicrobial actions, ethylene scavenging, imparting greater mechanical strength and barrier properties (Bumbudsanpharoke et al., 2015; Llorens et al., 2012). In this review, we have reviewed these materials. We have also included the potential toxicity of such materials and eventually the role of government in regulating such packaging.

2. Nanoparticles (NPs) as food packaging material

The advancement in nanotechnology has brought several opportunities for the design and fabrication of novel materials having some unique properties.

Therefore, NPs are being actively used in developing advanced intelligent packaging materials. Integrating NPs into polymeric matrix endows numerous benefits such as it makes packing composite much stronger, lighter and less permeable (Llorens et al., 2012; Videira-Quintela et al., 2021). Further, NPs having inherent antimicrobial activities if incorporated into the polymer helps in preserving food by harmful and spoilage bacteria, fungi and viruses and hence contribute to extend shelf life of food. It has a potential use in extending the shelf life of fresh fruits, salads and, also, meat-based products. Besides, NPs can also block harmful UV radiation and can perform oxygen and ethylene scavenging. In this section various metal NPs and metal oxides NPs that have been used as nanofillers to improve packaging quality and performance (Ahmad et al., 2021; Mihaly Cozmuta et al., 2015; Reig et al., 2014; Videira-Quintela et al., 2021; Wyser et al., 2016; Zhang et al., 2017) are discussed.

2.1. Metal oxides as food packaging material

2.1.1. ZnO as food packaging material

Zinc oxide (ZnO) is an inorganic compound which is widely used in our day-to-day life. ZnO nanoparticles have demonstrated excellent antimicrobial properties. It is easy to synthesize, economical and readily available. Further, it has been listed 'safe' by the Food and Drug Administration (21CFR182.8991) and hence is widely used as an additive for food preservation and packaging material to improve packaging properties. Several literature studies showcase that polymeric films with ZnO NPs in their network show better mechanical strength, durability and blockade properties (Emamhadi et al., 2020; Espitia et al., 2012). Pantani et al. have synthesized polylactic acid (PLA)-ZnO nanocomposite films that presented antimicrobial efficacy against both Gram-positive and Gram-negative bacteria while neat PLA have no such activity (Pantani et al., 2013). Also, PLA-ZnO nanocomposite effectively increased the tortuosity of the diffusive path by reducing the permeability of molecules in comparison with neat polyester matrix. Besides, Premanathan et al. also validated the antibacterial activity of ZnO against Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and gram-positive bacteria (*Staphylococcus aureus*) (Premanathan et al., 2011). They have found that antibacterial properties of ZnO NPs is more reflective against Gram positive bacteria. The sensitivity of ZnO more towards Gram positive bacteria might be because of its strong affinity with *Escherichia coli cells*. Similarly, chitosan and polyvinyl alcohol films incorporated with ZnO NPs illustrate antibacterial activity against *S. aureus* (Vicentini et al., 2010). Pirsa et al. described the modification of bacterial cellulose film by polypyrrole-ZnO nanocomposites (BC-PPy-ZnO) by chemical polymerization method (Pirsa & Shamusi, 2019). Composite was studied for the packaging of fresh chopped chicken meat. They reported that the use of BC-PPy-ZnO films evidently reduced the growth of microbes in chicken thigh and, also, regulated the increasing ph. Hence, the shelf life of chicken thigh was increased by using modified packaging material. In another study, Emamifar et al. reported that LDPE films with ZnO NPs inhibited the growth rate of *Lactobacillus plantarum* present in orange juice and thus prolonged its shelf life to 28 days without causing negative effects on sensory parameters (Emamifar et al., 2011).

According to published literature, the antimicrobial activity of ZnO NPs can be explained based on several mechanisms. The basic step is generation of reactive oxygen species which in turn create oxygen stress in the bacterial cell (as shown in Fig. 2). The detailed mechanism is discussed in the following section.

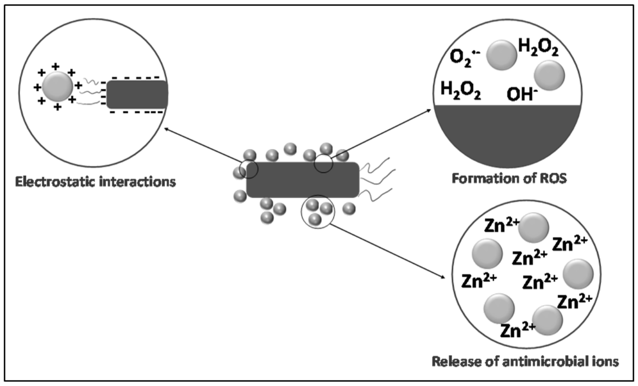

Figure 2. Possible mechanisms for the antimicrobial activity of ZnO NPs.

