



Metal oxide nanoparticles for safe active and intelligent food packaging

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ABSTRACT

Background: Food safety and food security remain the major concern of consumers and the food industry. Bacterial contamination continues to be a crucial food safety issue. Smart packaging incorporates both active and intelligent components. Intrinsic antibacterial activity, oxygen and ethylene scavenging (active) and the sensing (intelligent) properties of metal oxide nanoparticles are in research focus for application in smart food packaging, especially bio-nanocomposite films.

Scope and approach: Metal oxide nanoparticle properties are closely linked to their morphology resulting from the synthesis process. In this review, we cover current innovative synthesis methods for obtaining metal oxide nanoparticles and current incorporation techniques used to obtain smart (active and/or intelligent) packaging, focusing on bio-nanocomposites, commonly used metal oxides and future mixed metal or doped metal oxides. Taking into account safety, we focus on current legislation, and methods for risk assessment due to particle release from the packaging material and a summary of cytotoxic studies of metal oxide nanoparticles on human cells and the gut microbiota.

Key findings and conclusions: Antimicrobial effectiveness of metal oxide nanoparticles is highly dependent on morphology as a result of the synthesis method. Solution casting and electrospinning are innovative methods applied to synthesize metal oxide incorporated biopolymer films for active packaging with improved mechanical and barrier properties combined with active components (antimicrobial, ethylene scavenging). Metal oxides show sensitivity and selectivity to most gases produced during food spoilage. In selection of metal oxide for smart packaging, particle migration and cytotoxic activity are key issues requiring careful and detailed characterization.

1. Introduction

The food industry is under constant and crucial pressure to provide appetizing and safe food products. To satisfy these consumer demands, the food industry regularly improves both the food quality and packaging technology. Food packaging is essential in maintaining the safety and quality of products from processing and manufacturing, through handling and storage until it reaches the consumers. Petroleum-based plastic materials (like polyethylene terephthalate, polypropylene, polystyrene) are usually used to envelop food in order to protect its content from contamination and spoilage and to facilitate its transport and storage. However, plastic materials cannot fully protect food from the environment and, thus, cannot completely ensure product quality and safety. In addition, plastic undergoes continuous fragmentation, and may create micro- and nano-plastics that have potential toxic impacts on

human health. Plastic pollution has increased due to the COVID-19 pandemic (Silva et al., 2020). To improve plastic inability to stop light, oxygen and other gases from penetrating and reaching the consumables and causing their degradation, as well as to prolong shelf-life of food and protect human health, novel materials are employed to envelop food products.

Starting from the beginning of the twentieth century, three main approaches have been applied to improve food packaging. The first approach consists in improving plastic polymers by mixing them with other materials. Doping or formation of nanoparticle-polymer composites improves mechanical properties of the packaging material, which can enforce the temperature and humidity resistance properties or improve oxygen barriers (Khajavi et al., 2020). Biopolymers, as ecologically sound “green” materials often suffer from degradation and mechanical issues so application of these materials in food packaging

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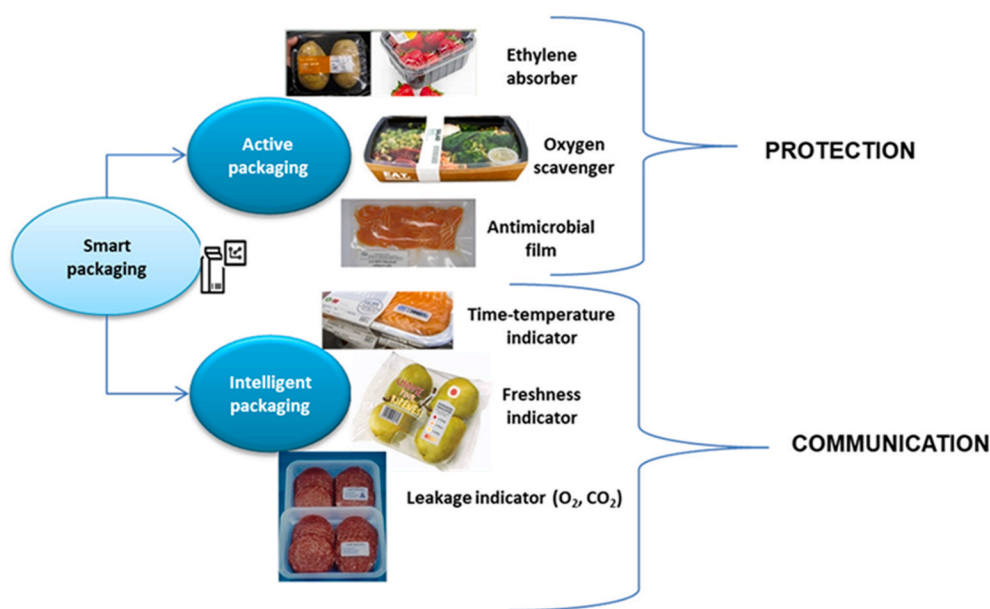


Fig. 1. Classification of smart packaging and its functions in the improvement of food quality.

can be accomplished in the form of nanocomposites. The second approach aims to develop “active packaging” in which particles added to the packaging material interact directly with food and protect it from UV, oxygen, ethylene or microbiological contamination (Rai et al., 2019; Vilela et al., 2018). Active packaging systems can be classified as active scavenging systems (absorbers) that remove undesired elements from the product, such as moisture, carbon dioxide oxygen, ethylene and odour and active releasing systems (emitters) that release into the packaging in the form of antioxidants, carbon dioxide or antimicrobial compounds (Yildirim et al., 2018). Finally, the third approach develops “intelligent packaging”, which allows real-time monitoring of food safety (Müller & Schmid, 2019; Rai et al., 2019). For this, sensing elements are combined with the packaging material to transform the food envelope into a miniaturized device for tracking. Intelligent packaging may provide monitoring of food freshness and quality, its storage condition, and, in that way, improve safety and convenience, and help to extend food shelf-life. Thus, enhanced functionality of food packaging is obtained by smart packaging that includes both active and intelligent components, as shown in Fig. 1.

Nanomaterials and nanoparticles are used in the development of all three advanced packaging approaches. Adding nanomaterials including nano-metal oxides to different polymers to form nanocomposites can make packaging lighter, stronger and less permeable (Y. Huang, Mei, Chen, & Wang, 2018). Nanomaterials with an intrinsic antimicrobial activity incorporated in active and intelligent packaging contribute to extending the shelf-life of products by keeping food safe from harmful and spoilage bacteria, fungi and viruses, and by providing freshness during longer storage time. Metal oxide nanoparticles (NPs) have unique properties and morphology and a great potential for application in food industry NPs in nanocomposite packaging can perform oxygen and ethylene scavenging and UV- blocking as part of active packaging functions contributing to extending the product shelf life (Gaikwad, Singh, & Lee, 2018; Gaikwad, Singh, & Negi, 2020).

The objective of this review is to provide an overview of the methodologies and procedures carried out in earlier literature on the development of active and intelligent packaging utilizing metal oxide nanoparticles. As the physicochemical properties of nanoparticles and their stability in nanobiocomposites are essential for the development of packaging films we describe the state-of-the art techniques for nanoparticle synthesis, characterization and incorporation in polymers. Antibacterial properties of active packaging containing metal oxides and

current available data on the antiviral aspect is presented. Antifungal and antiviral activities, also significant for food protection, are briefly mentioned. To point out that the cytotoxicity of nanoparticles is the main barrier for their applications in food packaging, we provide a condensed assessment of toxicity of metal oxide nanoparticles at the level of cells, mucus and microbiota. It is noteworthy that new regulations, consumer attitudes and acceptability, the societal involvement and impact, have been comprehensively described in some recent reviews (Garcia, Shin, & Kim, 2018; Omerović et al., 2021). Finally, an overview of the current research covering the potential for utilizing metal oxide nanoparticles in smart packaging for oxygen and ethylene scavenging, moisture control and in food safety sensors is also given.

2. Legislation

The active packaging technology is defined in the European regulations as “new types of materials and articles designed to actively maintain or improve the condition of the food” (1935/2004/EC) and as “deliberately incorporate components that would release or absorb substances into or from the packaged food or the environment surrounding the food” (450/2009/EC). The intelligent packaging technology is “designed to monitor the condition of the food” (1935/2004/EC). Both technologies are closely linked to the development and research in nanotechnology. Although the European Food Safety Authority’s (EFSA) estimates that the most common agri-food applications of nanomaterials are in active packaging (as nanofillers to endow composite films) and as additives, the approval procedures for particular nanoparticles are long and on a case-by-case basis. This arises mainly from the lack of validated risk assessment protocols for food packaging. In other countries, especially in North America and Asia Pacific, that dominate the field, the legislation bodies have provided a set of legal frames for food sector applications of nanomaterial based active and intelligent packaging. The commercialization of active and intelligent packaging in Europe is far behind markets in Japan, USA and Australia, where these products are treated within conventional legislation for food contact materials. The increasing demand of the food industry and the rise in acceptance among consumers for packaging solutions based on emerging nanotechnologies is reflected by the predicted revenue of about \$15 billion in 2020.

The ongoing global spread of a pandemic caused by SARS-CoV-2 has enhanced development of active packaging that aims to prevent the

Antimicrobial mechanisms of ZnO

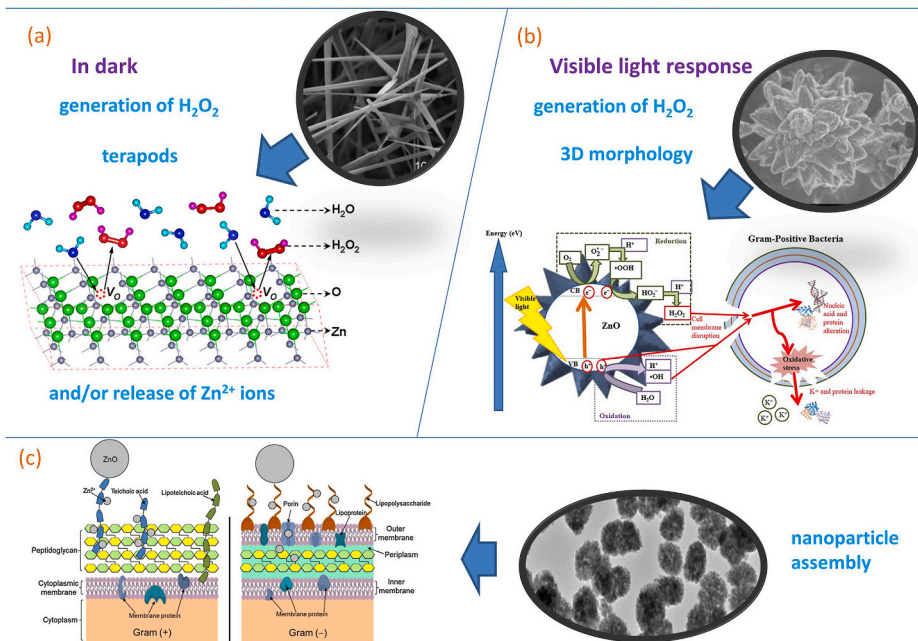


Fig. 2. Schematic presentation of antibacterial mechanisms of ZnO NPs with different morphology: (a) terapod NPs, that mainly generate H_2O_2 and release Zn^{2+} -ions in aqueous solution, adapted with permission from (Xu et al., 2013); (b) flower NPs, shown to generate various ROS upon visible light illumination, that injure bacterial cells by causing an oxidative stress, cell content leakage or by damaging nucleic acid and proteins, adapted with permission from (Quek et al., 2018); (c) ZnO nanoparticle assembly were shown to be highly efficient antimicrobial agent towards Gram-positive and Gram-negative bacteria, under different conditions. Adapted with permission from (Joe et al., 2017).

transmission of the virus in order to protect consumers. For this, packaging film is covered with an external active coating layer based on nanoparticles or nanoparticles embedded in a polymer matrix (Imani et al., 2020; Mizielińska, Nawrotek, Stachurska, Ordon, & Bartkowiak, 2021).

3. Synthesis and antimicrobial properties of metal oxide NPs

Incorporation of metal oxide NPs in food packaging leads to improved mechanical, thermal and barrier properties combined with excellent antimicrobial activity. The synthesis method greatly influences properties of NPs including their antimicrobial and cytotoxic effects (Y. Huang et al., 2018; Stankic, Suman, Haque, & Vidic, 2016). NPs due to their small size have a larger surface area per mass, thus a larger number of active surface states available for reaction with foodborne pathogens. These interactions are greatly affected by the size, shape and crystal structure of the NPs. Zinc oxide (ZnO) and titanium dioxide (TiO_2) are metal oxides most commonly used as antimicrobial agents especially in active food packaging, but other metal oxides have shown increased potential as antibacterial agents too.

3.1. ZnO nanoparticles

ZnO NPs display a large surface to volume ratio, highly crystalline structure, improved mechanical properties, high thermal conductivity, and high optical absorption in the UV region beneficial for interactions with bacteria. ZnO is generally recognized as a safe (GRAS) material by the FDA that can be applied in the field of food and drug industry, particularly as an antibacterial and antifungal agent. A broad spectrum of bacteria are sensitive to ZnO NPs (da Silva et al., 2020; Tam et al., 2008; Vidic et al., 2013; Zanet et al., 2019).

