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Metal Oxide Nanoparticles for Safe Active and Intelligent Food Packaging

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Highlights:

- Easy to fabricate, safe and cost-effective nanomaterials for food smart packaging.
- Antimicrobial biomaterials for food packaging are developed from metal oxide nanoparticles.
- Oxygen and ethylene molecules from the headspace of food packaging are absorbed.
- The safety of packaging material is evaluated on human cells, intestinal barrier, and microbiota
- Packaging for indicating food quality are developed utilizing metal oxide nanoparticles.

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.

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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 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 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 (Karunakaran, 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 vapour 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 m^2g^{-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, Amininezhad, & 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 genotoxicity concerns of TiO_2, nor the possibility that TiO_2 after ingestion can accumulate in the body. However, TiO_2 NPs are not banned from applications in the food industry. Sol-gel processing is the most common synthesis method for TiO_2. TiO_2 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 TiO_2 NPs are synthesized using plant extracts, showing good antibacterial activity against (Subhapriya & Gomathipriya, 2018).

Antimicrobial performance of TiO_2 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 TiO_2/Pt particles during photoelectrochemical oxidation. However, TiO_2 is thermodynamically unstable, tends to agglomerate and is difficult to remove from a treated solution. Since TiO_2 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 TiO_2 or forming nanocomposites. Thus, antibacterial activity of visible-light-irradiated nitrogen- and carbon-doped TiO_2 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 amyloliquifacience* (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 Cu_2O NPs, MgO NPs, Fe_3O_4 NPs, $FeMnO_3$ and α-Fe_2O_3 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, Peighambardoust, Peighambardoust, 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 terephalate (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 TiO_2 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, Shahraz, 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. TiO_2 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). 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-SiO_2 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 TiO_2. 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 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-TiO_2 nanofibers improved the storage life of cherry tomatoes by absorbing ethylene (Böhmer-Maas, Fonseca, Otero, da Rosa Zavareze, & Zambiazi, 2020) Electrospun zein/sodium alginate nanofibers loaded with TiO_2 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 Zn^{2+} dissociation from ZnO and diffusion through the film (Espitia, et al., 2012; Petchwattana, Covavisaruch, Wibooranawong, & Naknaen, 2016). Zn^{2+} 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, moulds 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 $FeO(OH)xH_2O$, Fe_2O_3 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 TiO_2 bionanocomposite films (Fathi, Almasi, & Pirouzifard, 2019).

Ethylene (C_2H_4) 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 H_2O and CO_2. Application of metal oxides, as photocatalytic ethylene scavengers in bionanocomposite films has included TiO_2 with chitosan (Kaewklin, Siripatrawan, Suwanagul, & Lee, 2018) and TiO_2-zein nanofibers (Böhmer-Maas, et al., 2020) both used to preserve and prolong the shelf-life of tomatoes. Nanocomposites with TiO_2 such as Bi_2WO_6-TiO_2 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 Bi_2WO_6 (GBW) reduced the band gap of Bi_2WO_6 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 WO_3 (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 WO_3-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 TiO_2 NPs have been shown to produce a large quantity of ROS upon UV radiation. For instance, one hour illumination of TiO_2 NPs completely irradiated *E. coli* due to the formation of H_2O_2. During photocatalysis, electron-hole pairs are formed on TiO_2 after nanoparticle absorbed energy larger than their energy band gap. Holes react with water molecules on the surface of TiO_2 and generate surface active oxygen species, such as hydroxyl radicals (·OH), superoxide radicals ($O_2^{\cdot -}$) or hydrogen peroxide (H_2O_2). 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 H_2O_2 in OH^- and H^+ and form $O_2^{\cdot -}$ from dissolved oxygen, which in turn can react with H^+ and form a hydroperoxyl radical (HO_2^*). It produces hydrogen peroxide anions, which subsequently react with H^+ and produce

H_2O_2. 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, $FeMnO_3$, ZnO, or TiO_2 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 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, TiO_2 and La_xMnO_3 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 Zn^{2+}-ions. Different anions significantly affect nanoparticle suspension stability, and release of metal ions from NPs. The pro-oxidative and pro-inflammatory effects of TiO_2 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-*n*ZnO) 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-*n*ZnO 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 influenced 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, TiO_2, 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 colour 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 colour changing intelligent packaging composed of a biodegradeable polymer (chitosan, starch etc.), metal oxide (ZnO, TiO_2) 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 TiO_2 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 CO_2, NH_3, H_2S, H_2O and also dimethylamine and trimethylamine released during food spoilage. Recent research includes development of a Ni-SnO_2 sensor using a simple sol-gel spin coating method for the detection of 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 TiO_2 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 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, CO_2 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 TiO_2 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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Table 1