a) Release of antimicrobial Zn^{2+} ions:

Several researchers believe that the antibacterial activity of ZnO stems from the release of Zn^{2+} from the packaging material (Kasemets et al., 2009; Reddy et al., 2007; Wang et al., 2009). Solubility of ZnO in a medium depends on the concentration and time. For instance, Reddy et al. analyzed the toxicity of ZnO NPs (having different concentrations) on *E. coli* (Reddy et al., 2007). They observed complete inhibition of *E. coli* growth at concentrations ≥3.4 mM while with 1 mM of ZnO, an increase in the number of colony-forming units was observed which shows the preference of microorganisms for lower concentrations of Zn^{2+} in medium. Hence, low concentrations of Zn^{2+} ions can induce a comparatively high tolerance by the microorganism.

b) Formation of reactive oxygen species:

This mechanism is based on the semiconductive properties of ZnO NPs. Whenever there is an activation of ZnO NPs by UV or visible radiation with energy higher than 3.3 eV (band gap of ZnO), shift of electrons into the conduction band from the valance band creates a hole in valance band and an excess electron in conduction band (Espitia et al., 2012; Seven et al., 2004). These electron holes and free electrons reacts with different molecules such as H_2O, O_2 etc. forming several reactive oxygen species (ROS such as $OH^{\bullet}$, H_2O_2, $HO_2^{\bullet}$, $O_2^{\bullet-}$, etc.) (Gordon et al., 2011; Zhang et al., 2008). These ROS being very reactive and strong oxidizing agent are toxic to the bacteria cell. More active H_2O_2 can penetrate the bacterial cell and causes further damage to the bacteria.

c) Interaction of NPs with microorganisms:

This mechanism has been explained well through the study of antimicrobial effect of ZnO NPs against *E. coli* (Zhang et al., 2008). Due to the presence of carboxylic groups on the bacterial surface, the global charge at its cell surface is negative. ZnO on the other hand have a positive charge, therefore, there exists an electrostatic interaction between the bacteria and ZnONPs due to which there is a strong binding between the two which causes cell membrane damages to bacteria (Stoimenov et al., 2002; Zhang et al., 2008).

It is well known that the properties of NPs greatly depend on their size and may vary as size changes. On this note, Yamamoto studied the influence of different sized ZnO NPs (ranging from 0.1 to 0.8 µm) on its antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* (Yamamoto, 2001). Author assessed that for both bacteria's, antibacterial activity of NPs is inversely related to the particle size and decreases as size of ZnO NPs increases (Fig. 3).

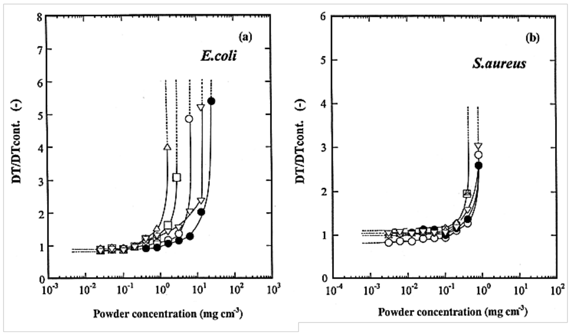

Figure 3. Influence of different sized ZnO NPs on antibacterial activity against (a) *E. coli* and (b) *S. aureus*. ZnO concentrations: (Δ) 0.1 µm (□) 0.2 µm (○) 0.3 µm (▽) 0.5 µm and (●) 0.8 µm. Reproduced with permission from ref (Yamamoto, 2001).

2.1.2. TiO2 as food packaging material

Nano-sized TiO_2 has been actively used for the development of active packaging films having improved functional properties (Kaewklin et al., 2018; Zhang & Rhim, 2022). Apart from food packaging it also finds applications in the food industry, cosmetics, construction, medicine, electronics, etc. A broad applicability of TiO_2 NPs is accredited to its multiple advantages including high stability, biocompatibility, low toxicity, antibacterial activity, photocatalytic activity, high refractive index and good ultraviolet blocking power. TiO_2 NPs have been incorporated in a number of polymeric films such as chitosan, hydroxypropyl methylcellulose, sago starch, gelatin and gellan gum, etc. (Baek et al., 2018; Goudarzi et al., 2017; He et al., 2016; Kaewklin et al., 2018; Razali et al., 2020). Various advantages of using TiO_2 NPs in polymeric films have been depicted in Table 1.

