# Polymers and Biopolymers with Antiviral Activity: Potential Applications for Improving Food Safety

**(Review)**

Walter Randazzo[1,2], María José Fabra[2], Irene Falcó[1,2], Amparo López-Rubio[2], Gloria Sánchez[2]

[1]*Department of Microbiology and Ecology, University of Valencia. Av. Dr. Moliner, 50. 46100 Burjassot. Valencia. Spain*

[2]*Department of Preservation and Food Safety Technologies, IATA-CSIC, Avda. Agustin Escardino 7, 46980 Paterna, Valencia, Spain*

Corresponding author: Gloria Sánchez. Department of Preservation and Food Safety Technologies, Institute of Agrochemistry and Food Technology (IATA-CSIC). Av. Agustín Escardino, 7. 46980 Paterna. Valencia. Spain.

Tel.: + 34 96 3900022; Fax: + 34 96 3939301; E-mail: gloriasanchez@iata.csic.es

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**List of abbreviations**

| | |
|---|---|
| AdV2 | Adenovirus serotype 2 |
| EDAX | Energy dispersive analysis of X-rays |
| EFSA | European Food Safety Authority |
| EGCG | Epigallocatechin gallate |
| ELISA | Enzyme-linked immunosorbent assay |
| EMA | Ethidium monoazide |
| FCV | Feline calicivirus |
| FDA | Food and Drug Administration |
| FFS | Film-forming solutions |
| GRAS | Generally recognized as safe |
| GSE | Grape seed extract |
| GTE | Green tea extract |
| HAV | Hepatitis A virus |
| HEV | Hepatitis E virus |
| HIV-1 | Human immunodeficiency virus |
| HuNoV | Human norovirus |
| MHC | Micrometer-sized magnetic hybrid colloid |
| MNV | Murine norovirus |
| Mw | Molecular weight |
| NP | Nanoparticle |
| PHA | Polyhydroxyalkanoate |
| PHBV | Hydroxybutyrate-co-3-hydroxyvalerate |
| PGM | Porcine gastric mucin |
| PLA | Polylactic acid |
| PMA | Propidium monoazide |
| PP | Polypropylene |

| | | |
|---|---|---|
| 64 | RH | Relative humidity |
| 65 | RTE | Ready-to-eat |
| 66 | SEM | Scanning electron microscopy |
| 67 | $TCID_{50}$ | Tissue culture infectious dose 50 |
| 68 | TV | Tulane virus |

**Abstract**

Gastroenteritis and hepatitis, caused by human noroviruses (HuNoVs) and hepatitis A virus (HAV), respectively, are the most common illnesses resulting from the consumption of food contaminated with human enteric viruses. Food-grade polymers can be tailor designed to improve food safety, either as novel food-packaging materials imparting active antimicrobial properties, applied in food contact surfaces to avoid cross-contamination, or as edible coatings to increase fresh produce's shelf life. The incorporation of antimicrobial agents into food-grade polymers can be used to control the food microbiota and even target specific foodborne pathogens to improve microbiological food safety and to enhance food quality. Enteric viruses are responsible for one fifth of acute gastroenteritis cases worldwide and the development of food-grade polymers and biopolymers with antiviral activity for food applications is a topic of increased interest, both for academia and the food industry, even though developments are still limited. This review compiles existing studies in this widely unexplored area and highlights the potential of these developments to improve viral food safety.

## Introduction

Foodborne pathogens are a matter of increasing concern for consumers, industries and public institutions (WHO, 2015). Food, in fact, represents a vehicle of disease transmission caused by a wide range of pathogenic microorganisms, most notably pathogenic bacteria and enteric viruses (EFSA, 2016). Despite accounting for the major causes of foodborne outbreaks in high-income countries (EFSA, 2015; Shah et al., 2017), human enteric viruses have received comparatively less attention than other foodborne pathogens, such as *Salmonella*, *Listeria*, *Escherichia coli,* or *Campylobacter*. To date, almost 150 different types of human enteric viruses are known, which cause a variety of illnesses in humans, mainly gastroenteritis (such as human noroviruses (HuNoVs), sapoviruses, rotavirus, and astroviruses). They may also cause diverse additional disorders, such as hepatitis caused by hepatitis A virus (HAV) and hepatitis E virus (HEV), poliomyelitis (poliovirus), or meningitis (enteroviruses), even if reported to a lesser extent. In addition, they confer a high risk of morbidity and mortality in vulnerable populations, such as immunocompromised patients, children, the elderly and pregnant women (Rodríguez-Lázaro et al., 2012). Among them, HuNoVs and HAV have been determined to be the viruses of greatest concern from a food safety perspective (EFSA, 2016). Additionally, HEV has recently been identified as an emerging pathogen in Europe due to its potential for zoonotic transmission through the consumption of pork meat products (EFSA, 2011a, 2017).