Some examples of synthesis and antibacterial application of other metal oxides

Nanoparticle	Size (nm)	Synthesis method	Pathogen	Reference
Cu_2O	400	One-step reduction	*S. aureus, E. coli*	(Yan, et al., 2021)
Cu_2O	150	Sol-gel	*E. coli*	(Ma, Guo, Guo, & Ge, 2015)
Cu_2O	36-450	In-situ mediated solution	*E. coli*	(Deng, et al., 2014)
Fe_2O_3	45, 70	Green hydrothermal	*E. coli, S. aureus, Vibrio fisheri*	(Vihodceva, et al., 2021)
Fe_3O_4	5-20	Modified co-precipitation	*E. coli*	(Gabrielyan, Hakobyan, Hovhannisyan, & Trchounian, 2019)
Fe_3O_4	6-9	Low temperature solution route	*E. coli, P. aureuginosa, L. monocytogenes*	(Al-Shabib, et al., 2018)
MgO	50	Green synthesis	*E. coli*	(Khan, et al., 2020)
MgO	50	Combustion	*E. coli, B. subtilis*	(Vidic, et al., 2013)
Zn-MgO	5-100	Chemical vapour	*B. subtilis, S. aureus, Salmonella enterica, E. coli, Saccharomyces cerevisiae*	(Zanet, et al., 2019)
$FeMnO_3$	200-1000	Sol gel	*B. subtilis*	(Vasiljevic, et al., 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	Chitosin	*E. coli, S. typhimurium, S. aureus, L. monocytogenes*	Disk	(Bi, et al., 2020)
ZnO	10-30 nm	White brined chees	Chitosan	*E. coli* O157:H7	plating	(Al-Nabulsi, et al., 2020)
ZnO	50	RTE poultry meat	Alginate	*S. typhimurium, S. aureus*	plate count	(Akbar & Anal, 2014)
ZnO	23–62	Chicken fillet; cheese	Chitosan	*E. coli, S. aureus, P. aeruginosa*	disk	(Amjadi, et al., 2019)
ZnO	<25 nm	Bread	Chitosan, cellulose	yeasts/fungi/ molds	culturing	(Noshirvani, Ghanbarzadeh, Mokarram, & Hashemi, 2017)
ZnO		Chicken meat	Cellulose, polypyrrole	*E. coli*	culturing	(Pirsa & Shamusi, 2019)
ZnO		Chicken meat	Cellulose	*Campylobacter*	Culturing, sequencing	(Hakeem, et al., 2020)
Ag/ZnO		Chicken meat	LDPE[1]	*E. coli, P. aeruginosa, L. monocytogenes*	plate count	(Panea, Ripoll, González, Fernández-Cuello, & Albertí, 2014)