Various methods have been used to synthesize ZnO NPs by controlling synthesis parameters resulting in different ZnO particle morphologies (Fig. 2). Some examples include the sol-gel method used to synthesize ZnO and Ag doped ZnO nanoparticles (Karanakaran, Rajeswari, & Gomathisankar, 2011), ZnO nanorods focusing on the influence of calcination temperature on structure, morphology and antimicrobial activity (Ismail, Menazea, Kabary, El-Sherbiny, & Samy, 2019),

co-precipitation used to obtain a flower-like morphology with high antibacterial activity against *Enterococcus faecalis* and *Micrococcus luteus* in the presence of visible light irradiation (Quek, Lam, Sin, & Mohamed, 2018), the ultrasonic method used to synthesize ZnO NPs and investigate antibacterial activity and effect of particle size of ZnO against *Escherichia coli* and *Staphylococcus aureus* (Applerot et al., 2009), and the chemical vapor based method used to synthesize ZnO, MgO and mixed ZnO–MgO NPs and investigate their antibacterial efficiency to *E. coli* and *Bacillus subtilis* (Vidic et al., 2013). Cluster-like ZnO NPs were synthesized by the hydrothermal method and grown on PDA-PET substrate. Growth of *Gluconobacter cerinus* was inhibited by destroying the membrane of bacterial cells, while the UV protection capacity increased up to 500 fold (Cheng et al., 2019). This method was also used to prepare ZnO nanorods. Antibacterial activity against *E. coli* and *Bacillus atrophaeus* on different substrates was investigated (Tam et al., 2008). The hydrothermal method using different stabilizing agents - polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA) and poly (α,γ , l-glutamic acid) (PGA) was used to synthesize ZnO NPs with different shape and morphology (Stanković, Dimitrijević, & Uskoković, 2013). Hexagonal prismatic rods (PVP), spherical (PVA) and ellipsoid (PGA) shaped particles with different sizes were obtained. The highest antibacterial activity against *E. coli* and *S. aureus* was achieved nanospherical ZnO particles with an average diameter around 30 nm and the largest specific surface area – $25.70 \text{ m}^2\text{g}^{-1}$. Different ZnO NP morphologies were also obtained using the solvothermal method. Antibacterial activity against *E. coli* and *S. aureus* was tested showing that flower-like ZnO NPs had higher efficiency than rod and sphere-like shaped NPs (Talebian, Aminezhad, & Doudi, 2013). ZnO has also shown exceptional antifungal properties (Q. Sun, Li, & Le, 2018).

3.2. TiO_2 nanoparticles

TiO_2 is a well-known low cost metal oxide with high chemical stability widely used in photocatalysis. As one of the most versatile compounds, TiO_2 is used in extraordinarily diverse food products and technologies. However, in 2016 the EFSA highlighted the need for more research on TiO_2 safety. Since this year, the EFSA no longer considers TiO_2 safe when used as a food additive because they cannot rule out the

Table 1

Some examples of synthesis and antibacterial application of other metal oxides.

Nanoparticle	Size (nm)	Synthesis method	Pathogen	Reference
Cu ₂ O	400	One-step reduction	<i>S. aureus</i> , <i>E. coli</i>	Yan et al. (2021)
Cu ₂ O	150	Sol-gel	<i>E. coli</i>	Ma, Guo, Guo, and Ge (2015)
Cu ₂ O	36–450	In-situ mediated solution	<i>E. coli</i>	Deng et al. (2014)
Fe ₂ O ₃	45, 70	Green hydrothermal	<i>E. coli</i> , <i>S. aureus</i> , <i>Vibrio fischeri</i>	Vihodceva et al. (2021)
Fe ₃ O ₄	5–20	Modified co-precipitation	<i>E. coli</i>	Gabrielyan, Hakobyan, Hovhannisyan, and Trchounian (2019)
Fe ₃ O ₄	6–9	Low temperature solution route	<i>E. coli</i> , <i>P. aureginosa</i> , <i>L. monocytogenes</i>	Al-Shabib et al. (2018)
MgO	50	Green synthesis	<i>E. coli</i>	Khan et al. (2020)
MgO	50	Combustion	<i>E. coli</i> , <i>B. subtilis</i>	Vidic et al. (2013)
Zn–MgO	5–100	Chemical vapor	<i>B. subtilis</i> , <i>S. aureus</i> , <i>Salmonella enterica</i> , <i>E. coli</i> , <i>Saccharomyces cerevisiae</i>	Zanet et al. (2019)
FeMnO ₃	200–1000	Sol gel	<i>B. subtilis</i>	Vasiljevic et al. (2020)

genotoxicity concerns of TiO₂, nor the possibility that TiO₂ after ingestion can accumulate in the body. However, TiO₂ NPs are not banned from applications in the food industry. Sol-gel processing is the most common synthesis method for TiO₂. TiO₂ colloids obtained using the sol-gel method combined with pectin to form aerogels, have shown potential for application in food packaging (Nešić et al., 2018). Recent synthesis methods include biosynthesis (a “green” synthesis method), where TiO₂ NPs are synthesized using plant extracts, showing good antibacterial activity against (Subhapriya & Gomathipriya, 2018).

Antimicrobial performance of TiO₂ was first investigated by Matsunaga et al., (Matsunaga, Tomoda, Nakajima, & Wake, 1985). Growth of *Lactobacillus acidophilus*, *Saccharomyces cerevisiae* and *E. coli* was completely inhibited when incubated with TiO₂/Pt particles during photoelectrochemical oxidation. However, TiO₂ is thermodynamically unstable, tends to agglomerate and is difficult to remove from a treated solution. Since TiO₂ photocatalyst is only active under UV irradiation at levels dangerous for human cells, irradiation in the visible regime could overcome this problem. One way is doping TiO₂ or forming nanocomposites. Thus, antibacterial activity of visible-light-irradiated nitrogen- and carbon-doped TiO₂ against several microbials such as *Shigella flexneri*, *Listeria monocytogenes*, *Vibrio parahaemolyticus*, *Streptococcus pyogenes*, *S. aureus*, and *Acinetobacter baumannii*, was investigated, with nitrogen doping showing better bactericidal activity against microbials (Wong et al., 2006). Nitrogen-doped mesoporous titania thin films prepared by the sol–gel method using Pluronic P123 as the template resulted in a reduced band gap and improved visible light induced antibacterial activity against *Bacillus amyloquifaciens* (Soni, Dave, Henderson, & Gibaud, 2013).

3.3. Other metal oxide nanoparticles

Other metal oxides have shown increased potential for application as antimicrobial agents in food packaging, such as Cu₂O NPs, MgO NPs, Fe₃O₄ NPs, FeMnO₃ and α-Fe₂O₃ NPs alone or in the form of nanocomposites. Some recent examples are shown in Table 1.

Nanocomposites composed of metal doped metal oxides and mixed metal oxides, such as for example Ag/ZnO/CuO as small amounts have achieved high antimicrobial activity (Dehghani, Peighambari, Peighambari, Hosseini, & Regenstein, 2019) or CuO/montmorillonite nanocomposite incorporated in chitosan film (Nouri, Yaraki, Ghorbanpour, Agarwal, & Gupta, 2018).

Table 2 presents some successful examples of active packaging systems improved with various metal oxide NPs.

4. Nanoparticle-biopolymer composites for active packaging

Classical food protecting films are made from polymers such as polyamide (PA), polystyrene (PS), polypropylene (PP), polyethylene (PE), polyvinylchloride (PVC), and polyethylene terephthalate (PET) as raw materials. These plastics have been widely used because of their high accessibility, low cost and good mechanical properties (Omerović et al., 2021). However, they cannot be recycled and are not completely biodegradable. Efforts have been made to replace petroleum plastics with bio-based degradable materials including polysaccharides (chitosan, zein, alginate, starch, carboxymethyl cellulose), poly(α-hydroxyester)s, polyhydroxybutyrates (PHB), poly(glycolic acid) (PGA), polylactic acid (PLA), their co-polymers poly(lactide-co-glycolide) (PLGA), poly caprolactone (PCL), and polyvinyl alcohol (PVA). However, biopolymers have drawbacks as they provide poor mechanical, thermal, and barrier properties.

Conjugation of metal oxide NPs with biopolymers in the form of nanoparticle-biopolymer composites improves the mechanical and barrier properties of biopolymers and provides antimicrobial properties (Fig. 3). One form is coating the packaging film with antimicrobial NPs, such as TiO₂ or ZnO coated PE films (Othman, Abd Salam, Zainal, Kadir Basha, & Talib, 2014; Tankhiwale & Bajpai, 2012). PE films coated with a chitosan-ZnO nanocomposite achieved a high antimicrobial activity to *Salmonella enterica*, *E. coli* and *S. aureus* (Al-Naamani, Dobretsov, & Dutta, 2016). Metal oxide NPs can also be incorporated in the polymer film. Enhanced mechanical and oxygen barrier properties were achieved with ZnO incorporated in PP films that depended on the concentration and shape of ZnO NPs (Lepot et al., 2011). Low density polyethylene (LDPE) films containing ZnO NPs showed high antibacterial activity to *B. subtilis* (Esmailzadeh, Sangpour, Shahrzaz, Hejazi, & Khaksar, 2016).

Some examples of active packaging with quantitatively improved mechanical and barrier properties are given in Table 3.

4.1. Incorporation of metal oxide NPs in packaging films

Although the number of biodegradable materials for food packaging continuously increases, there is still a lack of eco-friendly packaging biocomposite with good mechanical, thermal and physical properties that can be used industrially. Methods commonly used to incorporate metal oxide NPs into biocomposites include solvent casting and electrospinning.

The solvent (solution) casting method is a well-known technique for the preparation of polymer nanocomposites. Metal oxides as nanofillers and the polymer are firstly solved in a solvent (Fig. 4). The metal oxide and polymer solution is mixed to achieve homogeneous dispersion. This is followed by solvent evaporation and casting resulting in the formation of a metal oxide polymer nanocomposite. TiO₂ NPs incorporated in a gellan gum (biopolymer) film showed good antibacterial activity against *S. aureus*, *Streptococcus*, *E. coli* and *Pseudomonas aeruginosa* (Razali, Ismail, & Amin, 2019). Zinc oxide NPs incorporated using this technique into a chitosan/carboxymethyl cellulose blend (Youssef, El-Sayed, El-Sayed, Salama, & Dufresne, 2016) displayed improved mechanical and thermal properties and good antibacterial activity against *S. aureus*, *P. aeruginosa*, *E. coli* and *Candida albicans*, thus increasing the shelf life of the tested soft white cheese. Mixed Zn–MgO NPs incorporated in alginate film prevented proliferation of *L. monocytogenes* in cold smoked salmon meat (Vizzini, Beltrame, Zanet, Vidic, & Manzano, 2020).

Table 2

Some recent examples of antibacterial packaging films containing metal oxide NPs.