Hence it is clear that TiO_2 NPs are supreme fillers in food packaging materials. It exhibits excellent antibacterial properties and, also, inhibits harmful effects of UV radiation on food. It is biocompatible and has been approved by the US Food and Drug Administration to be used as food additives, provided that the amount of it is less than 1% of the total mass of the food (Zhang & Rhim, 2022). Besides this, TiO_2 also increases the physical, chemical and functional strength and gas barrier properties of the films. It also helps in boosting the shelf life of the food.

2.1.3. Other metal oxide nanoparticles as food packaging material

At present, metal oxides, other than TiO_2 and ZnO, are also gaining much attention as popular fillers to polymeric matrix to improve features of packaging materials. In this regard, Cu_2O NPs, CuO NPs, MgO NPs, Fe_3O_4 NPs, α-Fe_2O_3 have been potentially used by researchers (Al-Shabib et al., 2018; Khan et al., 2020; Saravanakumar et al., 2020; Vihodceva et al., 2021; Yan et al., 2021). Mixed metal oxides and metal-doped metal oxide polymeric films also show a very high antimicrobial activity and thus, are potential candidates for food packaging (Al-Tayyar et al., 2020; Azizi-Lalabadi et al., 2020; Panea et al., 2014; Vasiljevic et al., 2020). Table 2 summarizes some literature examples of other metal oxides and their antimicrobial properties.

2.2. Metal nanoparticles as food packaging material

For depicting the macrostructure, steel specimens were macro etched by keeping it in a 50% Hydrochloric acid solution at 80°C temperature for 30 minutes. For microstructure characterization, specimens

Metal NPs are also being actively used in developing both active and advanced intelligent packaging materials. NPs of silver and gold are non-toxic and possess excellent antimicrobial properties, high scope for functionalization and high thermal resistance (Hoseinnejad et al., 2018; Souza & Fernando, 2016). These NPs, once attached to the bacterial membrane, can cause modifications in membrane potential, adenosine triphosphate level and inhibit the binding of *t*RNA to ribosome. Therefore, they are quite effective antimicrobial agents in food packaging.

There are various factors that regulate the antimicrobial activity of NPs such as size, morphology, composition, concentration and target species. A study by Durán et al. demonstrates that if size of Ag NPs is large, silver ions rather than NPs are the dominant antimicrobial agents (Durán et al., 2016). Therefore, the antimicrobial action of silver can be attributed to two forms: Ag^0 and Ag^+ species. In various studies, stabilization of Ag NPs has been done by incorporating them into different polymer matrix. These polymeric matrixes are generally classified as non-degradable polymeric matrix and biodegradable edible coating film (Carbone et al., 2016). Moura et al. developed hydroxypropyl methylcellulose (HPMC)-based bactericidal nanocomposites containing silver nanoparticles (41 nm and 100 nm), HPMC/Ag NPs, that was found effective against *E. coli* and *S. aureus* (de Moura et al., 2012). The synthesized nanocomposites films possessed good mechanical, barrier properties and increased tensile strength of the films. The tensile strength of neat HPMC was found to be 28.3 ± 1.0 while that of HPMC/Ag NPs (41 nm) was 51.0 ± 0.9 MPa. Moreover, improved shelf stability was observed. Similarly, Bahrami and their group also reported a trinary bio-composite film based on Tragacanth/Hydroxypropyl methylcellulose/Beeswax reinforced Ag NPs (2, 4 and 8%) (Bahrami et al., 2019). In this case, AgNPs decreased the tensile strength of composite from 33.64 to 16.12 MPa. However, water vapor permeability was increased to $4.57\text{-}2.16\times10^{-13}$ g m/m^{2}sPa. Authors studied antimicrobial activity of bio-composite films against food-borne pathogens using disc diffusion method. Different gram-positive pathogen, such as *B. cereus*, *S. aureus*, *S. pneumonia* and *L. monocytogenes* and gram-negative pathogens including *E. coli*, *S. typhimorum*, *Ps. Aeruginosa* and *K. pneumoniae* were tested and it was found that bio-composites inhibited the growth of these pathogens in a dose-dependent manner. Furthermore, the concentration of Ag NPs was important as a higher percentage of Ag NPs to matrix showed a greater inhibition zones diameter against bacteria. Moreover, it was observed that gram-positive pathogens were less susceptible to the antimicrobial activity when compared to gram-negative ones.

Rajathi et al., reported a green and quick route to synthesize gold NPs using brown alga, *Stoechospermum marginatum* biomass (Rajathi et al., 2012). These NPs exhibited an inhibition zone against various bacterial pathogens (Table 3). A maximum and minimum zone of inhibition was observed against *E. faecalis* (11 mm) and *K. pneumoniae* (6 mm), respectively. However, no inhibition was found against *E. coli*.