Zn-MgO	5-10 nm	Smoke salmon meat	Alginate	*L. monocytogenes*	qPCR, plate count	(Vizzini, et al., 2020)
ZnO/TiO_2		Shrimp	PVA[5]/gelatin	*S. aureus, E. coli O157H7, L. monocytogenes*	count	(Azizi-Lalabadi, Ehsani, Ghanbarzadeh, & Divband, 2020)
ZnO	10-30 nm	Chicken meat	Gelatin	*S. aureus, Pseudomonas fluorescens*	Disk	(Ahmadi, Ahmadi, & Ehsani, 2020)
ZnO	130-200 nm	Food stimuli	SCP[4]	*E. coli*	Zone inhibition	(Tankhiwale & Bajpai, 2012)
ZnO	35-45 nm	Food stimuli	Chitosan+PE	*E.coli, S. enterica, S. aureus*	culturing	(Al-Naamani, et al., 2016)
ZnO	50 nm	Food stimuli	LDPE[1]	*B.subtilis, E. aerogenes*	Plate count	(Esmailzadeh, et al., 2016)
ZnO	8 nm	Soft white cheese	Chitosan + CMP[4]	*S. aureus, E. coli, P. aueruginosa*	Plate count	(Youssef, et al., 2016)
ZnO	30 nm	Food stimuli	Chitosan	*S. auereus, E.coli*	Disk	(J. Sun, et al., 2020a)
ZnO	30 nm	Food stimuli	Ethyl cellulose	*S. aureus, E. coli*	culturing	(Liu, et al., 2018)
ZnO	30 nm	Food stimuli	Zein	*S. aureus, E. coli*	Disk	(Amjadi, et al., 2020b)
ZnO	<20 nm	Spinach	Olive flounder bone gelatin	*L. monocytogenes*	Disk	(Beak, Kim, & Song, 2017)
TiO_2		fresh pear	LDPE[1]	*P. aeruginosa, R. mucilaginosa*	plate count	(Bodaghi, et al., 2013)
TiO_2	<100 nm	food stimuli	PLA[3]	*E. coli, L. monocytogenes*		(W. Li, et al., 2017)
TiO_2	25 nm	Lettuce	LDPE[1]	*E. coli*	Plate count	(Othman, et al., 2014)
TiO_2		Lamb meat	Whey protein isolate /cellulose nanofibre / rosemary essential oil	*L. monocytogenes, E. coli O157:H7, S. aureus*	Micro dilution method	(Sani, Ehsani, & Hashemi, 2017)
CuO	191 nm	Food stimuli	PHBV[5]	*S. enteria, L. monocytogenes*	Plate count	(Castro Mayorga, Fabra Rovira, Cabedo Mas, Sánchez Moragas, & Lagarón Cabello, 2018)
CuO	<50 nm	Pepper	Microcrystalline cellulose, sodium alginate	*Salmonella spp., Listeria spp.*	Plating	(Saravanakumar, Sathiyaseelan, Mariadoss, Xiaowen, & Wang, 2020)
$ZnO-SiO_2$	25-100 nm	Bread	PVA/Chitosan	*S. aureus, E. coli*	Plate count	(Al-Tayyar, et al., 2020)
Cu_2O	400 nm	Cherry tomato	PVA-chitosan	*S. aureus, E. coli*	Plate count	(Yan, et al., 2021)

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

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-SiO_2	Chitosan-PVA	With increased content of metal oxide NPs, WVTR[1] 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)
TiO_2	Chitosan	WVTR[1] 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 od 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-Bi_2WO_6	Starch	WPR[6] was improved (4.98×10^{-7} g/ (m^2·h·Pa) after addition of Bi_2WO_6	TS[2] gradually increased with higher content of NPs from 11.06 to 23.19 MPa	(J. Xie, et al., 2020)
Bi_2WO_6-TiO_2	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 & 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	(Abdullah, et al., 2020)

			EAB[4] from 43.71% to 16.84%	
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, & 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 & Sarbon, 2021)

[1]WVTR, water vapor transmission rate; [2]TS, ensile strength; [3]OP, oxygen permeability; [4]EAB, elongation at break; [5]WVP, water vapor permeability; [6]WVR, water vapour resistance; [7]WCA, water contact angle.

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, & 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 & 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	(Bigiani, et al., 2020)

	through detection of change in ethylene concentration	
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)

Figure legends:

Figure 1.

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

Figure 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).

Figure 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.

Figure 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).

Figure 5.

(A) Representative thin section electron micrographs of macrophage cells incubated with 0.1 mg/ml Mg-*n*ZnO 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).

Figure 6.

List of improved packaging functions obtained utilizing metal oxide NPs.