Nanoparticle	Size	Food	Film	Pathogen	method	Reference
SiO ₂	15 nm	Soybean oil	Chitosan	<i>E. coli</i> , <i>S. typhimurium</i> , <i>S. aureus</i> , <i>L. monocytogenes</i>	Disk	Bi et al. (2020)
ZnO	10–30 nm	White brined chees	Chitosan	<i>E. coli</i> O157:H7	plating	Al-Nabulsi et al. (2020)
ZnO	50	RTE poultry meat	Alginate	<i>S. typhimurium</i> , <i>S. aureus</i>	plate count	Akbar and Anal (2014)
ZnO	23–62	Chicken fillet; cheese	Chitosan	<i>E. coli</i> , <i>S. aureus</i> , <i>P. aeruginosa</i>	disk	Amjadi et al. (2019)
ZnO	<25 nm	Bread	Chitosan, cellulose	yeasts/fungi/molds	culturing	Noshirvani, Ghanbarzadeh, Mokarram, and Hashemi (2017)
ZnO		Chicken meat	Cellulose, polypyrrole	<i>E. coli</i>	culturing	Pirsa and Shamus (2019)
ZnO		Chicken meat	Cellulose	<i>Campylobacter</i>	Culturing, sequencing	Hakeem et al. (2020)
Ag/ZnO		Chicken meat	LDPE ^a	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>L. monocytogenes</i>	plate count	Panea, Ripoll, González, Fernández-Cuello, and Albertí (2014)
Zn–MgO	5–10 nm	Smoke salmon meat	Alginate	<i>L. monocytogenes</i>	qPCR, plate count	Vizzini et al. (2020)
ZnO/TiO ₂		Shrimp	PVA ⁵ /gelatin	<i>S. aureus</i> , <i>E. coli</i> O157H7, <i>L. monocytogenes</i>	count	Azizi-Lalabadi, Ehsani, Ghanbarzadeh, and Divband (2020)
ZnO	10–30 nm	Chicken meat	Gelatin	<i>S. aureus</i> , <i>Pseudomonas fluorescens</i>	Disk	Ahmadi, Ahmadi, and Ehsani (2020)
ZnO	130–200 nm	Food stimuli	SCP ⁴	<i>E. coli</i>	Zone inhibition	Tankhiwale and Bajpai (2012)
ZnO	35–45 nm	Food stimuli	Chitosan + PE	<i>E. coli</i> , <i>S. enterica</i> , <i>S. aureus</i>	culturing	Al-Naamani et al. (2016)
ZnO	50 nm	Food stimuli	LDPE ^a	<i>B. subtilis</i> , <i>E. aerogenes</i>	Plate count	Esmailzadeh et al. (2016)
ZnO	8 nm	Soft white cheese	Chitosan + CMP ⁴	<i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i>	Plate count	Youssef et al. (2016)
ZnO	30 nm	Food stimuli	Chitosan	<i>S. aureus</i> , <i>E. coli</i>	Disk	(J. Sun et al., 2020a)
ZnO	30 nm	Food stimuli	Ethyl cellulose	<i>S. aureus</i> , <i>E. coli</i>	culturing	Liu et al. (2018)
ZnO	30 nm	Food stimuli	Zein	<i>S. aureus</i> , <i>E. coli</i>	Disk	Amjadi et al. (2020b)
ZnO	<20 nm	Spinach	Olive flounder bone gelatin	<i>L. monocytogenes</i>	Disk	Beak, Kim, and Song (2017)
TiO ₂		fresh pear	LDPE ^a	<i>P. aeruginosa</i> , <i>R. mucilaginosa</i>	plate count	Bodaghi et al. (2013)
TiO ₂	<100 nm	food stimuli	PLA ³	<i>E. coli</i> , <i>L. monocytogenes</i>		(W. Li et al., 2017)
TiO ₂	25 nm	Lettuce	LDPE ^a	<i>E. coli</i>	Plate count	Othman et al. (2014)
TiO ₂		Lamb meat	Whey protein isolate/cellulose nanofibre/rosemary essential oil	<i>L. monocytogenes</i> , <i>E. coli</i> O157:H7, <i>S. aureus</i>	Micro dilution method	Sani, Ehsani, and Hashemi (2017)
CuO	191 nm	Food stimuli	PHBV ⁵	<i>S. enteria</i> , <i>L. monocytogenes</i>	Plate count	(Castro Mayorga, Fabra Rovira, Cabedo Mas, Sánchez Moragas, & Lagarón Cabello, 2018)
CuO	<50 nm	Pepper	Microcrystalline cellulose, sodium alginate	<i>Salmonella</i> spp., <i>Listeria</i> spp.	Plating	Saravanakumar, Sathiyaseelan, Mariadoss, Xiaowen, and Wang (2020)
ZnO–SiO ₂	25–100 nm	Bread	PVA/Chitosan	<i>S. aureus</i> , <i>E. coli</i>	Plate count	Al-Tayyar et al. (2020)
Cu ₂ O	400 nm	Cherry tomato	PVA-chitosan	<i>S. aureus</i> , <i>E. coli</i>	Plate count	Yan et al. (2021)

^a LPDE, Low-Density Polyethylene; LLDPE, linear low density polyethylene; ²SEM, scanning electron microscopy; ³PLA, poly(lactic acid); ⁴Carboxymethyl cellulose; ⁵PVA, polyvinyl alcohol.

Bionanocomposite films using konjac glucomannan/chitosan (KGC) with nano-ZnO and mulberry anthocyanin extract (MAE) by a modified casting method (J. Sun et al., 2020a) exhibited beside improved mechanical and thermal properties of films, good UV–Vis light barrier properties and relatively high pH-sensitive properties, strong antioxidant activity and good antibacterial activity against *E. coli* and *S. aureus*. ZnO NPs have also been utilized in soy protein isolate films together with cinnamaldehyde showing improved oxygen barrier and antifungal properties (Wu et al., 2019). ZnO–SiO₂ infused in PVA/chitosan films exhibited exceptional antimicrobial properties and extending the shelf-life of bread (Al-Tayyar, Youssef, & Al-Hindi, 2020).

Compared to other techniques used for the preparation of polymer matrices for food packaging, electrospinning is a versatile technique for fabrication of nanofibers with different morphologies and structures improving mechanical and thermal but also barrier properties of significance for food packaging. In this process (Fig. 4) a mixture of metal oxide and polymer solution is first placed into a syringe (plastic or glass) lying horizontally or vertically on a pressure and solution-flow rate controlled pump. The solution is pumped through a syringe, to a metallic needle connected to the electric power supply and a droplet is formed.

The electrospinning process starts at a critical high voltage (10–25 kV) when the formed droplet changes shape to a Taylor cone and ejects an electrically charged jet. The jet within the electric field is directed toward the collector with opposite charge, leading to solvent evaporation and fibre formation. Although, more complex than the solvent casting method, electrospinning is a well-adapted method for industrial scale applications.

Different metal oxides have been incorporated into biodegradable polymer matrices, though most often ZnO or TiO₂. ZnO dispersed in cellulose acetate (CA) fibrous membrane was prepared by the electrospinning process and showed improved water repellent properties compared to pure CA membrane and a strong antibacterial activity against *S. aureus*, *E. coli* and *Citrobacter* (Anitha, Brabu, Thiruvadigal, Gopalakrishnan, & Natarajan, 2012). Nanoparticle agglomeration was suppressed and the contact area between fibres and microbes was increased. ZnO NPs incorporated into ethylcellulose/gelatin nanofibers obtained by electrospinning also showed excellent surface hydrophobicity, water stability and antimicrobial activity against *S. aureus* and *E. coli* (Liu et al., 2018). Hybrid electrospun nanofibers composed of ZnO NPs and rosemary essential oil incorporated zein/κ-carrageenan showed

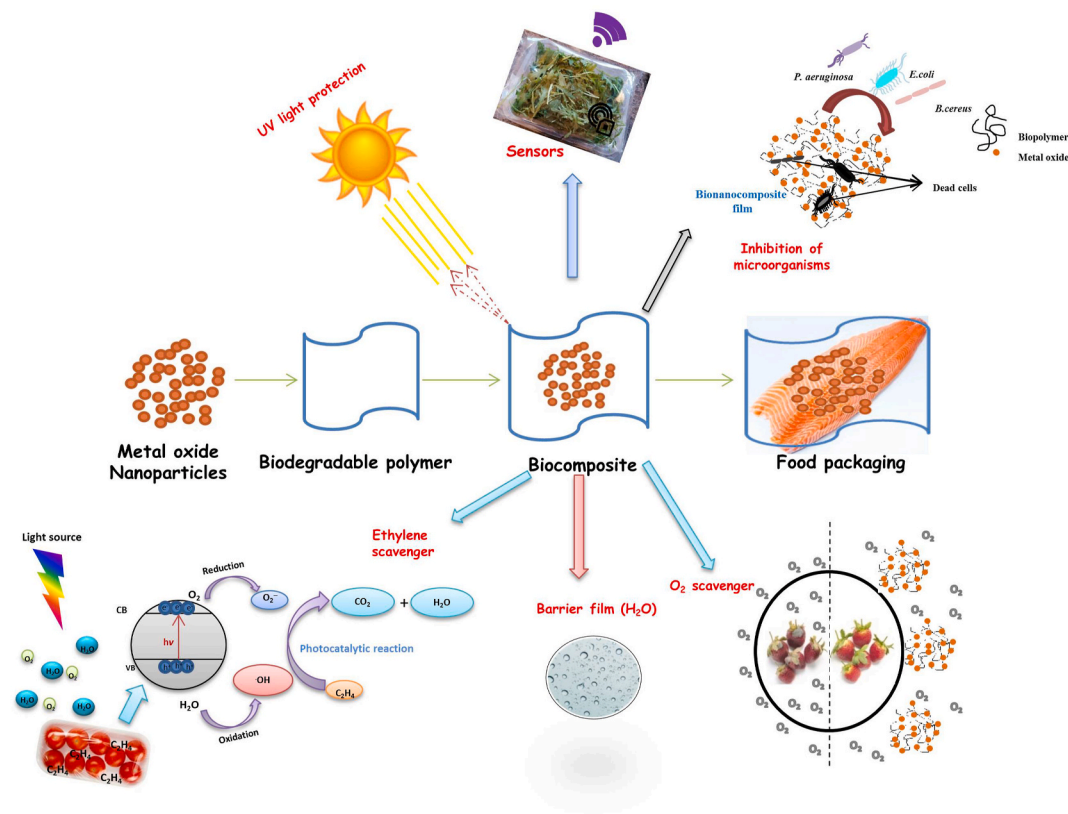


Fig. 3. Schematic representation of the preparation of smart food packaging using metal oxide NPs as coating or incorporated in a biodegradable polymer and its application in the inhibition of microorganisms, UV light protection, barrier, oxygen and ethylene scavenging and sensing.

Table 3

Some examples of packaging films containing metal oxide NPs with quantitatively improved mechanical and barrier properties.

Nanoparticles	Biopolymer	Barrier properties	Mechanical properties	References
ZnO–SiO₂	Chitosan-PVA	With increased content of metal oxide NPs, WVTR ^a decreased from 980.86 to 500.60 g/(m ² day)	With increased content of metal oxide NPs, TS ² increased from 7.45 MPa up to 37.5 MPa	Al-Tayyar et al. (2020)
ZnO	Soy protein	OP ³ values were decreased by 33.8%, with addition of NPs	TS ² and EAB ⁴ were raised up to 2.11 MPa and 164.0%, with addition of NPs, respectively	Wu et al. (2019)
CuO	Montmorillonite	WVP ⁵ was significantly reduced after incorporation of nanocomposite	TS ² was improved 59% after incorporation of NPs	Nouri et al. (2018)
TiO₂	Chitosan	WVTR ^a was decreased from 26 to 19 g m ⁻² d ⁻¹ with addition of NPs	An increase of TS ² from 10 to 16 MPa and decrease of EAB ⁴ from 57 to 53%, after addition of NPs to biopolymer	Kaewklin et al. (2018)
ZnO	Chitosan/Carboxymethyl cellulose	Final contact angle values increased after addition of NPs	At higher level of NPs, TS ² was increased from 6.8 to 12.6 MPa	Youssef et al. (2016)
GO–Bi₂WO₆	Starch	WPR ⁶ was improved (4.98×10^{-7} g/(m ² ·h·Pa) after addition of Bi ₂ WO ₆)	TS ² gradually increased with higher content of NPs from 11.06 to 23.19 MPa	(J. Xie et al., 2020)
Bi₂WO₆–TiO₂	Starch		With increased NPs, TS ² increased while EAB ⁴ decreased	Wang et al. (2019)
ZnO	Glucomannan/Chitosan	WVP ⁵ reduced from 2.61 (g mm/m ² ·day.kPa) to 1.82 (g mm/m ² ·day.kPa)	Optimum concentration of NPs improved TS ² and EAB ⁴ (52 MPa and 12.81 ± 0.42%, respectively)	(J. Sun et al., 2020b)
ZnO	Alginate		At lower level of ZnO NPs, TS ² increased from 2.35 to 4.75 MPa, while EAB ⁴ decreased from 602 to 131%	Akbar and Anal (2014)
ZnO	Ethyl cellulose/Gelatine	WCA ⁷ was increased with higher levels of ZnO NPs	Optimum concentration of NPs improved values of TS ² and EAB ⁴	Liu et al. (2018)
ZnO	Starch	WCA ⁷ exhibited higher value with the addition of ZnO NPs	Optimum concentration of NPs improved values of TS ² from 5.65 MPa to 10.29 MPa, and decreased EAB ⁴ from 43.71% to 16.84%	Abdullah et al. (2020)
ZnO	Gelatin/starch	The WVP ⁵ values decreased and melting temperature increased after addition of NPs	At higher level of NPs, TS ² was increased from 23 to 50 MPa, while EAB ⁴ decreased	Lee, Said, and Sarbon (2020)
ZnO	Gelatin/chitosan	Addition of NPs increased WVP ⁵ values	The incorporation of NPs increased TS ² from 0.20 to 0.22 MPa and decreased the EAB ⁴	Ahmad and Sarbon (2021)

^a WVTR, water vapor transmission rate; ²TS, tensile strength; ³OP, oxygen permeability; ⁴EAB, elongation at break; ⁵WVP, water vapor permeability; ⁶WVR, water vapor resistance; ⁷WCA, water contact angle.