Table 1. Effect of incorporation of TiO$_2$ NPs in various polymeric films.

Entry	Polymeric film	Advantages	Ref.
	Chitosan	• Increased food preservation ability • Decreased water vapor permeability (WVP) • Increased tensile strength • Better ethylene photodegradation ability • Improved mechanical and barrier properties of chitosan film	(Kaewklin et al., 2018)
	Gelatin	• Increased opacity • Decreased WVP • Increased tensile strength • Increased elongation at break (EB) • Better antimicrobial activity for *E. coli* after irradiating 120 min with UV light (365 nm) which were 54.38% for *E. coli* and 44.89% for Staphylococcus aureus respectively	(He et al., 2016)
	Starch/poly(vinyl alcohol)/	• Increased tensile strength • Increased opacity • Decreased WVP • UV blocking ability of starch/TiO2/PVA film increased as TiO$_2$ filler content rose	(Kochkina & Butikova, 2019)
	Carboxymethyl cellulose	• Increased opacity • Decreased WVP and moisture uptake • Better UV blocking properties	(Fathi Achachlouei and Zahedi, 2018)
	Oleic acid /Polylactic acid	• Increased opacity • Decreased WVP • Better O$_2$ and water barrier properties • Better UV blocking properties • Oleic acid improve the dispersion of TiO$_2$ in Polylactic acid and made it better packaging film	(Baek et al., 2018)
	Starch	• Increased EB • Decreased WVP • Increased hydrophobicity due to increased TiO$_2$ content • Increased UV-shielding property	(Goudarzi et al., 2017)
	Hydroxypropyl methylcellulose	• Increased EB	(Baek et al., 2018)
	Gellan gum	• Increased thickness • High tensile strength • Antimicrobial activity • Decreased water vapor permeability	(Razali et al., 2020)

Table 2. Other metal oxides used in food packaging and their antibacterial application.

Entry	Nanoparticles	Biopolymer	Food-item	Pathogen	Ref.
1.	Cu_2O	Polyvinyl alcohol-chitosan	Cherry tomato	*E. coli* and *S. aureus*	(Yan et al., 2021)
2.	CuO	Microcrystalline cellulose, sodium alginate	Pepper	*S. enteria* and *L. monocytogenes*	(Saravanakumar et al., 2020)
3.	MgO	-	-	*E. coli*	(Khan et al., 2020)
4.	Fe_2O_3	-	-	*E. coli*, *S. aureus* and *Vibrio fisheri*	(Vihodceva et al., 2021)
5.	Fe_3O_4	-	-	*E. coli*, *P. aureuginosa* and *L. monocytogenes*	(Al-Shabib et al., 2018; Gabrielyan et al., 2019)
6.	$FeMnO_3$	-	-	*B. subtilis*	(Vasiljevic et al., 2020)
7.	Zn-MgO	Alginate	Smoke salmon meat	*B. subtilis*, *S. aureus*, *Salmonella enterica*, *E. coli* and *Saccharomyces cerevisiae*	(Vizzini et al., 2020)
8.	Ag/ZnO	Low-density polyethylene	Chicken meat	*E. coli*, *P. aeruginosa* and *L. monocytogenes*	(Panea et al., 2014)
9.	ZnO/TiO_2	Polyvinyl alcohol /gelatin	Shrimp	*S. aureus*, *E. coli* O157H7 and *L. monocytogenes*	(Azizi-Lalabadi et al., 2020)
10	$ZnO\text{-}SiO_2$	polyvinyl alcohol /chitosan	Bread	*S. aureus* and *E. coli*	(Al-Tayyar et al., 2020)

Table 3. Antibacterial activity of gold nanoparticles (Arockiya Aarthi Rajathi et al., 2012).