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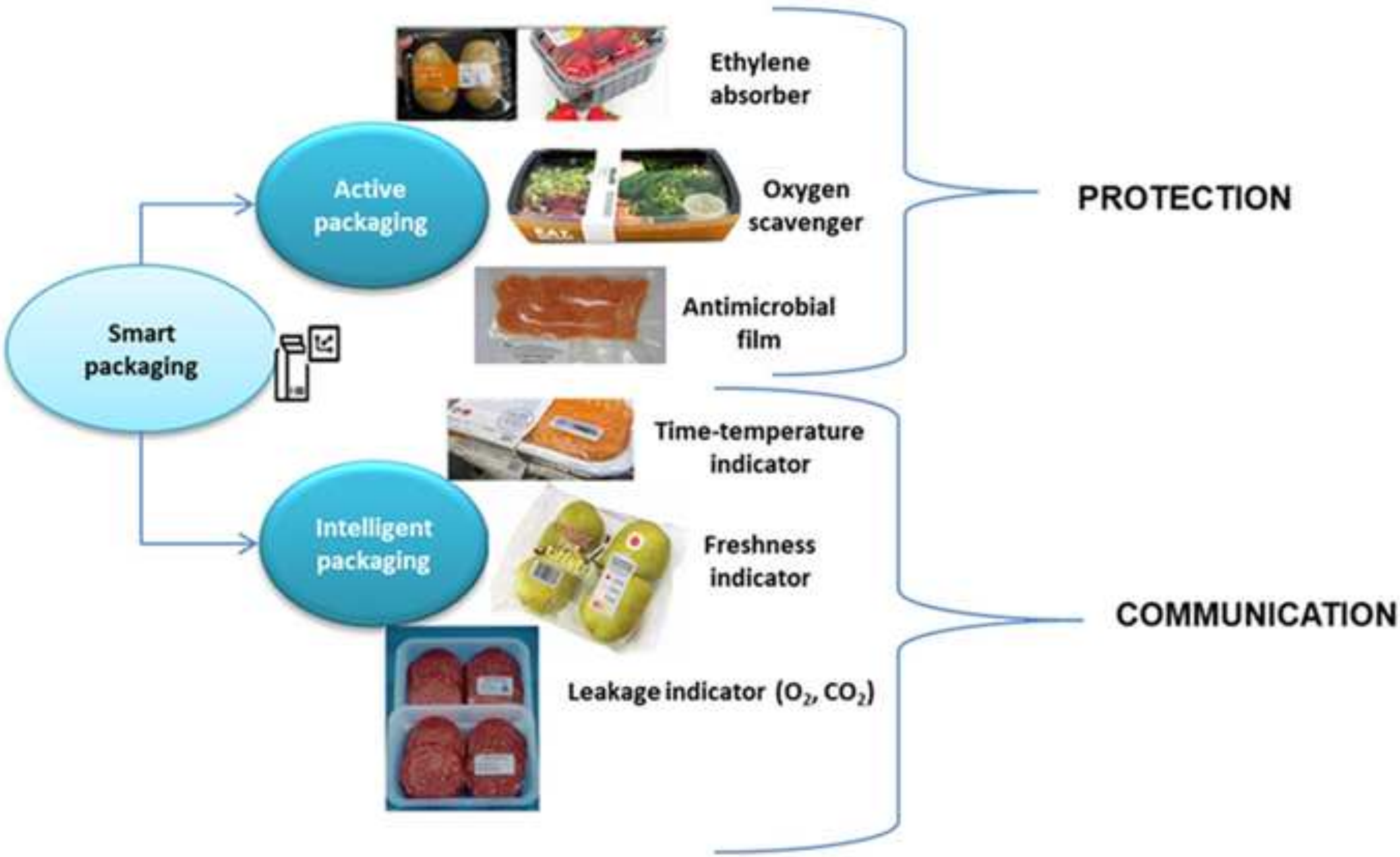
Smart packaging
Active packaging
Intelligent packaging
Ethylene absorber
Oxygen scavenger
Antimicrobial film
Time-temperature indicator
Freshness indicator
Leakage indicator (O_2, CO_2)
PROTECTION
COMMUNICATION