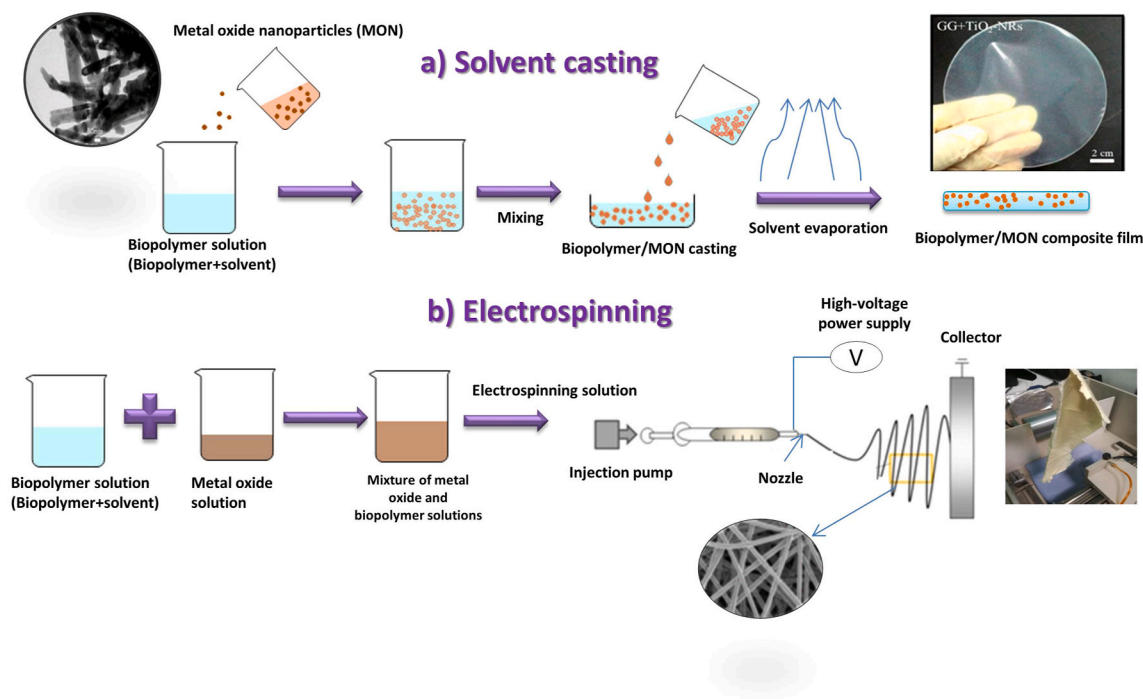


Fig. 4. Schematic representation of biopolymer – metal oxide film synthesis using solvent casting (a) and electrospinning (b) methods. Adapted in part with permission from (Liu et al., 2018; Razali et al., 2019).

good biocompatibility, and high antibacterial and antioxidant activity (Amjadi, Almasi, Ghorbani, & Ramazani, 2020b). ZnO/GO nanocomposites incorporated into gelatin fibres by a side-by-side electrospinning technique showed high antibacterial activity and complete degradation within 7 days (H. Li et al., 2020). High surface area electrospun zein-TiO₂ nanofibers improved the storage life of cherry tomatoes by absorbing ethylene (Böhmer-Maas, Fonseca, Otero, da Rosa Zavareze, & Zambiasi, 2020). Electrospun zein/sodium alginate nanofibers loaded with TiO₂ NPs and betanin showed good antioxidant and antibacterial activity against *E. coli* and *S. aureus* (Amjadi, Almasi, Ghorbani, & Ramazani, 2020a).

5. Nanoparticle migration from nanocomposites and food stimulants

The antibacterial efficiency of NPs imbedded into a packaging film is usually inferior of that used for film production. Cierech et al. have shown that the concentration of released ZnO NPs from a nanocomposite was several times lower than the concentration of the nanoparticle in the film (Cierech et al., 2019). This parameter has to be evaluated for packaging films. Migration of nanoparticles into enveloped food is a diffusion process when low molecular mass particles initially incorporated in the package are released into the contained product or into the space around. The release is usually experimentally measured using food stimulants instead of particular food matrices. In 1985, the EC promulgated a list of food simulants that can be used to test migration of constituents of plastic materials and particles intended to come into contact with foodstuffs (EC, 1985). Among food simulants 95% (v/v) aqueous ethanol and 3% (w/v) aqueous acetic acid are frequently used. To estimate release, packaging films are cut into pieces, weighed and immersed in a simulant solution. The solution is kept at a given temperature (for instance, room or refrigerated temperatures) and the amount of released NPs is measured regularly during the defined period of time. Such studies enable correlation of the migration kinetics of NPs or their ions from the film and their antibacterial, oxygen and ethylene scavenging and moisture absorption activities.

The migration of metal oxide NPs to food simulants takes several

steps. For instance, in the case of ZnO, the first step was shown to be Zn²⁺ dissociation from ZnO and diffusion through the film (Espitia et al., 2012; Petchwattana, Covavisaruch, Wiboonanawong, & Naknaen, 2016). Zn²⁺ ions then leave the film surface and enter into the food simulant. This process of mass transferring from the film surface to the food continues until the thermodynamic equilibrium is reached. Practical application of active packaging depends strongly on the possibility to achieve the release of active compounds in a controlled manner. Controlled release can be obtained through the design of nanoparticle-biopolymer composites, method of NPs incorporation, choice of NPs shape, size, polarity, and weight, utilization of two or more active compounds in the same packaging film or addition of cross-linking agents into the film (Appendini & Hotchkiss, 2002). The main challenge in designing the nanobiopolymer system is slowing the migration rate of active compounds to obtain prolonged activity of the packaging film. Techniques utilized for the design of controlled release in active food packaging have been review recently (Almasi, Jahanbakhsh Oskouie, & Saleh, 2020).

6. Oxygen and ethylene scavenging and moisture absorption in active packaging

In many cases food deterioration is caused by oxygen, ethylene or excess of moisture. Active packaging systems incorporating metal oxide nanoparticles offer an advantage of actively contributing to reducing food waste, by scavenging oxygen and ethylene and/or by moisture absorption.

The presence of oxygen in packaging has a detrimental influence on shelf-life and quality of packaged food, as it leads to oxidation of the product and proliferation of bacteria, molds and insects (Yildirim et al., 2018). Iron based scavengers are most common where the oxygen scavenging mechanism is triggered by moisture resulting in irreversible oxidation of iron into a stable ferric oxide trihydrate complex (Gaikwad et al., 2018). Sachets have been proved effective, but the future lies in incorporation of the oxygen scavenging component into packaging films, such as coated LDPE/PET films modified with FeO(OH)xH₂O, Fe₂O₃ and ascorbic acid (Wołosiak Hnat et al., 2019) or

moisture-activated nanostructures with a Zn/ZnO core-shell structure (Gomes, Ferreira, & Carvalho, 2017) or a nanocomposite based on ethylene acetate containing ZnO/Fe + montmorillonite nanoparticles (Eskandarabadi et al., 2019). Another way for oxygen scavenging is UV light activation, with research focusing on TiO₂ bionanocomposite films (Fathi, Almasi, & Pirouzifard, 2019).

Ethylene (C₂H₄) is a plant growth regulator that influences/accelerates ripening and senescence (Gaikwad et al., 2020; Wei, Seidi, Zhang, Jin, & Xiao, 2020; Yildirim et al., 2018). In packed food ethylene accelerates chlorophyll degradation rates especially in leafy products and causes excessive softening of fruit leading to shortening of product shelf life (Yildirim et al., 2018). In active packaging scavengers with catalytic roles are incorporated in bionanocomposite films (Wei et al., 2020). When exposed to UV or visible light the photocatalytic component in the active packaging degrades ethylene to H₂O and CO₂. Application of metal oxides, as photocatalytic ethylene scavengers in bionanocomposite films has included TiO₂ with chitosan (Kaewklin, Siripatrawan, Suwanagul, & Lee, 2018) and TiO₂-zein nanofibers (Böhmer-Maas et al., 2020) both used to preserve and prolong the shelf-life of tomatoes. Nanocomposites with TiO₂ such as Bi₂WO₆-TiO₂ incorporated into starch films can perform catalytic degradation of ethylene in the visible light region (Wang, Wang, Ye, & Song, 2019). A degradation rate of 12.47% achieved for a film containing 4 wt% BT. Another approach is to focus on other metal oxides with photocatalytic properties in the visible light region. Graphene oxide (GO) added to Bi₂WO₆ (GBW) reduced the band gap of Bi₂WO₆ and was combined with starch in a nanocomposite film (J. Xie, Huang, Wang, Ye, & Song, 2020). The highest reaction rate constant (9.91×10^{-4}) was achieved with 0.5% GO addition. Nanocomposites of monoclinic WO₃ (band gap between 2.5 and 2.8 eV) enhanced with Pt loaded on zeolite (ZSM-5) have shown good potential for ethylene removal (Kim, Jeong, & Kim, 2019). The catalytic mechanism of these granules on ethylene was adsorption, migration and decomposition with hydroxyl radicals due to WO₃-Pt migrating into the micropores of the ZSM-5 matrix.

Excess moisture is not good in high water activity food such as meat and poultry (Gaikwad, Singh, & Ajji, 2019). Physical absorption is the working mechanism of moisture absorbers that are mostly applied in the form of sachets and pads. Calcium oxide is the only metal oxide used for these applications (Gaikwad et al., 2019). Metal oxide NPs in active packaging can prevent moisture or other gases entering the packed food acting as a packaging barrier against water and increasing the film tensile strength (Khajavi et al., 2020). Addition of Mg doped ZnO quantum dots to zein films achieved a better barrier with a more cohesive polymer network and reduced intermolecular space between chains (Schmitz, de Albuquerque, Alberton, Riegel-Vidotti, & Zimmermann, 2020).

7. Antimicrobial mechanisms of metal oxide nanoparticles

Prior to their integration into a packaging film, nanoscaled engineering materials and particles are tested for their ability to inhibit proliferation of microorganisms in pure cultures. The methods used to estimate antimicrobial efficiency include disk diffusion, broth dilution, agar dilution, and the microtiter plate-based method (Auger et al., 2019; Auger et al., 2018; Stankic et al., 2016; Vasiljevic et al., 2020; Vidic et al., 2013). The broth dilution method is most commonly used as it enables determination of the minimum inhibitory concentration (MIC) through culture turbidity and the minimum bactericidal concentration (MBC) through plating of serial dilutions and viable colony counts. The microtiter plate-based method performed on a 96-well plate is a modification of the broth dilution method. Multiple tests are easily performed due to miniaturization. The agar diffusion method has been standardized as an official method for detecting bacteriostatic activity in an indirect way. Monitoring of the optical density at the wavelength of 600 nm of the bacterial culture in the presence and absence of NPs enables determination of growth curves and estimation of the growth inhibition.

Other methods including modified standard procedures methods are also used such as the conductometric assay, SEM, urease inhibition assay, flow cytometry viability assay (Sirelkhatim et al., 2015). Finally, molecular methods like those based on polymer chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA) can be used to determine the antibacterial effect of NPs (Manzano, Viezzi, Mazerat, Marks, & Vidic, 2018; Vidic, Manzano, Chang, & Jaffrezic-Renault, 2017; Vidic et al., 2019; Vizzini et al., 2020).

Application of nanomaterials showing good antibacterial efficiency *in vitro* in food packaging needs additional validation because the food structure and composition may influence NP antibacterial activity. Although inorganic NPs are less sensitive to temperature and pH variations than organic bactericidal compounds, the molecules and ions in the food matrices and the food microbial flora may inhibit their activity. The exact mechanism how metal oxide NPs prevent bacterial proliferation in foods is still under investigation. However, several mechanisms have been suggested including the generation of reactive oxidative species (ROS), with or without light radiation, release of antimicrobial metal ions, and mechanical damaging upon NPs binding to microorganisms (Stankic et al., 2016). In addition, small NPs (<10 nm diameter) penetrate bacterial cells, and subsequently may release toxic ions or generate ROS intracellularly. Fig. 2 illustrates some of the described antimicrobial mechanisms. Some authors described that multiple mechanisms took place. ZnO NPs were shown to directly interact with *Campylobacter jejuni* cells, destabilize the membrane and penetrate the bacterial cell where they induced oxidative stress (Y. Xie, He, Irwin, Jin, & Shi, 2011).

ZnO and TiO₂ NPs have been shown to produce a large quantity of ROS upon UV radiation. For instance, 1 h illumination of TiO₂ NPs completely irradiated *E. coli* due to the formation of H₂O₂. During photocatalysis, electron-hole pairs are formed on TiO₂ after nanoparticle absorbed energy larger than their energy band gap. Holes react with water molecules on the surface of TiO₂ and generate surface active oxygen species, such as hydroxyl radicals ($\cdot\text{OH}$), superoxide radicals ($\text{O}_2^{\cdot-}$) or hydrogen peroxide (H₂O₂). These active species react with a microbial, destroy its structure and at the end kill it (Stankic et al., 2016). Similarly, nano-ZnO upon radiation forms ROS due to positively charged holes and defects at the surface that react with surrounding water molecules. The holes separate H₂O₂ in $\text{OH}^{\cdot-}$ and H^+ and form $\text{O}_2^{\cdot-}$ from dissolved oxygen, which in turn can react with H^+ and form a hydroperoxyl radical (HO₂ $^{\cdot}$). It produces hydrogen peroxide anions, which subsequently react with H^+ and produce H₂O₂. All mentioned ROS can damage and eradicate bacterial cells. A higher concentration and smaller size of NPs provide higher production of ROS and, thus, increased antibacterial efficiency.