Bacterial pathogens	Au NPs	Positive control (tetracycline)	Negative control (chloroauric acid)
P. aeruginosa	8	13	0
K. oxytoca	7	14	0
E. faecalis	11	9	0
K. pneumoniae	6	12	0
V. cholerae	8	15	0
E. coli	0	12	0
S. typhii	6	13	0
S. paratyphii	8	13	0
V. parahaemolyticus	9	17	0
P. vulgaris	8	14	0

3. Legislation for use of metal oxide/metal nanoparticles based antimicrobial films in food packaging applications

When it comes to food packaging, regulatory aspects play a crucial role. This is solely due to the essential nature of food commodities and their widespread outreach. National regulations for customary food contact materials are enacted for most of the nations but for novel materials including nanocomposites they are yet to be finalized and are non-uniform for different regions (economies). As a matter of fact, even the definition of nanomaterials is still debatable in different legislations. Besides, a single point agreement on the quantification of migration into food and subsequent toxicity is still far-fetched. The primary reason for this is the lack of standard, validated risk assessment criteria. In North America and Asia Pacific, the legislative bodies have provided a set of legal frames for the application of nanomaterial-based active and intelligent packaging within the food sector. Here, these materials are treated within the boundaries of conventional laws for food contact material. The legal framework in Europe is more rigid towards nanomaterials-based food packaging. At the same time, public acceptance for such materials has definitely increased. The development of active packaging got a boost by the global spread of the pandemic caused by SARS-CoV-2. Consumers are now ready to trust and invest in active packaging which can prevent the transmission of viruses and other pathogens (Imani et al., 2020; Mizielińska et al., 2021; Nikolic et al., 2021).

In this section, we will be dealing with the regulatory aspects of major economies with regard to nanomaterial-based packaging.

3.1. United States

The Food and Drug Administration of the US has not established very specific rules in the context of the use of nanomaterials in food packaging. It has rather handed a “Guidance for industry” and enlisted Generally Recognized as Safe (GRAS) substances. FDA however, warns that a GRAS status does not necessarily ensures the safeness of a material at nanoscale and thereby a case-to-case study is necessary (Administration, 2014; US, 2014). The FDA put an onus on the industry to warrant that their products meet the safety standards and pre-market monitoring of the material is mandatory. Another factor that the FDA has taken into consideration is that if the food contact material has an antimicrobial function, then it is regulated under Section 409 of the Federal Food, Drug and Cosmetic Act (FD&CA), and it also has to be registered with the Environmental Protection Agency (EPA) under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) (Misko, 2015).

Additionally, since August 2017, nanomaterials have to be reported as per the Toxic Substances Control Act (TSCA) (Agency). SnO_2, CuO, Al_2O_3,TiO_2, and ZnO are metal oxides enlisted under threshold of regulation exemptions for particular uses in food packaging and are exempted from the regulatory demands for food additives.

3.2. European Union

The most comprehensive and detailed regulations regarding nanotechnology in the food sector have been issued by the European Union. The EU has drafted an expansive “Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain” wherein the applicability of such products as food contact material has been gauged (Committee, 2011). The document comprises regulations regarding physicochemical characterization requirements of nanomaterials and testing approaches to ascertain the risks. However, the gap in knowledge as well as suitable testing tools led government to circulate certain decision trees in the industry which guide them to make choices to ensure consumer safety. Due to gaps in knowledge and lack of suitable testing methods certain decision trees are presented to guide industry make choices which ensure consumer safety.

In 2011, the commission Regulation (EU) No. 10/2011 on plastics and articles intended to come into contact was set (Commission, 2011). The main postulates of the commission are as follows:

a) The nanomaterials should be studied on case-to-case basis and no generalized regulations could be made for the same.
b) Though migration limits of (packaging material) 10mg/dm^2 for a cubic packaging for 1kg of food, equivalent to 60mg/kg of food were set, yet these limits did not apply to nanoparticles (owing to their high reactivity).
c) The regulations clearly mentioned that authorization of a material in bulk form does not imply authorization in nanoform (e.g., aluminum oxide and titanium oxide).

There are a few nanomaterials which have been approved for plastic based food packaging materials which can be included only under certain sets of conditions. They include butadiene ethyl acrylate-methyl methacrylate styrene copolymer (cross-linked with divinylbenezene, cross-linked with 1,3-butanediol dimethacrylate, or not cross-linked), carbonblack, TiN, SiO_2 (silanatedor not), ZnO, and (methacrylic acid, ethyl acrylate, n-butyl acrylate, methyl methacrylate and butadiene) copolymer (COMMISSION, 2015, 2016, 2017; Union, 2011).

ZnO was originally authorized in bulk form with a specific migration limit of 25mg/kg of food as Zn. The fact that any such migration would be ionic and not in the nano dimensions the migration limit was decreased to 5mg/kg of food (Union, 2011). Furthermore, ZnO nanoparticles [uncoated or coated with 3- (methacryloxy) propyl trimethoxysilane] were approved for use as UV-light absorbers in unplasticized polymers, and a migration limit of 0.05 mg/kg was set for the coated form (COMMISSION, 2017).

The stringent regulations greater consumer guardedness towards nanotechnology are the major reasons for lesser popularity and availability of such products in the EU as compared to the US and China (Bott et al., 2014; Bumbudsanpharoke et al., 2015; Mihindukulasuriya & Lim, 2014).