Figure 2

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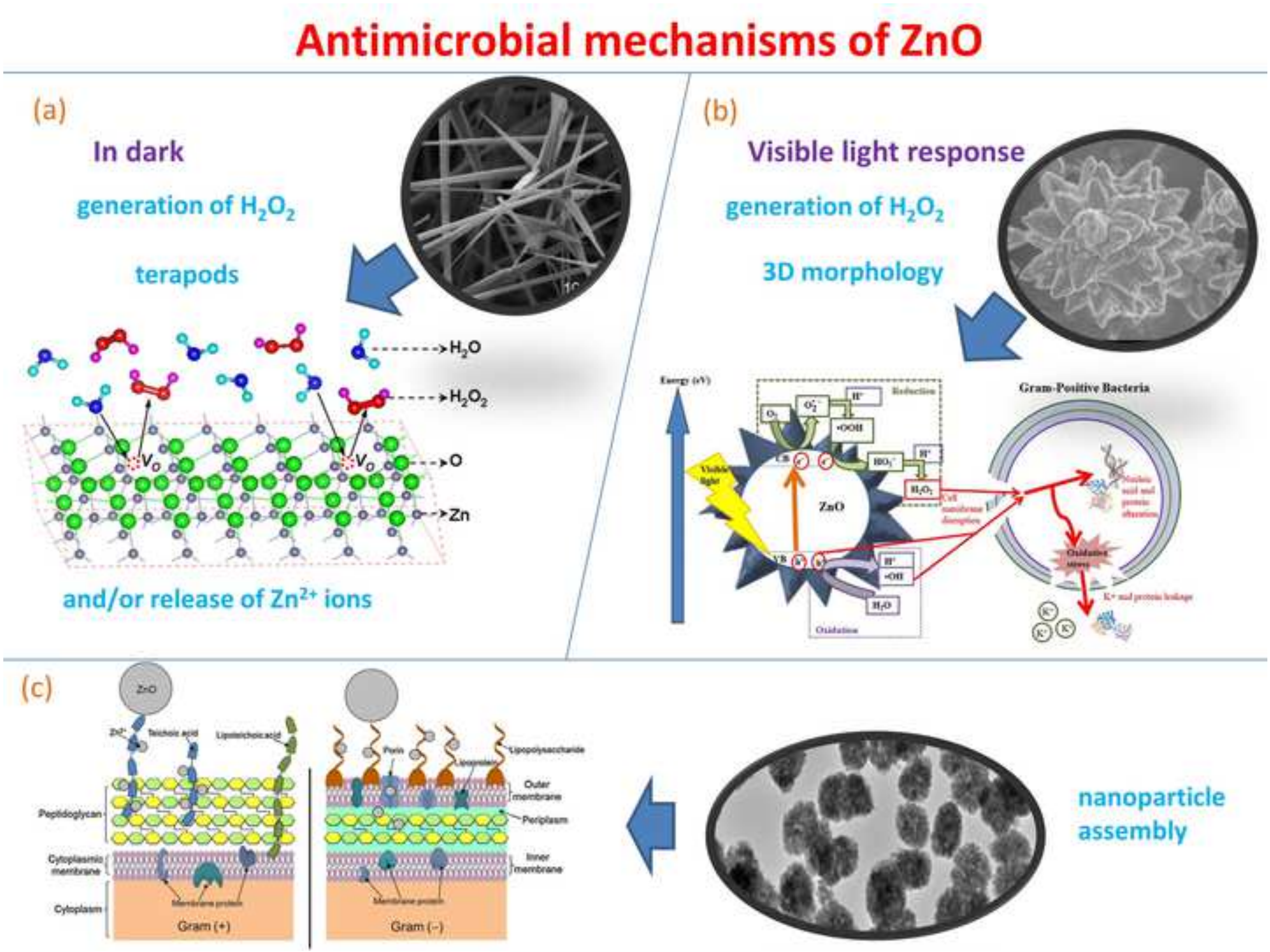