A moderate release of metal ions from CuO, FeMnO₃, ZnO, or TiO₂ NPs was shown to be tolerated by a variety of microorganisms (Auger et al., 2019; Stankic et al., 2016; Vasiljevic et al., 2020). Bacterial cells can finely tune import and efflux of metal ions, maintaining metal homeostasis (Randazzo et al., 2020). However, tuning is possible to some extent and high concentrations of metal ions released from NPs cause bacterial death. The tolerance of various microorganisms to particular NPs can be explained by their capacity for metal ion homeostasis. The solubility of metal and metal oxide particles, and the release of ions into solution depend on particle concentration, time and medium (Vasiljevic et al., 2020; Vidic et al., 2014).

Other modes of action of metal and metal oxide particles on bacterial cells have been proposed because transcriptomic and proteomic analyses have indicated that nanoparticles inhibit enzymes, inactivate proteins and perturb the bacterial metabolism and bioenergetics. Moreover, metal oxide NPs modify the expression of proteins involved in bacterial information processing, protection from oxidative stress, cell envelope dynamics and cell division (Auger et al., 2019; Auger et al., 2018; Zanet et al., 2019).

Finally the activity of incorporated NPs in packaging films is determined using a standard ASTM E2180-01 method designed for evaluation

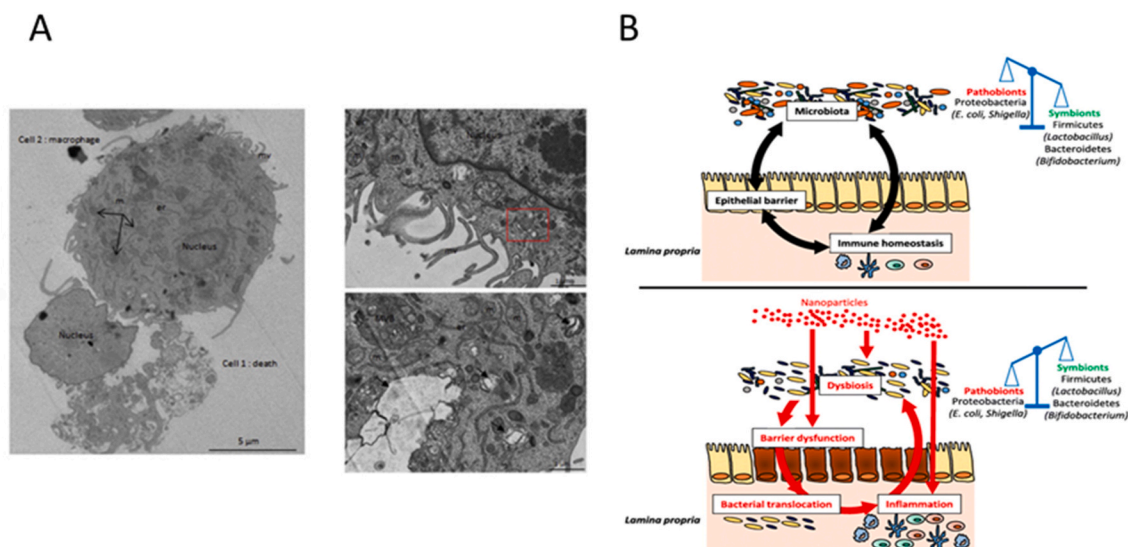


Fig. 5. (A) Representative thin section electron micrographs of macrophage cells incubated with 0.1 mg/ml Mg-nZnO for 24 h m, mitochondria; er, endoplasmic reticulum; mv, microvilli; MVB, Multi Vesicular Body; red rectangle points autophagy. Adapted with permission from (Auger et al., 2019). (B) Potential impact of NP ingestion on the crosstalk between the microbiota and the immune system. Adapted with permission from (Lamas et al., 2020). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

of antimicrobial agents in polymeric materials. The method can indicate the antimicrobial activity of polymer films containing NPs in a plastic matrix or in a coating layer by quantifying differences in antimicrobial activity between untreated plastics or polymers and those with bound or incorporated antimicrobial agents. It can be also applied to compare the numbers of pathogen survivors on NP-treated and control hydrophobic surfaces. The official ISO method 22196:2011 is used for measurements of antibacterial activity on plastics and other non-porous surfaces. Such measurements are needed because active NPs in the polymer matrix are only those that migrate from film to products or those on the film surface that are in contact with the food product, as explained above.

8. Antiviral activity of metal oxide nanoparticles

Transmission of viruses via contaminated surfaces is one of the important routes for their spreading. The antiviral activity of some metal oxide NPs has motivated research into the development of consumer protective packaging. For instance, CuO, ZnO, TiO₂ and La_xMnO₃ have shown a virucidal activity towards enveloped viruses, such as Influenza A virus, yellow fever virus, respiratory virus, and non-enveloped viruses, such as rhinovirus-2 (Imani et al., 2020). Since surfaces coated with NPs showed higher virucidal effectiveness against enveloped viruses than non-enveloped it was suggested that the main mechanism involved ROS generation. ROS efficiently damaged the outer lipid envelope but has a lesser effect on protein capsid (Imani et al., 2020).

Another proposed mechanism is that metal oxide NPs prevent virus entry into the human cells (El-Megharbel, Alsawat, Al-Salmi, & Hamza, 2021). Recently, ZnO NPs were shown to target the ACE2 receptor of SARS-CoV-2 which is a key protein enabling virus entry into host cells (Hamdi et al., 2021).

9. Toxicity of metal oxide nanoparticles

Humans may be exposed to nanoparticle dissolute from food packaging films either directly through food or indirectly by ingestion of inhaled particles. It is, thus, very important to test potential cytotoxicity of nano-enforcers used in active packaging. Cytotoxicity of NPs has most commonly been evaluated by measuring cell viability after cell exposure to nanoparticles in a buffer or in a cell culture medium. Metal oxide NPs have been shown to reduce cell viability, induce membrane lipid

peroxidation and damage DNA in various mammalian cell lines (Sahu & Hayes, 2017; Vidic et al., 2013). The cytotoxic pattern varies for different metal oxides and cell types and is dose- and time-dependent. In general, smaller nanoparticles are more active and can be internalized by cells faster than larger ones. Cytotoxicity is also dependent on the medium used to suspend them. Thus, cytotoxicity drastically decreases in a cell medium supplemented with serum compared to buffer or serum-free medium (Vidic et al., 2014). Small NPs may aggregate into entities of different sizes and shapes, depending on the medium, resulting in a modified surface and reactivity (Stankic et al., 2016). Biocompatibility of NPs is largely determined by their surface. Ingested nanoparticles could both stimulate and/or suppress immune responses depending on their surface chemistry (Dobrovolskaia, Germolec, & Weaver, 2009).

The cytotoxicity of ZnO NPs on human immune cells was correlated with the intracellular solubility of nanoparticles into Zn²⁺-ions. Different anions significantly affect nanoparticle suspension stability, and release of metal ions from NPs. The pro-oxidative and pro-inflammatory effects of TiO₂ and ZnO NPs were lowered using a medium containing some anions such as chloride and phosphate (Ng et al., 2013). When exposed to Mg doped ZnO (Mg-nZnO) NPs murine macrophages mainly rested unchanged but some cells indicated signs of necrosis as observed using electron microscopy (Fig. 5A). Healthy macrophages displayed pseudopodia to cell debris suggesting phagocytosis of damaged cells. Cytotoxicity was shown to be concentration-dependent, because macrophages were able to neutralize the toxic effect of Mg-nZnO NPs at concentrations lower than 1 mg/ml while higher concentrations disturbed membranes in macrophages and induced cell death (Auger et al., 2019).

The importance of considering the interrelationship between NPs, mucus and the gut microbiota was recently underlined by EFSA's report on the assessment of risks associated with human exposure to nanoparticles used in the food industry (Hardy et al., 2018). Exposure to large numbers of ingested NPs, persistent enough to survive gastrointestinal processing, has become regular for many populations. The surface area of the gastrointestinal tract (GIT) provides a large zone for interaction with ingested NPs. NPs can move through the intestinal barrier in a multistep route involving diffusion through the mucus layer, contact with enterocytes or Microfold cells, and via paracellular transport or cellular entry (da Silva et al., 2020). It is likely that NPs accumulate in

specialized intestinal cells at the base of large lymphoid follicles (Peyer's patches) and that a degree of absorption goes beyond this, from lymphatics to blood circulation to tissues. Gene-sequencing analysis of the 16S rRNA of the gut bacteria showed that NPs can readily influence the composition and richness of the bacterial community. In a healthy human gut, most commensal bacteria belong to phyla Firmicutes and Bacteroides playing critical roles in digestion, immunological functions of the GIT including immune system maturation, maintaining intestinal permeability, and protection against pathogens. Alteration of the intestinal microbiota (called dysbiosis) (Fig. 5B), in its ecology (microbial population) and/or metabolic functions (production of bacterial metabolites) is known to promote a number of chronic digestive and metabolic disorders. Several studies suggest that NPs, including Ag, TiO₂, and ZnO impact the microbiota, characterized by an alteration of the Firmicutes/Bacteroidetes ratio, depletion of *Lactobacillus* strains and an increase in the abundance of Proteobacteria (Lamas, Breyner, & Houdeau, 2020). Indeed, NPs detrimental effects may resemble the microbiome shifts in inflammatory bowel disease, colorectal cancer or obesity where gut dysbiosis play a key pathogenic role. Moreover, recent evidence indicates that disturbance of the microbiota-gut-brain axis induced by ZnO NPs may result in neurobehavioral impairment by affecting gut microbiota (Chen et al., 2020).

Published studies on cytotoxicity of metal oxide NPs are limited. Moreover, these studies have used different cell models, various media, cells, applied different methods for nanomaterial characterization, and different experimental conditions for cytotoxicity testing. Therefore, data from these studies is difficult to interpret and the mechanism of toxicity of metal oxide NPs is currently unknown. Extensive development of active packaging indicates that the test methods need to be standardized and validated, positive and negative controls need to be identified and cytotoxicity data need to be harmonized. Indeed, insufficient information is available concerning the safety risk of NPs present in consumer products.

10. Intelligent packaging – application of metal oxide NPs in food safety sensors

The food industry regularly performs microbiological and chemical tests of the products during production and before distribution. However, in most cases, there is no such control when food items arrive to the market. Intelligent packaging does not interact with food, but monitors the condition of the packaged product and informs on food quality degradation using indicators (labels) and sensors, and enables traceability with unique codes and tags such as bar codes, RFID tags, smart tags or NFC codes (Müller & Schmid, 2019; Rai et al., 2019). Environmental conditions monitored inside or outside the packaging include time temperature, freshness and gas leakage indicators and relative humidity sensors. Freshness indicators, usually color changing labels on the container/package, show the change in pH or characteristic gases released during food spoilage monitored by sensors inside the packaging (Fuertes et al., 2016). Recent research has also focused on multifunctional pH dependent color changing intelligent packaging composed of a biodegradable polymer (chitosan, starch etc.), metal oxide (ZnO, TiO₂) and pH sensitive component (phenolic compounds such as anthocyanin extracted from apple pomace, black plum peel or butterfly pea flowers (Lan et al., 2021; Mary et al., 2020; Zhang et al., 2019). UV activated oxygen indicators commonly use TiO₂ nanoparticles (Wen et al., 2019). Progress in affordable printed and flexible electronics and the development of advanced bionanocomposite materials has resulted in many advances in intelligent packaging. Wireless passive RFID tags can monitor different food spoilage indicators (Raju, Bridges, & Bhadra, 2020). Metal oxides have been extensively investigated and applied as sensing materials for a wide range of different gases including CO₂, NH₃, H₂S, H₂O and also dimethylamine and trimethylamine released during food spoilage. Recent research includes development of a Ni–SnO₂ sensor using a simple sol-gel spin coating method for the detection of

Table 4

Some examples of intelligent packaging films utilizing metal oxide NPs.