3.3. Other economies

Though other economies lack exhaustive regulations like those issued by the European Union, some guidance documents are in place to have at least a set of rules for industries to abide by. As several food packaging products available in the market already contain nanomaterials, several government and local agencies have conducted research plans to evaluate safety of such materials (Bumbudsanpharoke et al., 2015).

For instance, Canada lacks specific regulations for nanomaterials, and the current regulatory framework does not distinguish between bulk and nanoform of same material. But under the current circumstances, the Canadian Government is taking a stepwise approach for developing a regulatory framework for nanomaterials and has a website for nanotechnology ("NanoCanada").

The southern continents of Australia and New Zealand issued a handbook entitled “Nanotechnologies in Food Packaging: An Exploratory Appraisal of Safety and Regulation” in 2016 (Hagen & Drew, 2016). This report included a comprehensive literature review on migration of nanomaterials from packaging material into food and reported negligible migration of nanoparticles into food. It, however, emphasized that due to an incomplete assessment of the migration, the ambiguity of the study remains.

The other major economies like China, Japan and Korea lack such regulations, though the governments of these countries have identified this knowledge gap and are working towards establishing well-defined, stringent regulations to ensure the consumer’s safety (Bumbudsanpharoke et al., 2015).

4. Potential toxicity of metal oxide/metal nanoparticles-based antimicrobial films in food packaging applications

The application of metal oxide/metal nanoparticles in food packaging films can revolutionize the food industry. Besides exhibiting antimicrobial properties, these films possess improved flexibility, barrier properties, mechanical strength and thermal resistance (Bumbudsanpharoke et al., 2015; Chaudhry et al., 2008). They are capable of imparting functional properties as active film materials and increase the shelf life of food products and improve food safety. But a fact, however, that remains is that nano-engineered films are food contact materials, and certain aspects of concern are associated with their use. In this regard, Jokarel et al. posed six questions which greatly help in comprehending the potential commercial applicability of nanoparticles-based antimicrobial films in food packaging (Jokar et al., 2017). These questions are as follows (Fig 4):

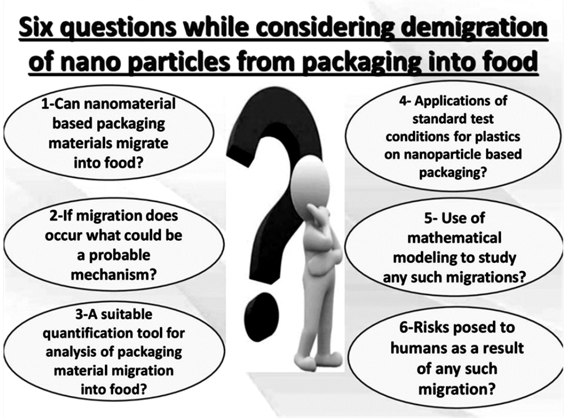

Figure 4. Six questions for applicability of nanoparticles in food packaging.

After thorough investigation, the group reported that though several studies have been conducted on the migration of nanoparticles from food contact materials to food, a conclusive answer is still yet to be reached. They attributed this to the absence of a suitable analytical method to detect and quantify nanoparticles in such a small size and concentration range. They strongly advocated the use of analytical tools, like single-particle inductively coupled plasma mass spectrometry (SP-ICP-MS), for such studies (Hetzer et al., 2017; Ramos et al., 2016). They also identified three subprocesses in nanoparticle migration, which are as follows (Jokar et al., 2017) (Fig.5):

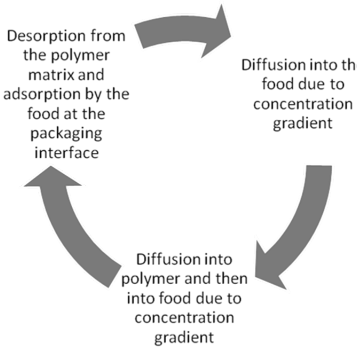

Figure 5. Possible routes of migration of nanoparticles from food contact material to food.

Another area of concern that was raised by them was the influence of nanoparticles on the gastrointestinal absorption and the role of the gut environment on the physical and chemical aspects of nanomaterials (McClements et al., 2017). The lack of knowledge and comprehension in this area is the major reason behind the absence of common established legislation regarding nanotechnology application in the global context.

The following sections review case-based studies done on the aspects of safety assessment and migration of nanoparticles from food contact material to food.