Figure 3

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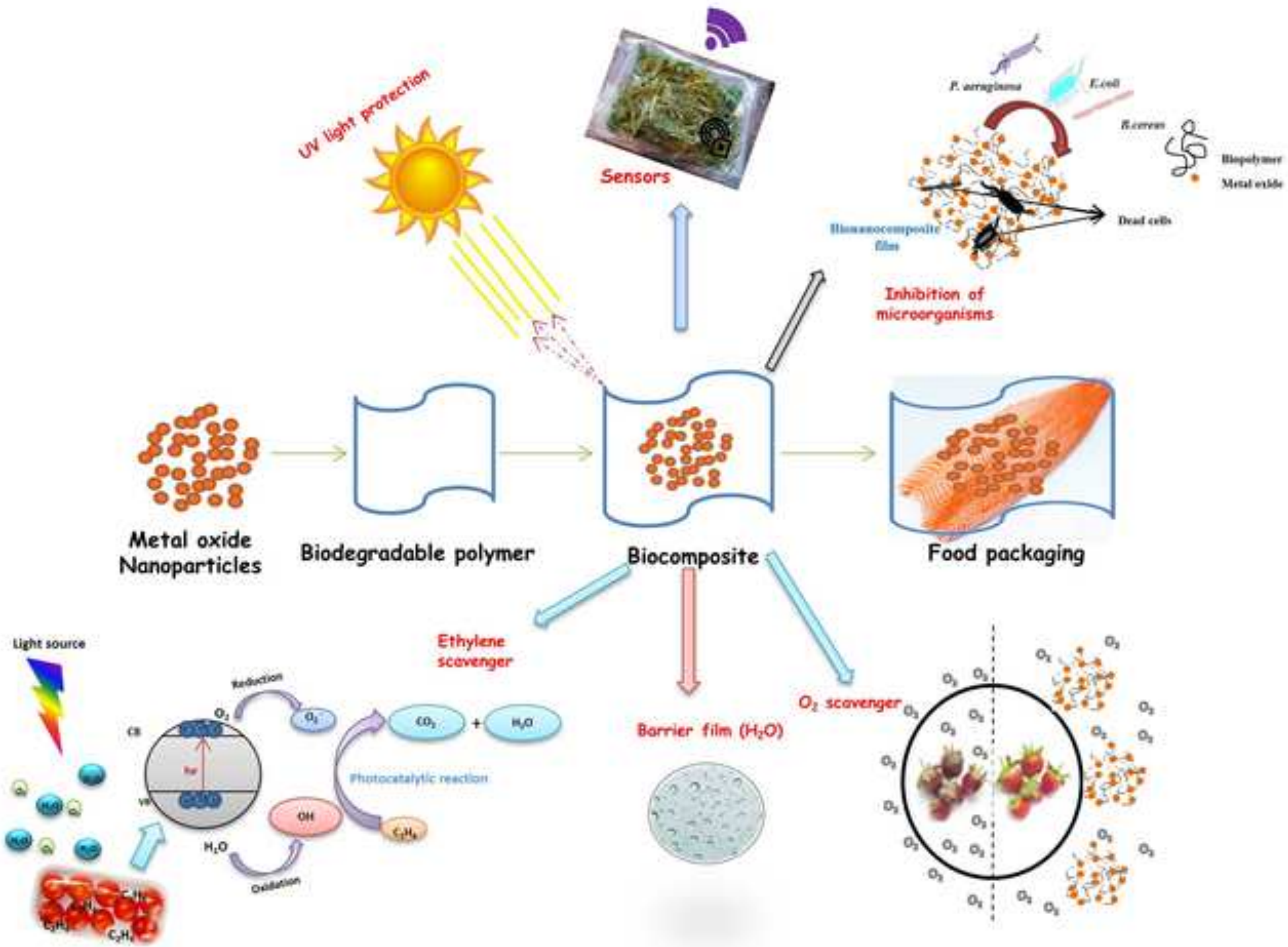