Nanoparticle	Intelligent packaging function	Reference
TiO ₂	UV activated visible colorimetric oxygen indicator using Ag-loaded TiO ₂ nanotubes/methylene blue and hydroxyethylcellulose and glycerol	Wen et al. (2019)
Graphene oxide -TiO ₂	Self-adhesive UV activated colorimetric oxygen detection using graphene oxide TiO ₂ and methylene blue	Son et al. (2015)
TiO ₂	UV activated water based colorimetric oxygen indicator comprising a redox dye (methylene blue), colloidal semiconductor (TiO ₂) and a sacrificial electron donor (tartaric acid) ink-jet printed on polyester film	Lawrie, Mills, and Hazafy (2013)
IrO _x	Wireless pH sensor for monitoring pH level changes in fish meat using an IrO _x sensing electrode, sensitivity –49.7 mV/pH	(W.-D. Huang et al., 2011)
ZnO	Starch-PVA composite films with incorporated ZnO nanoparticles, capable of color change in response to pH variation (acidic, neutral, alkaline)	Jayakumar et al. (2019)
TiO ₂	Starch films incorporating anthocyanins from butterfly pea flowers and TiO ₂ nanoparticles, showed noticeable color change in the pH range 1–12, tested on prawn storage	Mary et al. (2020)
TiO ₂	Chitosan films incorporating apple polyphenols and TiO ₂ nanoparticles, showed noticeable pH responsive color changing properties in the pH range 3–13, tested on monitoring salmon meat	Lan et al. (2021)
TiO ₂	Chitosan films incorporating anthocyanin from black plum peel extract and TiO ₂ nanoparticles, pH sensitive in the pH range 2–13	Zhang et al. (2019)
ZnO	Bacterial-cellulose-polypyrrole-ZnO nanoparticle films used for monitoring chicken thigh meat, change of electrical resistance can be linked with storage time and temperature, rate of microbial growth, sensory properties and pH	Pirsa and Shamusi (2019)
ZnO	Gelatin films incorporating ZnO nanoparticles and glycerol used for monitoring relative humidity change at room temperature through change in electrical impedance	Pereira et al. (2020)
MnO ₂	Chemical vapor deposition of MnO ₂ co-sputtered with Ag and Au, used for monitoring fruit ripening through detection of change in ethylene concentration	Bigiani et al. (2020)
Ni–SnO ₂	Thin film Ni–SnO ₂ sensor used for ethylene detection in apple fruit	Beniwal (2019)
Nb–TiO ₂	Radio-frequency deposited niobium doped titanium dioxide nanotubes were used for dimethylamine detection and monitoring seafood quality	Galstyan et al. (2020)

ethylene in apple fruit quality monitoring (Beniwal, 2019). Manganese oxide nanoarchitectures with Au/Ag NPs also showed ethylene sensing potential (Bigiani et al., 2020). Niobium doping of TiO₂ nanotubes resulted in good selectivity and ability to detect low concentrations (5–50 ppm) of dimethylamine (Galstyan et al., 2020). Gelatin based nanocomposite films incorporating ZnO NPs showed good potential as a relative humidity sensing layer at room temperature in food packaging (Pereira, Picciani, Calado, & Tonon, 2020). Table 4 shows some recent examples of intelligent food packaging utilizing metal oxide NPs.

11. Conclusions

Effective utilization of metal oxide nanoparticles in smart packaging using biopolymers has been demonstrated through a review of recent



Fig. 6. List of improved packaging functions obtained utilizing metal oxide NPs.

research. Besides improving film properties, such as tensile strength and water barrier, packaging with metal oxides has shown improved antimicrobial (antibacterial, antifungal and antiviral), barrier, UV blocking, oxygen and ethylene scavenging and moisture absorption potential. An added benefit of using metal oxides in smart packaging is incorporation in food safety sensors as part of the intelligent packaging component for providing information on the product to consumers and promotion of consumer confidence in consumer safety, while to the distributors it could bring increased sales and waste reduction.

The food industry is constantly developing new packaging films, and smart packaging based on nanoparticles has been gaining in popularity over the last years due to multiple benefits as illustrated in Fig. 6. The possibility to efficiently disperse and incorporate metal oxide NPs within a packaging substrate provides active packaging film with increased efficacy. Currently, the most commercially important categories of active packaging are oxygen scavengers and moisture absorbers, followed by ethylene scavengers, CO₂ emitters and scavengers, and temperature control packaging. All of them are expected to be used more in the future because they enable shelf life extension, prevention of recalls costs, and brand reputation damage.

The most prevalent nano-sized antimicrobial metal oxides in active packaging are ZnO and TiO₂ NPs. One of the main concerns regarding use of metal oxide NPs in smart packaging is their safety, so migration from the packaging and cytotoxicity present key issues for their future utilization in smart packaging. A recent safety assessment of titanium dioxide as a food additive has deemed it unsafe emphasizing the significance of this aspect when evaluating the application of any metal oxide in the food industry thus opening the door to further research of the suitability other metal oxide NPs for this purpose. In addition, the green synthesis route represents a potential solution to improve metal oxide NPs' safety and biocompatibility. Finally, the migration tests of NPs from packaging to food or simulants have to be involved in safety assessment. By adapting parameters such as type and composition of film or coating material, pH, and film/coating thickness, the migration of NPs can be controlled to minimize the risk of nanoparticle toxicity.

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References

- Abdullah, A. H. D., Putri, O. D., Fikriyyah, A. K., Nissa, R. C., Hidayat, S., Septiyanto, R. F., et al. (2020). Harnessing the excellent mechanical, barrier and antimicrobial properties of zinc oxide (ZnO) to improve the performance of starch-based bioplastic. *Polymer-Plastics Technology and Materials*, 59, 1259–1267.
- Ahmadi, A., Ahmadi, P., & Ehsani, A. (2020). Development of an active packaging system containing zinc oxide nanoparticles for the extension of chicken fillet shelf life. *Food Sciences and Nutrition*, 8, 5461–5473.
- Ahmad, A. A., & Sarbon, N. M. (2021). A comparative study: Physical, mechanical and antibacterial properties of bio-composite gelatin films as influenced by chitosan and zinc oxide nanoparticles incorporation. *Food Bioscience*, 101250.
- Akbar, A., & Anal, A. K. (2014). Zinc oxide nanoparticles loaded active packaging, a challenge study against *Salmonella typhimurium* and *Staphylococcus aureus* in ready-to-eat poultry meat. *Food Control*, 38, 88–95.
- Al-Naamani, L., Dobretsov, S., & Dutta, J. (2016). Chitosan-zinc oxide nanoparticle composite coating for active food packaging applications. *Innovative Food Science & Emerging Technologies*, 38, 231–237.
- Al-Nabulsi, A., Osaili, T., Sawalha, A., Olaimat, A. N., Albiss, B. A., Mehyar, G., et al. (2020). Antimicrobial activity of chitosan coating containing ZnO nanoparticles against *E. coli* O157: H7 on the surface of white brined cheese. *International Journal of Food Microbiology*, 334, 108838.
- Al-Shabib, N. A., Husain, F. M., Ahmed, F., Khan, R. A., Khan, M. S., Ansari, F. A., et al. (2018). Low temperature synthesis of superparamagnetic iron oxide (Fe₃O₄) nanoparticles and their ROS mediated inhibition of biofilm formed by food-associated bacteria. *Frontiers in Microbiology*, 9, 2567.
- Al-Tayyar, N. A., Youssef, A. M., & Al-Hindi, R. R. (2020). Antimicrobial packaging efficiency of ZnO-SiO₂ nanocomposites infused into PVA/CS film for enhancing the shelf life of food products. *Food Packaging and Shelf Life*, 25, 100523.
- Almasi, H., Jahanbakhsh Oskouie, M., & Saleh, A. (2020). A review on techniques utilized for design of controlled release food active packaging. *Critical Reviews in Food Science and Nutrition*, 1–21.
- Amjadi, S., Almasi, H., Ghorbani, M., & Ramazani, S. (2020a). Preparation and characterization of TiO₂NPs and betanin loaded zein/sodium alginate nanofibers. *Food Packaging and Shelf Life*, 24, 100504.
- Amjadi, S., Almasi, H., Ghorbani, M., & Ramazani, S. (2020b). Reinforced ZnONPs/rosemary essential oil-incorporated zein electrospun nanofibers by κ-carrageenan. *Carbohydrate Polymers*, 232, 115800.
- Amjadi, S., Emaminia, S., Nazari, M., Davudian, S. H., Roufegarinejad, L., & Hamishehkar, H. (2019). Application of reinforced ZnO nanoparticle-incorporated gelatin bionanocomposite film with chitosan nanofiber for packaging of chicken fillet and cheese as food models. *Food and Bioprocess Technology*, 12, 1205–1219.
- Anitha, S., Brabu, B., Thiruvadigal, D. J., Gopalakrishnan, C., & Natarajan, T. (2012). Optical, bactericidal and water repellent properties of electrospun nano-composite membranes of cellulose acetate and ZnO. *Carbohydrate Polymers*, 87, 1065–1072.
- Appendini, P., & Hotchkiss, J. H. (2002). Review of antimicrobial food packaging. *Innovative Food Science & Emerging Technologies*, 3, 113–126.
- Apperlot, G., Lipovsky, A., Dror, R., Perkas, N., Nitzan, Y., Lubart, R., et al. (2009). Enhanced antibacterial activity of nanocrystalline ZnO due to increased ROS-mediated cell injury. *Advanced Functional Materials*, 19, 842–852.
- Auger, S., Henry, C., Péchaux, C., Lejal, N., Zanet, V., Nikolic, M. V., et al. (2019). Exploring the impact of Mg-doped ZnO nanoparticles on a model soil microorganism *Bacillus subtilis*. *Ecotoxicology and Environmental Safety*, 182, 109421.
- Auger, S., Henry, C., Péchaux, C., Suman, S., Lejal, N., Bertho, N., et al. (2018). Exploring multiple effects of Zn 0.15 Mg 0.85 O nanoparticles on *Bacillus subtilis* and macrophages. *Scientific Reports*, 8, 1–14.
- Azizi-Lalabadi, M., Ehsani, A., Ghanbarzadeh, B., & Divband, B. (2020). Polyvinyl alcohol/gelatin nanocomposite containing ZnO, TiO₂ or ZnO/TiO₂ nanoparticles doped on 4A zeolite: Microbial and sensory qualities of packaged white shrimp during refrigeration. *International Journal of Food Microbiology*, 312, 108375.
- Beak, S., Kim, H., & Song, K. B. (2017). Characterization of an olive flounder bone gelatin-Zinc oxide nanocomposite film and evaluation of its potential application in spinach packaging. *Journal of Food Science*, 82, 2643–2649.