4.1. Safety assessment of silver nanoparticles

Silver metal plays no role in animal biology and the average daily intake through food ranges from 20-80 micrograms (De Matteis, 2017; Medici et al., 2019). It has been reported that silver nanoparticles can enter the different organs of body through the blood stream via the mucus layer of the gastrointestinal track (Ferdous & Nemmar, 2020). The other entry points are lungs, nasal mucosa, epithelial layer of skin and conjunctiva of eyes. Bioaccumulation of nano silver reportedly takes place in the spleen, liver, skin, mucous, bone marrow and muscles (Naseer et al., 2018).

The biologically active form of silver is its soluble cationic form, Ag^+, which can be ionized by body fluids as well. The health impact of the intake of silver nanoparticles is a matter of concern (Boudreau et al., 2016). Boudreau and et al. performed a 13-week study on Spargue-Dawley rats to evaluate and compare the toxicity of ionic and particulate silver nanoparticles (Hadrup & Lam, 2014). The study focused on the difference in the bioaccumulation, morphology, distribution and toxicity of nano silver and the ionic silver (source silver acetate). It was observed that the uptake of silver nanoparticles showed no significant effect on the body weight, reproductive system, blood and genetic material. Another significant observation has been that silver nanoparticles were largely found within the cells, while ionic silver was mainly found in the extracellular membranes. A considerable size dependency was also observed in the case of tissue accumulation of silver nanoparticles.

Through studies in animals, it has been found out that the oral toxicity of silver is associated with weight loss, interference with liver enzymes, neurotransmitter levels, distended heart and immunological effects (Copper & Jolly, 1970).

The physio-chemical properties of silver in gut showed an interesting behavior because of the difference in pH in various organs. The neutral pH of the mouth impended accumulation and dissolution but led to the generation of biomolecular corona. The acidic pH of the stomach prevented aggregation but promoted dissociation. In the small intestine, silver existed only in its biomolecular form (Ahmad et al., 2021).

The potential cytotoxicity, genotoxicity and increased inflammatory response of silver makes it mandatory to have an extensive migration study conducted before using it as a potential food packaging material.

Gallocchio et al. worked on silver nanoparticle migration from a commercially available packaging to chicken meatballs. They created a conceivable domestic storage condition and tested the packaging's efficiency in preventing bacterial spoilage (Gallocchio et al., 2016). The study revealed a rather slow migration and no significant contribution of the nanoparticles to slow down bacterial proliferation. In another attempt to study a possible migration of silver nanoparticles to food, Tiimob and coworkers tested the migration of eggshell-silver tailored co-polyester polymer blend film to distilled water and chicken breast (Tiimob et al., 2017). With the aid of atomic absorption spectroscopy, they concluded that the silver nanoparticles took 168 h to migrate to chicken breast, and 72 h to distilled water. Su et al. performed pH-based studies to estimate the role of organic additives (Irganox 1076, Irgafos 168, Chimassorb 944, Tinuvin 622, UV-531 and UV-P) on the release of silver from nanosilver-polyethylene composite films. They employed inductively coupled plasma mass spectrometry for their analysis. The sample contained an acidic food simulant (3% acetic acid) and found that the release silver nanoparticles was governed by two processes: (a) the extent of silver oxidation was a key player in inhibition or promotion of silver nanoparticle migration; (b) the reaction between the organic additives and silver nanoparticles promoted the migration of silver nanoparticles from the packaging film to an acidic food stimulant (Su et al., 2017). It was also observed that the silver release was promoted by high humidity and temperatures. Hosseini et al. measured the migration of silver nanoparticles from polyethylene packaging containing titania and silver nanoparticles. They studied the migration to a species of prawns, Penaeus semisulcatus, and established that the titrimetric analysis has a better sensitivity than other methods to study nanoparticle migration (Hosseini et al., 2017). Hannon and their group studied the release of silver nanoparticles (spray-coated on the surface of polyester and low density polyethylene) from packaging material to milk (Hannon et al., 2018). The results suggested that the spray coating process reduced the migration of silver nanoparticles.