Figure 4

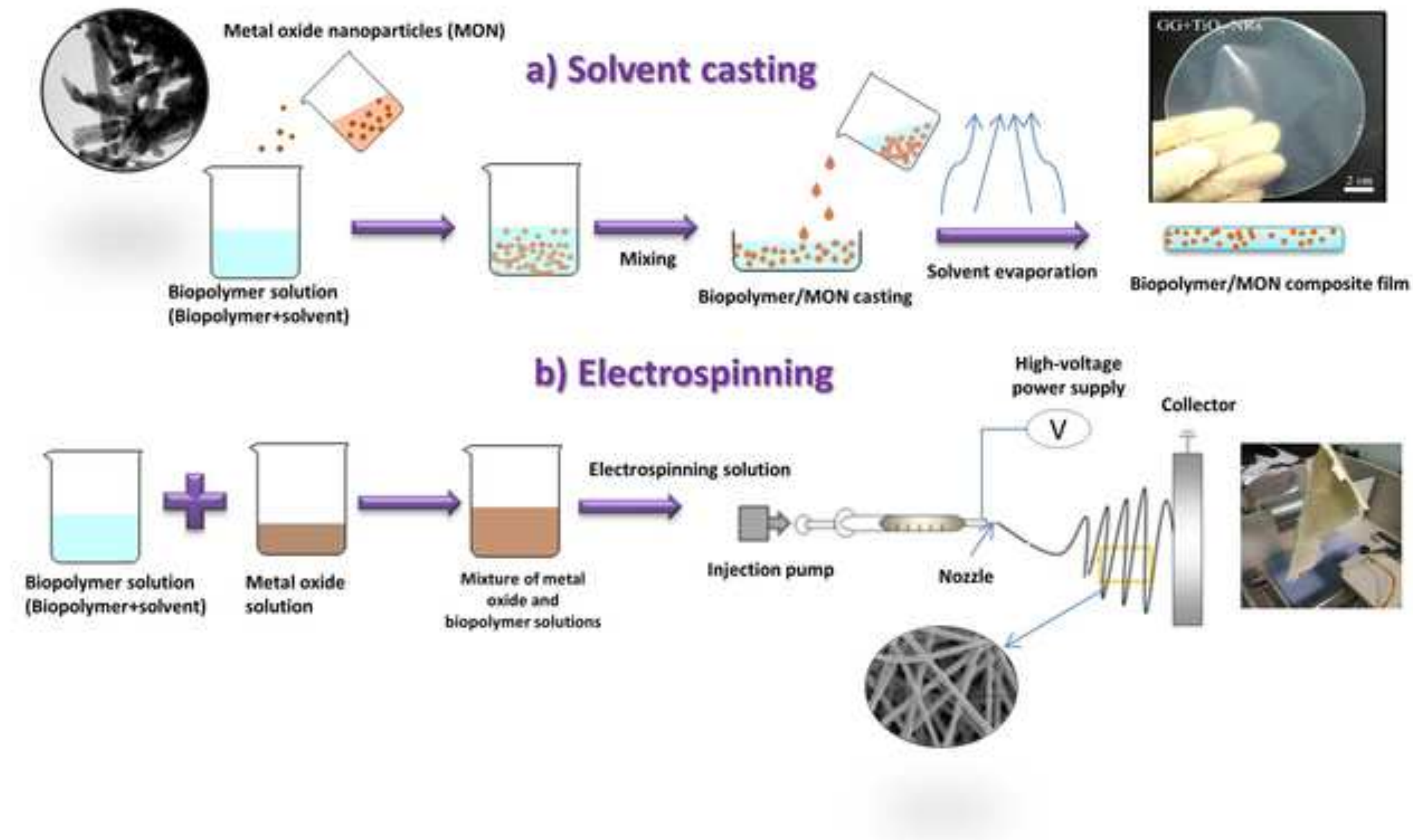

Metal oxide nanoparticles (MON)
a) Solvent casting
Biopolymer solution
(Biopolymer+solvent)
Mixing
Biopolymer/MON casting
Solvent evaporation
Biopolymer/MON composite film
b) Electrospinning
High-voltage
power supply
V
Collector
Electrospinning solution
Biopolymer solution
(Biopolymer+solvent)
Metal oxide
solution
Mixture of metal
oxide and
biopolymer solutions
Injection pump
Nozzle