- Beniwal, A. (2019). Apple fruit quality monitoring at room temperature using sol-gel spin coated Ni-SnO 2 thin film sensor. *Journal of Food Measurement and Characterization*, 13, 857–863.
- Bigiani, L., Zappa, D., Comini, E., Maccato, C., Gasparotto, A., & Barreca, D. (2020). Manganese oxide nanoarchitectures as chemoresistive gas sensors to monitor fruit ripening. *Journal of Nanoscience and Nanotechnology*, 20, 3025–3030.
- Bi, F., Zhang, X., Liu, J., Yong, H., Gao, L., & Liu, J. (2020). Development of antioxidant and antimicrobial packaging films based on chitosan, D- α -tocopheryl polyethylene glycol 1000 succinate and silicon dioxide nanoparticles. *Food Packaging and Shelf Life*, 24, 100503.
- Bodaghi, H., Mostofi, Y., Oromiehie, A., Zamani, Z., Ghanbarzadeh, B., Costa, C., et al. (2013). Evaluation of the photocatalytic antimicrobial effects of a TiO₂ nanocomposite food packaging film by in vitro and in vivo tests. *LWT-Food Science and Technology*, 50, 702–706.
- Böhmer-Maas, B. W., Fonseca, L. M., Otero, D. M., da Rosa Zavareze, E., & Zambiasi, R. C. (2020). Photocatalytic zein-TiO₂ nanofibers as ethylene absorbers for storage of cherry tomatoes. *Food Packaging and Shelf Life*, 24, 100508.
- Castro Mayorga, J. L., Fabra Rovira, M. J., Cabedo Mas, L., Sánchez Moragas, G., & Lagarón Cabello, J. M. (2018). Antimicrobial nanocomposites and electrospun coatings based on poly (3-hydroxybutyrate-co-3-hydroxyvalerate) and copper oxide nanoparticles for active packaging and coating applications. *Journal of Applied Polymer Science*, 135, 45673.
- Cheng, D., He, M., Li, W., Wu, J., Ran, J., Cai, G., et al. (2019). Hydrothermal growing of cluster-like ZnO nanoparticles without crystal seeding on PET films via dopamine anchor. *Applied Surface Science*, 467, 534–542.
- Chen, J., Zhang, S., Chen, C., Jiang, X., Qiu, J., Qiu, Y., et al. (2020). Crosstalk of gut microbiota and serum/hippocampus metabolites in neurobehavioral impairments induced by zinc oxide nanoparticles. *Nanoscale*, 12, 21429–21439.
- Cierach, M., Wojnarowicz, J., Kolenda, A., Krawczyk-Balska, A., Prochiewicz, E., Woźniak, B., et al. (2019). Zinc Oxide Nanoparticles cytotoxicity and release from newly formed PMMA-ZnO nanocomposites designed for denture bases. *Nanomaterials*, 9, 1318.
- Dehghani, S., Peighambari, S. H., Peighambari, S. J., Hosseini, S. V., & Regenstein, J. M. (2019). Improved mechanical and antibacterial properties of active LDPE films prepared with combination of Ag, ZnO and CuO nanoparticles. *Food Packaging and Shelf Life*, 22, 100391.
- Deng, Y., Zhao, J., Li, Q., Xu, X., Lin, H., & Li, Y. (2014). A generic in situ seed-mediated size-control method in the case of cuprous oxide nanocubes and their antibacterial activities. *CrystEngComm*, 16, 5184–5188.
- Dobrovol'skaia, M. A., Germolec, D. R., & Weaver, J. L. (2009). Evaluation of nanoparticle immunotoxicity. *Nature Nanotechnology*, 4, 411–414.
- EC. (1985). Council Directive 85/572/EEC of 19 December 1985. Laying down the list of simulants to be used for testing migration of constituents of plastic materials and articles intended to come into contact with foodstuffs. *Official Journal of the European Communities*, 327, 14–21.
- El-Megharbel, S. M., Alsawat, M., Al-Salmi, F. A., & Hamza, R. Z. (2021). Utilizing of (zinc oxide nano-spray) for disinfection against “SARS-CoV-2” and testing its biological effectiveness on some biochemical parameters during (COVID-19 pandemic)—ZnO nanoparticles have antiviral activity against (SARS-CoV-2)”. *Coatings*, 11, 388.
- Eskandarabadi, S. M., Mahmoudian, M., Farah, K. R., Abdali, A., Nozad, E., & Enayati, M. (2019). Active intelligent packaging film based on ethylene vinyl acetate nanocomposite containing extracted anthocyanin, rosemary extract and ZnO/Fe-MMT nanoparticles. *Food Packaging and Shelf Life*, 22, 100389.
- Esmailzadeh, H., Sangpour, P., Shahraz, F., Hejazi, J., & Khaksar, R. (2016). Effect of nanocomposite packaging containing ZnO on growth of *Bacillus subtilis* and *Enterobacter aerogenes*. *Materials Science and Engineering: C*, 58, 1058–1063.
- Espitia, P. J. P., Soares, N. d. F. F., dos Reis Coimbra, J. S., de Andrade, N. J., Cruz, R. S., & Medeiros, E. A. A. (2012). Zinc oxide nanoparticles: Synthesis, antimicrobial activity and food packaging applications. *Food and Bioprocess Technology*, 5, 1447–1464.
- Fathi, N., Almasi, H., & Pirouzfard, M. K. (2019). Sesame protein isolate based bionanocomposite films incorporated with TiO₂ nanoparticles: Study on morphological, physical and photocatalytic properties. *Polymer Testing*, 77, 105919.
- Fuertes, G., Soto, I., Carrasco, R., Vargas, M., Sabattin, J., & Lagos, C. (2016). Intelligent packaging systems: Sensors and nanosensors to monitor food quality and safety. *Journal of Sensors*, 1–8. <https://doi.org/10.1155/2016/4046061>, 2016.
- Gabrielyan, L., Hakobyan, L., Hovhannisyan, A., & Trchounian, A. (2019). Effects of iron oxide (Fe₃O₄) nanoparticles on *Escherichia coli* antibiotic-resistant strains. *Journal of Applied Microbiology*, 126, 1108–1116.
- Gaikwad, K. K., Singh, S., & Ajji, A. (2019). Moisture absorbers for food packaging applications. *Environmental Chemistry Letters*, 17, 609–628.
- Gaikwad, K. K., Singh, S., & Lee, Y. S. (2018). Oxygen scavenging films in food packaging. *Environmental Chemistry Letters*, 16, 523–538.
- Gaikwad, K. K., Singh, S., & Negi, Y. S. (2020). Ethylene scavengers for active packaging of fresh food produce. *Environmental Chemistry Letters*, 1–16.
- Galstyan, V., Ponzoni, A., Kholmanov, I., Natile, M. M., Comini, E., & Sberveglieri, G. (2020). Highly sensitive and selective detection of dimethylamine through Nb-doping of TiO₂ nanotubes for potential use in seafood quality control. *Sensors and Actuators B: Chemical*, 303, 127217.
- García, C. V., Shin, G. H., & Kim, J. T. (2018). Metal oxide-based nanocomposites in food packaging: Applications, migration, and regulations. *Trends in Food Science & Technology*, 82, 21–31.
- Gomes, B., Ferreira, P., & Carvalho, S. (2017). Zinc nanostructures for oxygen scavenging. *Nanoscale*, 9, 5254–5262.
- Hakeem, M. J., Feng, J., Nilghaz, A., Ma, L., Seah, H. C., Konkel, M. E., et al. (2020). Active packaging of immobilized zinc oxide nanoparticles controls *Campylobacter jejuni* in raw chicken meat. *Applied and Environmental Microbiology*, 86.
- Hamdi, M., Abdel-Bar, H. M., Elmowafy, E., El-Khouly, A., Mansour, M., & Awad, G. A. (2021). Investigating the internalization and COVID-19 antiviral computational analysis of optimized nanoscale zinc oxide. *ACS Omega*, 6, 6848–6860.
- Hardy, A., Benford, D., Halldorsson, T., Jeger, M. J., Knutsen, H. K., More, S., et al. (2018). Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health. *EFSA Journal*, 16.
- Huang, W.-D., Deb, S., Seo, Y.-S., Rao, S., Chiao, M., & Chiao, J. (2011). A passive radio-frequency pH-sensing tag for wireless food-quality monitoring. *IEEE Sensors Journal*, 12, 487–495.
- Huang, Y., Mei, L., Chen, X., & Wang, Q. (2018). Recent developments in food packaging based on nanomaterials. *Nanomaterials*, 8, 830.
- Imani, S. M., Ladouceur, L., Marshall, T., MacLachlan, R., Soleymani, L., & Didar, T. F. (2020). Antimicrobial nanomaterials and coatings: Current mechanisms and future perspectives to control the spread of viruses including SARS-CoV-2. *ACS Nano*, 14, 12341–12369.
- Ismail, A., Menazea, A., Kabary, H. A., El-Sherbiny, A., & Samy, A. (2019). The influence of calcination temperature on structural and antimicrobial characteristics of zinc oxide nanoparticles synthesized by Sol-Gel method. *Journal of Molecular Structure*, 1196, 332–337.
- Jayakumar, A., Heera, K., Sumi, T., Joseph, M., Mathew, S., Praveen, G., et al. (2019). Starch-PVA composite films with zinc-oxide nanoparticles and phytochemicals as intelligent pH sensing wraps for food packaging application. *International Journal of Biological Macromolecules*, 136, 395–403.
- Joe, A., Park, S.-H., Shim, K.-D., Kim, D.-J., Jhee, K.-H., Lee, H.-W., et al. (2017). Antibacterial mechanism of ZnO nanoparticles under dark conditions. *Journal of Industrial and Engineering Chemistry*, 45, 430–439.
- Kaewklin, P., Siripatrawan, U., Suwanagul, A., & Lee, Y. S. (2018). Active packaging from chitosan-titanium dioxide nanocomposite film for prolonging storage life of tomato fruit. *International Journal of Biological Macromolecules*, 112, 523–529.
- Karunakaran, C., Rajeswari, V., & Gomathisankar, P. (2011). Enhanced photocatalytic and antibacterial activities of sol-gel synthesized ZnO and Ag-ZnO. *Materials Science in Semiconductor Processing*, 14, 133–138.
- Khajavi, M. Z., Ebrahimi, A., Yousefi, M., Ahmadi, S., Farhoodi, M., Alizadeh, A. M., et al. (2020). Strategies for producing improved oxygen barrier materials appropriate for the food packaging sector. *Food Engineering Reviews*, 12, 346–363.
- Khan, M. I., Akhtar, M. N., Ashraf, N., Najeeb, J., Munir, H., Awan, T. I., et al. (2020). Green synthesis of magnesium oxide nanoparticles using *Dalbergia sissoo* extract for photocatalytic activity and antibacterial efficacy. *Applied Nanoscience*, 10, 2351–2364.
- Kim, S., Jeong, G. H., & Kim, S.-W. (2019). Ethylene gas decomposition using ZSM-5/WO₃-Pt-nanorod composites for fruit freshness. *ACS Sustainable Chemistry & Engineering*, 7, 11250–11257.
- Lamas, B., Breyner, N. M., & Houdeau, E. (2020). Impacts of foodborne inorganic nanoparticles on the gut microbiota-immune axis: Potential consequences for host health. *Particle and Fibre Toxicology*, 17, 1–22.
- Lan, W., Wang, S., Zhang, Z., Liang, X., Liu, X., & Zhang, J. (2021). Development of red apple pomace extract/chitosan-based films reinforced by TiO₂ nanoparticles as a multifunctional packaging material. *International Journal of Biological Macromolecules*, 168, 105–115.
- Lawrie, K., Mills, A., & Hazafy, D. (2013). Simple inkjet-printed, UV-activated oxygen indicator. *Sensors and Actuators B: Chemical*, 176, 1154–1159.
- Lee, S., Said, N., & Sarbon, N. (2020). The effects of zinc oxide nanoparticles on the physical, mechanical and antimicrobial properties of chicken skin gelatin/tapioca starch composite films in food packaging. *Journal of Food Science and Technology*, 1–9.
- Lepot, N., Van Bael, M., Van den Rul, H., D'haen, J., Peeters, R., Franco, D., et al. (2011). Influence of incorporation of ZnO nanoparticles and biaxial orientation on mechanical and oxygen barrier properties of polypropylene films for food packaging applications. *Journal of Applied Polymer Science*, 120, 1616–1623.
- Li, H., Chen, Y., Lu, W., Xu, Y., Guo, Y., & Yang, G. (2020). Preparation of electrospun gelatin mat with incorporated zinc oxide/graphene oxide and its antibacterial activity. *Molecules*, 25, 1043.
- Liu, Y., Li, Y., Deng, L., Zou, L., Feng, F., & Zhang, H. (2018). Hydrophobic ethylcellulose/gelatin nanofibers containing zinc oxide nanoparticles for antimicrobial packaging. *Journal of Agricultural and Food Chemistry*, 66, 9498–9506.
- Li, W., Zhang, C., Chi, H., Li, L., Lan, T., Han, P., et al. (2017). Development of antimicrobial packaging film made from poly (lactic acid) incorporating titanium dioxide and silver nanoparticles. *Molecules*, 22, 1170.
- Ma, J., Guo, S., Guo, X., & Ge, H. (2015). Preparation, characterization and antibacterial activity of core-shell Cu₂O@Ag composites. *Surface and Coatings Technology*, 272, 268–272.
- Manzano, M., Viezzi, S., Mazerat, S., Marks, R. S., & Vidic, J. (2018). Rapid and label-free electrochemical DNA biosensor for detecting hepatitis A virus. *Biosensors and Bioelectronics*, 100, 89–95.
- Mary, S. K., Koshy, R. R., Daniel, J., Koshy, J. T., Pothen, L. A., & Thomas, S. (2020). Development of starch based intelligent films by incorporating anthocyanins of butterfly pea flower and TiO₂ and their applicability as freshness sensors for prawns during storage. *RSC Advances*, 10, 39822–39830.
- Matsunaga, T., Tomoda, R., Nakajima, T., & Wake, H. (1985). Photoelectrochemical sterilization of microbial cells by semiconductor powders. *FEMS Microbiology Letters*, 29, 211–214.