4.2. Safety assessment of zinc oxide nanoparticles

The ZnO-based active packaging material does have a potential risk to seep in the food, thereby exposing consumers to these nanoparticles. The in vivo studies suggested that the major routes of ZnO nanoparticle entry are ingestion, inhalation and parenteral (Król et al., 2017). Ansar and et al. worked on male Wistar rats to study the neurotoxicity of zinc oxide nanoparticles (Ansar et al., 2017). They indicated that

ZnO nanoparticles resulted in various alterations in brain tissues and attributed it to the oxidative stress. The presence of ZnO nanoparticles resulted in elevated inflammatory cytokines and decreased glutathione and antioxidant levels. They further worked on attenuation of the toxicity induced by ZnO nanoparticles and observed that Hesperidin was beneficial in this regard as it relived oxidative stress. In a similar work Senapati et al observed that the age of mice played a crucial role in ZnO nanoparticles induced immune toxicity. The sub-acute exposure of BALB/c mice showed that the aged mice were more vulnerable to ZnO nanoparticles-induced immune-toxicity (Senapati et al., 2017). However, there is still a gap in the understanding of the potential exposure to ZnO nanoparticles contained in food packaging and its subsequent impact on human health. A 100 times higher than the recommended dietary allowance of zinc in food was observed by Moreno-Olivas's group (Moreno-Olivas et al., 2018). They found that the presence of ZnO nanoparticles severely affected the absorption and transportation of nutrients. The study led to an important observation: the fact that the ZnO nanoparticles significantly reduced glucose absorption by reducing the surface area of microvilli of intestinal cells. The authors also found out that these nanoparticles upregulated pro-inflammatory genes to bring about pro-inflammatory responses. The study stressed the need of the quantification of the number of nanoparticles and of disclosure about the type, amount and size of the nanoparticles used.

In order to reap the benefits of ZnO nanoparticles in antimicrobial food packaging and to avoid the toxic side effects, Chia and Leong modified the surface of ZnO nanoparticles by silica coatings (Chia & Leong, 2016). They employed tetraethoxysilane as a precursor to form a silica coating on the ZnO surface. Using synthetic gastrointestinal fluids for in-vitro studies, they observed that the presence of silica coating maintains the antimicrobial properties of ZnO nanoparticles while reducing their toxicity. They also highlighted the fact that silica coating is stable in both acidic and neutral conditions, hence it can survive the various conditions of different parts of the gastrointestinal track. The study, however, warned against excessive use of silica as a higher dose of silica induces cytotoxicity in colorectal epithelial cells.

4.3. TiO_2 safety assessments

The focus of the studies conducted on TiO_2 toxicity so far has been on exposure via inhalation. TiO_2 nanoparticles have been categorized as Group 2B carcinogen by the International Agency for Research on Cancer (Winkler et al., 2018). In a work on the effect of titania nanoparticles concentration on sperm cell velocity of rainbow trout, Ozgur and coworkers observed that nanoparticles concentration had a vital role in the regulation of superoxide dismutase and total glutathione levels (Özgür et al., 2018). Salarbashi and their group reported the existence of TiO_2 nanoparticles in plasma membranes of epithelial cell lines on a 10 day-exposure to free nanomaterials (Salarbashi et al., 2018). The interaction of TiO_2 nanoparticles and biomolecules was studied by Jo et al. (2016). They studied the chemical interaction between the nanoparticles and albumin and glucose and observed a change in the physico-chemical characteristics of biomolecules. The study also revealed that though food-grade nanoparticles were better absorbed via oral route, they were excreted through feces.

5. Conclusions

Extensive research supports the idea that metal oxide and metal nanoparticle-based nanocomposites enhance the mechanical barrier and antimicrobial properties of food packaging materials. They have been shown to have a detrimental effect on the growth of several bacterial strains, have good oxygen and water barriers and can be a potential alternative to petroleum-based plastics.

Migration studies conducted so far have demonstrated that the amount of nanomaterial seeping in food is negligible and that the associated risks tend to be low. A few studies have pointed out that when these nanocomposites are used just to enhance the mechanical and barrier properties, a functional barrier between food and packaging could be applied to further curtail the risk of migration. Another way of preventing migration could be the use of doped oxides instead of pure oxides. At the same time, the knowledge gaps in this area cannot be denied as there is still a lack of understanding of the migration, toxicity and characterization of nanoparticles and of human-based studies.

Another challenge in this area is the lack of regulation of the use of nanomaterials as food contact material, this is true even in developed economies such as those of the United States of America and the European Union. Most of the approvals and assessments are conducted on a case-to-case basis. It is important to point out that most of the approvals that have been granted are related to improving mechanical, optical and thermal properties and not to antimicrobial applications. However, due to the availability of nano-based food packaging in the global markets, it can be assumed that they could already being used even in areas for which they have not been approved.

At present, the concerns regarding health safety has grown rapidly; therefore, in order to have a larger public acceptability of such materials, a two- fold approach is needed which ensures new developments supported by sustainable science. It remains a challenge for both academia and industry to develop materials with strategic performance which address the issues of safety concerns, quantification of migration to food and the effect on human health.

Conflict of interest

The authors have no conflict of interest to declare. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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