Figure 5 Click here to access/download;Figure;Figure 5.tif

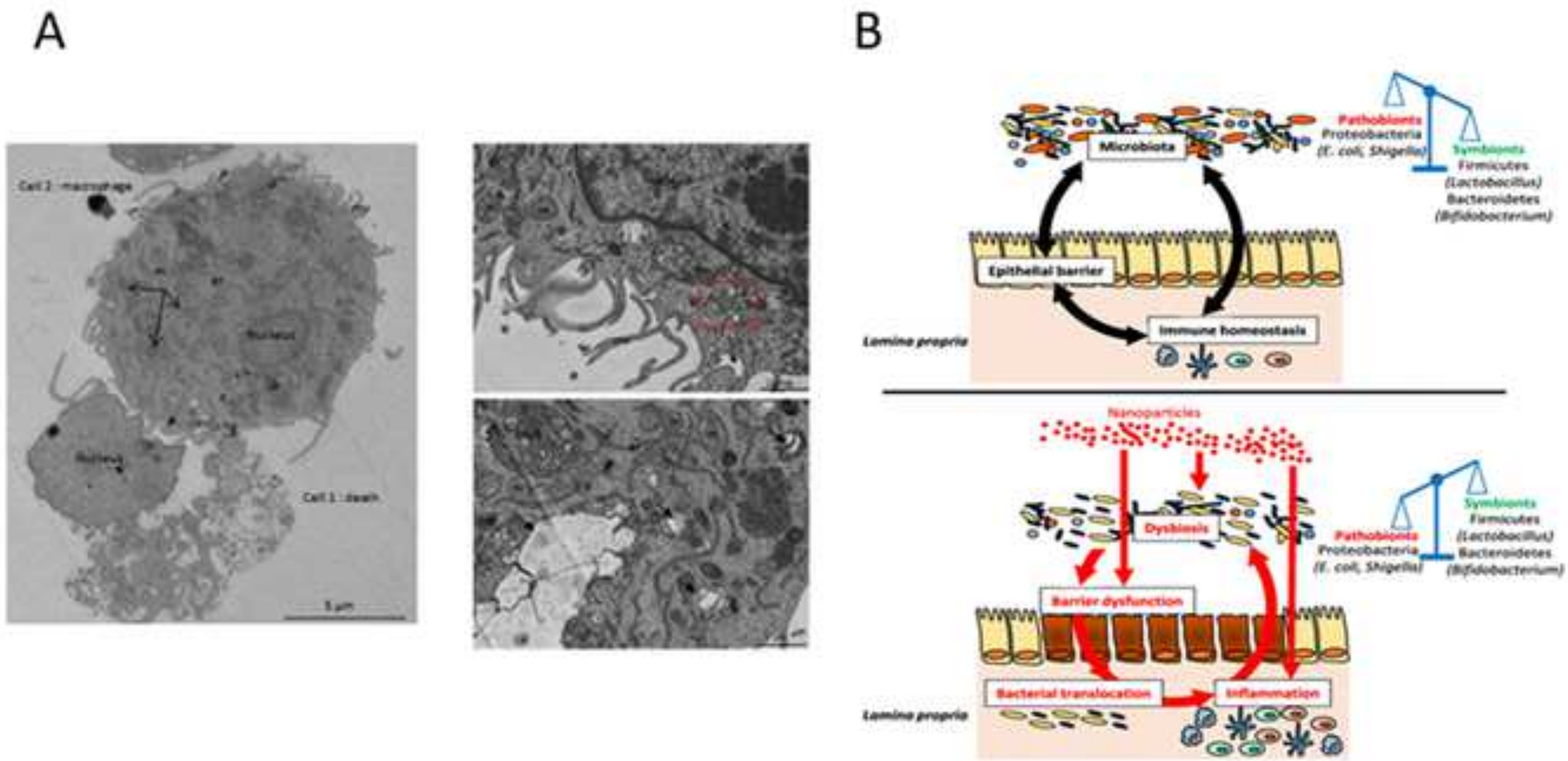
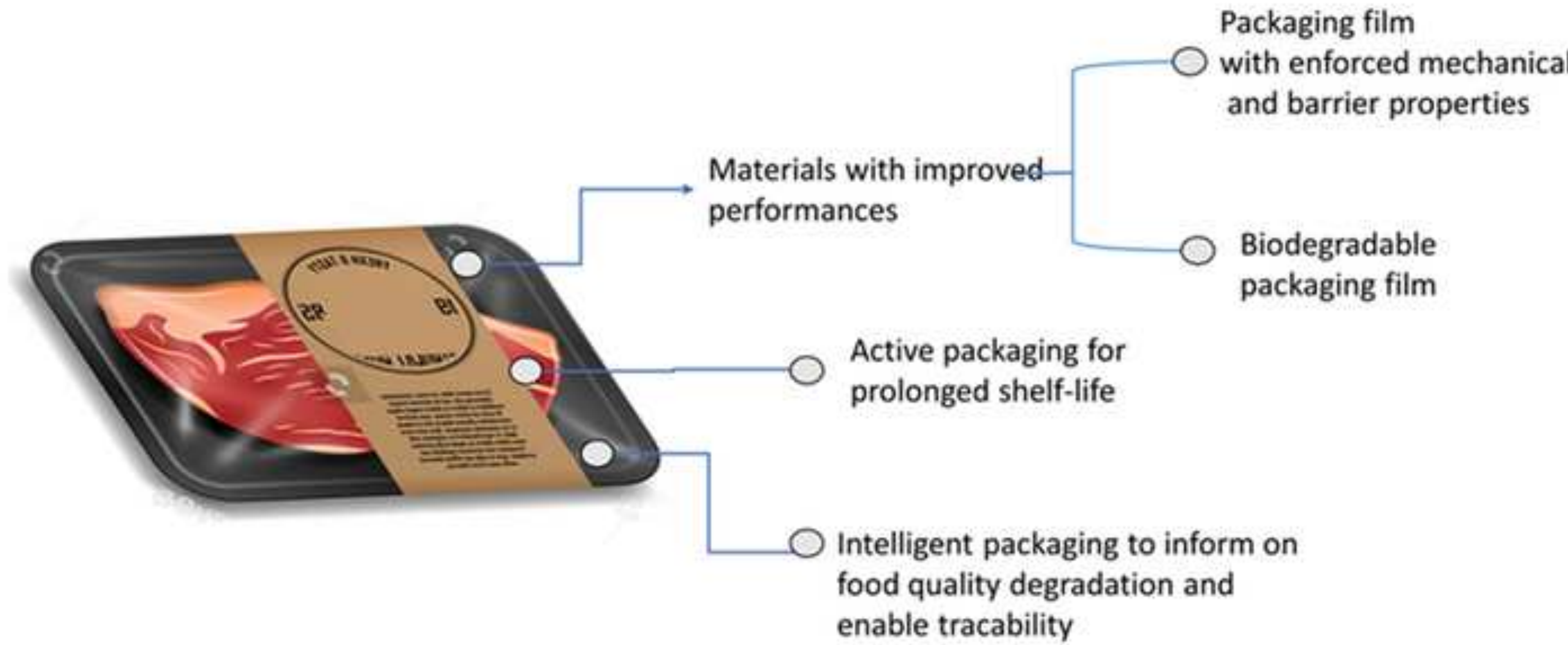


Figure 6



Packaging film
with enforced mechanical
and barrier properties
Materials with improved
performances
Biodegradable
packaging film
Active packaging for
prolonged shelf-life
Intelligent packaging to inform on
food quality degradation and
enable tracability