- Mizielnińska, M., Nawrotek, P., Stachurska, X., Ordon, M., & Bartkowiak, A. (2021). Packaging covered with antiviral and antibacterial coatings based on ZnO nanoparticles supplemented with geraniol and carvacrol. *International Journal of Molecular Sciences*, 22, 1717.
- Muller, P., & Schmid, M. (2019). Intelligent packaging in the food sector: A brief overview. *Foods*, 8, 16.
- Nesic, A., Gordic, M., Davidovic, S., Radovanovic, Z., Nedeljkovic, J., Smirnova, I., et al. (2018). Pectin-based nanocomposite aerogels for potential insulated food packaging application. *Carbohydrate Polymers*, 195, 128–135.
- Ng, A. M. C., Chan, C. M. N., Guo, M. Y., Leung, Y. H., Djurišić, A. B., Hu, X., et al. (2013). Antibacterial and photocatalytic activity of TiO₂ and ZnO nanomaterials in phosphate buffer and saline solution. *Applied Microbiology and Biotechnology*, 97, 5565–5573.
- Noshirvani, N., Ghanbarzadeh, B., Mokarram, R. R., & Hashemi, M. (2017). Novel active packaging based on carboxymethyl cellulose-chitosan-ZnO NPs nanocomposite for increasing the shelf life of bread. *Food Packaging and Shelf Life*, 11, 106–114.
- Nouri, A., Yaraki, M. T., Ghorbanpour, M., Agarwal, S., & Gupta, V. K. (2018). Enhanced Antibacterial effect of chitosan film using Montmorillonite/CuO nanocomposite. *International Journal of Biological Macromolecules*, 109, 1219–1231.
- Omerović, N., Džisalo, M., Živojević, K., Mladenović, M., Vunduk, J., Milenković, I., et al. (2021). Antimicrobial nanoparticles and biodegradable polymer composites for active food packaging applications. *Comprehensive Reviews in Food Science and Food Safety*, 20, 2428–2454.
- Othman, S. H., Abd Salam, N. R., Zainal, N., Kadir Basha, R., & Talib, R. A. (2014). Antimicrobial activity of TiO₂ nanoparticle-coated film for potential food packaging applications. *International Journal of Photoenergy*, 1–6. <https://doi.org/10.1155/2014/945930>, 2014.
- Panea, B., Ripoll, G., Gonzalez, J., FernandezCuello, A., & Alberti, P. (2014). Effect of nanocomposite packaging containing different proportions of ZnO and Ag on chicken breast meat quality. *Journal of Food Engineering*, 123, 104–112.
- Pereira, P. F., Picciani, P. H., Calado, V., & Tonon, R. (2020). Gelatin-based nanobiocomposite films as sensitive layers for monitoring relative humidity in food packaging. *Food and Bioprocess Technology*, 13, 1063–1073.
- Petchwattana, N., Covavisaruch, S., Wiboonanawong, S., & Naknaen, P. (2016). Antimicrobial food packaging prepared from poly (butylene succinate) and zinc oxide. *Measurement*, 93, 442–448.
- Pirsa, S., & Shamsi, T. (2019). Intelligent and active packaging of chicken thigh meat by conducting nano structure cellulose-polypyrrole-ZnO film. *Materials Science and Engineering: C*, 102, 798–809.
- Quek, J.-A., Lam, S.-M., Sin, J.-C., & Mohamed, A. R. (2018). Visible light responsive flower-like ZnO in photocatalytic antibacterial mechanism towards *Enterococcus faecalis* and *Micrococcus luteus*. *Journal of Photochemistry and Photobiology B: Biology*, 187, 66–75.
- Rai, M., Ingle, A. P., Gupta, I., Pandit, R., Paralikar, P., Gade, A., et al. (2019). Smart nanopackaging for the enhancement of food shelf life. *Environmental Chemistry Letters*, 17, 277–290.
- Raju, R., Bridges, G. E., & Bhadra, S. (2020). Wireless passive sensors for food quality monitoring: Improving the safety of food products. *IEEE Antennas and Propagation Magazine*, 62, 76–89.
- Randazzo, P., Anba-Mondoloni, J., Aubert-Frambourg, A., Guillot, A., Pechoux, C., Vidic, J., et al. (2020). *Bacillus subtilis* regulators MntR and Zur participate in redox cycling, antibiotic sensitivity, and cell wall plasticity. *Journal of Bacteriology*, 202.
- Razali, M. H., Ismail, N. A., & Amin, K. A. M. (2019). Fabrication and characterization of antibacterial titanium dioxide nanorods incorporating gellan gum films. *Journal of Pure and Applied Microbiology*, 13, 1909–1916.
- Sahu, S. C., & Hayes, A. W. (2017). Toxicity of nanomaterials found in human environment: A literature review. *Toxicology Research and Application*, 1, Article 2397847317726352.
- Sani, M. A., Ehsani, A., & Hashemi, M. (2017). Whey protein isolate/cellulose nanofibre/TiO₂ nanoparticle/rosemary essential oil nanocomposite film: Its effect on microbial and sensory quality of lamb meat and growth of common foodborne pathogenic bacteria during refrigeration. *International Journal of Food Microbiology*, 251, 8–14.
- Saravanakumar, K., Sathiyaseelan, A., Mariadoss, A. V. A., Xiaowen, H., & Wang, M.-H. (2020). Physical and bioactivities of biopolymeric films incorporated with cellulose, sodium alginate and copper oxide nanoparticles for food packaging application. *International Journal of Biological Macromolecules*, 153, 207–214.
- Schmitz, F., de Albuquerque, M. B. S., Alberton, M. D., Riegel-Vidotti, I. C., & Zimmermann, L. M. (2020). Zein films with ZnO and ZnO: Mg quantum dots as functional nanofillers: New nanocomposites for food package with UV-blocker and antimicrobial properties. *Polymer Testing*, 91, 106709.
- da Silva, A. B., Minitier, M., Thom, W., Hewitt, R. E., Wills, J., Jugdaohsingh, R., et al. (2020). Gastrointestinal absorption and toxicity of nanoparticles and microparticles: Myth, reality and pitfalls explored through titanium dioxide. *Current Opinion in Toxicology*, 19, 112–120.
- Silva, A. L. P., Prata, J. C., Walker, T. R., Duarte, A. C., Ouyang, W., Barcelò, D., et al. (2020). Increased plastic pollution due to COVID-19 pandemic: Challenges and recommendations. *Chemical Engineering Journal*, 126683.
- Sirelkhatim, A., Mahmud, S., Seeni, A., Kaus, N. H. M., Ann, L. C., Bakhori, S. K. M., et al. (2015). Review on zinc oxide nanoparticles: Antibacterial activity and toxicity mechanism. *Nano-Micro Letters*, 7, 219–242.
- Soni, S., Dave, G., Henderson, M., & Gibaud, A. (2013). Visible light induced cell damage of Gram positive bacteria by N-doped TiO₂ mesoporous thin films. *Thin Solid Films*, 531, 559–565.
- Son, E. J., Lee, J. S., Lee, M., Vu, C. H. T., Lee, H., Won, K., et al. (2015). Self-adhesive graphene oxide-wrapped TiO₂ nanoparticles for UV-activated colorimetric oxygen detection. *Sensors and Actuators B: Chemical*, 213, 322–328.
- Stankic, S., Suman, S., Haque, F., & Vidic, J. (2016). Pure and multi metal oxide nanoparticles: Synthesis, antibacterial and cytotoxic properties. *Journal of Nanobiotechnology*, 14, 1–20.
- Stanković, A., Dimitrijević, S., & Uskoković, D. (2013). Influence of size scale and morphology on antibacterial properties of ZnO powders hydrothermally synthesized using different surface stabilizing agents. *Colloids and Surfaces B: Biointerfaces*, 102, 21–28.
- Subhapiya, S., & Gomathipriya, P. (2018). Green synthesis of titanium dioxide (TiO₂) nanoparticles by *Trigonella foenum-graecum* extract and its antimicrobial properties. *Microbial Pathogenesis*, 116, 215–220.
- Sun, J., Jiang, H., Wu, H., Tong, C., Pang, J., & Wu, C. (2020a). Multifunctional bionanocomposite films based on konjac glucomannan/chitosan with nano-ZnO and mulberry anthocyanin extract for active food packaging. *Food Hydrocolloids*, 105942.
- Sun, J., Jiang, H., Wu, H., Tong, C., Pang, J., & Wu, C. (2020b). Multifunctional bionanocomposite films based on konjac glucomannan/chitosan with nano-ZnO and mulberry anthocyanin extract for active food packaging. *Food Hydrocolloids*, 107, 105942.
- Sun, Q., Li, J., & Le, T. (2018). Zinc oxide nanoparticle as a novel class of antifungal agents: Current advances and future perspectives. *Journal of Agricultural and Food Chemistry*, 66, 11209–11220.
- Talebian, N., Amininezhad, S. M., & Doudi, M. (2013). Controllable synthesis of ZnO nanoparticles and their morphology-dependent antibacterial and optical properties. *Journal of Photochemistry and Photobiology B: Biology*, 120, 66–73.
- Tam, K., Djurišić, A., Chan, C., Xi, Y., Tse, C., Leung, Y., et al. (2008). Antibacterial activity of ZnO nanorods prepared by a hydrothermal method. *Thin Solid Films*, 516, 6167–6174.
- Tankhiwale, R., & Bajpai, S. (2012). Preparation, characterization and antibacterial applications of ZnO-nanoparticles coated polyethylene films for food packaging. *Colloids and Surfaces B: Biointerfaces*, 90, 16–20.
- Vasiljević, Z. Z., Dojcinovic, M. P., Krstić, J. B., Ribić, V., Tadić, N. B., Ognjanovic, M., et al. (2020). Synthesis and antibacterial activity of iron manganite (FeMnO₃) particles against the environmental bacterium *Bacillus subtilis*. *RSC Advances*, 10, 13879–13888.
- Vidic, J., Haque, F., Guigner, J. M., Vidy, A., Chevalier, C., & Stankic, S. (2014). Effects of water and cell culture media on the physicochemical properties of ZnMgO nanoparticles and their toxicity toward mammalian cells. *Langmuir*, 30, 11366–11374.
- Vidic, J., Manzano, M., Chang, C.-M., & Jaffrezic-Renault, N. (2017). Advanced biosensors for detection of pathogens related to livestock and poultry. *Veterinary Research*, 48, 1–22.
- Vidic, J., Stankic, S., Haque, F., Ciric, D., Le Goffic, R., Vidy, A., et al. (2013). Selective antibacterial effects of mixed ZnMgO nanoparticles. *Journal of Nanoparticle Research*, 15, 1595.
- Vidic, J., Vizzini, P., Manzano, M., Kavanaugh, D., Ramarao, N., Zivkovic, M., et al. (2019). Point-of-need DNA testing for detection of foodborne pathogenic bacteria. *Sensors*, 19, 1100.
- Vihodceva, S., Šutka, A., Sihtmäe, M., Rosenberg, M., Otsus, M., Kurvet, I., et al. (2021). Antibacterial activity of positively and negatively charged hematite (α-Fe₂O₃) nanoparticles to *Escherichia coli*, *Staphylococcus aureus* and *Vibrio fischeri*. *Nanomaterials*, 11, 652.
- Vilela, C., Kurek, M., Hayouka, Z., Röcker, B., Yildirim, S., Antunes, M. D. C., et al. (2018). A concise guide to active agents for active food packaging. *Trends in Food Science & Technology*, 80, 212–222.
- Vizzini, P., Beltrame, E., Zanet, V., Vidic, J., & Manzano, M. (2020). Development and evaluation of qPCR detection method and Zn-MgO/Alginate active packaging for controlling *Listeria monocytogenes* contamination in cold-smoked salmon. *Foods*, 9, 1353.
- Wang, H., Wang, L., Ye, S., & Song, X. (2019). Construction of Bi₂WO₆-TiO₂/starch nanocomposite films for visible-light catalytic degradation of ethylene. *Food Hydrocolloids*, 88, 92–100.
- Wei, H., Seidi, F., Zhang, T., Jin, Y., & Xiao, H. (2020). Ethylene scavengers for the preservation of fruits and vegetables: A review. *Food Chemistry*, 127750.
- Wen, J., Huang, S., Jia, L., Ding, F., Li, H., Chen, L., et al. (2019). Visible colorimetric oxygen indicator based on Ag-loaded TiO₂ nanotubes for quick response and real-time monitoring of the integrity of modified atmosphere packaging. *Advanced Materials Technologies*, 4, 1900121.
- Wong, M.-S., Chu, W.-C., Sun, D.-S., Huang, H.-S., Chen, J.-H., Tsai, P.-J., et al. (2006). Visible-light-induced bactericidal activity of a nitrogen-doped titanium photocatalyst against human pathogens. *Applied and Environmental Microbiology*, 72, 6111–6116.
- Wołoszak-Hnat, A., Zych, K., Mężyńska, M., Kifonidis, A., Dajworski, M., Lisiecki, S., et al. (2019). LDPE/PET laminated films modified with FeO (OH) × H₂O, Fe₂O₃, and ascorbic acid to develop oxygen scavenging system for food packaging. *Packaging Technology and Science*, 32, 457–469.
- Wu, J., Sun, Q., Huang, H., Duan, Y., Xiao, G., & Le, T. (2019). Enhanced physico-mechanical, barrier and antifungal properties of soy protein isolate film by incorporating both plant-sourced cinnamaldehyde and facile synthesized zinc oxide nanosheets. *Colloids and Surfaces B: Biointerfaces*, 180, 31–38.
- Xie, Y., He, Y., Irwin, P. L., Jin, T., & Shi, X. (2011). Antibacterial activity and mechanism of action of zinc oxide nanoparticles against *Campylobacter jejuni*. *Applied and Environmental Microbiology*, 77, 2325–2331.
- Xie, J., Huang, L., Wang, R., Ye, S., & Song, X. (2020). Novel visible light-responsive graphene oxide/Bi₂WO₆/starch composite membrane for efficient degradation of ethylene. *Carbohydrate Polymers*, 246, 116640.

- Xu, X., Chen, D., Yi, Z., Jiang, M., Wang, L., Zhou, Z., et al. (2013). Antimicrobial mechanism based on H₂O₂ generation at oxygen vacancies in ZnO crystals. *Langmuir*, 29, 5573–5580.
- Yan, J., Li, M., Wang, H., Lian, X., Fan, Y., Xie, Z., et al. (2021). Preparation and property studies of chitosan-PVA biodegradable antibacterial multilayer films doped with Cu₂O and nano-chitosan composites. *Food Control*, 126, 108049.
- Yildirim, S., Röcker, B., Pettersen, M. K., Nilsen-Nygaard, J., Ayhan, Z., Rutkaite, R., et al. (2018). Active packaging applications for food. *Comprehensive Reviews in Food Science and Food Safety*, 17, 165–199.
- Youssef, A. M., El-Sayed, S. M., El-Sayed, H. S., Salama, H. H., & Dufresne, A. (2016). Enhancement of Egyptian soft white cheese shelf life using a novel chitosan/carboxymethyl cellulose/zinc oxide bionanocomposite film. *Carbohydrate Polymers*, 151, 9–19.
- Zanet, V., Vidic, J., Auger, S., Vizzini, P., Lippe, G., Iacumin, L., et al. (2019). Activity evaluation of pure and doped zinc oxide nanoparticles against bacterial pathogens and *Saccharomyces cerevisiae*. *Journal of Applied Microbiology*, 127, 1391–1402.
- Zhang, X., Liu, Y., Yong, H., Qin, Y., Liu, J., & Liu, J. (2019). Development of multifunctional food packaging films based on chitosan, TiO₂ nanoparticles and anthocyanin-rich black plum peel extract. *Food Hydrocolloids*, 94, 80–92.