Globally, foodborne hazards cause approximately 600 million illnesses annually, mainly due to infectious agents causing diarrheal diseases (550 million), with HuNoVs being responsible for 120 million cases attributed to water and food (WHO, 2015). Although the incidence rate of HAV infection has been on the decline in high-income countries, in part due to immunization availability, high-profile outbreaks continue to be reported,

112 with 14 million cases and over 28,000 deaths attributed to food and waterborne hepatitis
113 A worldwide every year (WHO, 2015).
114 Since these viral pathogens are mainly transmitted by the fecal-oral route, contaminated
115 food products, such as shellfish, leafy greens, and berries, are the main food products
116 associated with viral foodborne outbreaks. Contamination by food handlers or cross-
117 contamination through contaminated surfaces is mainly associated with ready-to-eat
118 products, such as salads and, bakery or delicatessen items, which are prepared or
119 handled raw or after the foods have been cooked. Contamination can also occur during
120 production, as for shellfish, usually harvested from waters affected by the discharge of
121 treated and untreated sewage (McLeod, Polo, Le Saux, & Le Guyader, 2017; Nappier,
122 Graczyk, & Schwab, 2008) or berries and leafy greens, contaminated in the fields by
123 pickers or through polluted irrigation waters (Le Guyader et al., 2004; López-Gálvez et
124 al., 2016; Randazzo, López-Gálvez, Allende, Aznar, & Sánchez, 2016), posing a higher
125 health risk because both foodstuffs are frequently eaten raw (Ethelberg et al., 2010). For
126 HuNoV outbreaks, shellfish represents the most commonly identified food vehicle in
127 Europe (EFSA, 2016), while leafy greens and fruits are the most frequently associated
128 foods in the United States (Hall, Wikswo, Pringle, Gould, & Parashar, 2014). In
129 addition, different studies have reported the transfer of viruses from the environment to
130 foods during preparation and handling (Kotwal & Cannon, 2014; Rönnqvist et al.,
131 2014). In this sense, it is worth to report that recently a standard method has been
132 established for the quantification of HAV and HuNoVs in several foodstuffs (soft fruit,
133 leaf, stem and bulb vegetables, bottled water, bivalve molluscan shellfish) or food
134 surfaces. The specifications include concentration procedures, RNA extraction and
135 target sequences to be detected by RT-qPCR (ISO 15216-1:2017, 2017).

The low infectious dose of most human enteric viruses (Atmar et al., 2014; Teunis et al., 2008), together with their high stability in the environment, make them extremely infectious and highly transmissible. As non-enveloped viruses, human enteric viruses tend to be more resistant to inactivation than foodborne bacteria to commonly used food manufacturing processes (Sánchez, 2015). Overall, mild food manufacturing processes show only marginal effects on the viral load, but when the processes are combined, the synergistic effects may enhance the level of human enteric virus inactivation (Kim, Lee, Kim, & Park, 2015; Seo, Lee, Lim, & Ko, 2012). An interesting future approach might be research into the effect of combining food processes on human enteric viruses.

In such a scenario, although the prevention of viral contamination by good hygienic, agricultural, and manufacturing practices remains the main strategy in pursuit (Codex Alimentarius, 2012), the use of polymers and biopolymers to develop antiviral materials with potential in food applications is envisaged as a promising alternative, which could help to avoid cross and/or recontaminations in line with the principles of the hurdle technology.

When browsing the extensive literature on antimicrobial materials, it is clear that biomedical applications dominate over food applications. In the food field, active packaging is an innovative solution to meet the consumer demands of fresh ready-to-eat food products together with the market trends of current food global trade, as it extends the shelf life and improves the safety of the food (López-Rubio et al., 2004). Many studies have successfully used active packaging to control foodborne pathogenic bacteria by applying of different antimicrobials, such as metals, chemicals, different essential oils, enzymes, and bacteriocins (Brandelli, Brum, & dos Santos, 2017; Maisanaba et al., 2017; Sardarodiyan & Mahdian, 2016). Additionally, some food-

160 packaging materials with antimicrobial activity are commercially available, such as
161 Zeomic™, AgIon™, Novaron™ and Cleanaid™ (Sung et al., 2013).
162 Despite the extensive research carried out to evaluate the efficacy of antimicrobial
163 packaging on foodborne pathogenic bacteria (Brandelli et al., 2017; Maisanaba et al.,
164 2017; Sardarodiyan & Mahdian, 2016) and molds (Nguyen Van Long, Joly, &
165 Dantigny, 2016), only limited information is available for their use against human
166 enteric viruses (Table 1).
167 This review analyzes the published literature on the current state of knowledge
168 regarding the development of polymers and biopolymers with antiviral activity for food
169 applications and the future perspectives of their application to enhance microbial food
170 safety.

171 **Polymers and biopolymers as carriers of active compounds**

172 In the last decades, the study of polymers of interest for food-related applications has
173 mainly aimed at improving the technological performance of packaging materials to
174 extend the shelf life of the food products and improve food safety. However, their use
175 has been customized providing them an active role for inhibiting the growth of spoilage
176 and pathogenic foodborne bacteria and, more recently, of human enteric viruses, thus
177 imparting antibacterial and antiviral properties of interest for food safety purposes. This
178 can be achieved by temporarily trapping biocidal substances within the polymer (Su et
179 al., 2015) or by covalent bonding (Thomassin, Lenoir, Riga, Jerome, & Detrembleur,
180 2007). In such a context, the stability and/or release of the active compounds
181 incorporated, which is based on their interactions with the polymeric material and on
182 the environmental conditions of its application (pH, temperature, relative humidity,
183 etc.), are key for guaranteeing their efficacy.

The large variety of materials and compositions available and the possibility of blending, chemically modifying them, or using nanotechnology tools to improve their performance have made polymers and biopolymers the materials of choice as carriers of active compounds for this type of application (López-Rubio, Gavara, & Lagaron, 2006). Albeit there are several factors that may affect the stability and/or release kinetics, including the inherent characteristics of the active compounds to be incorporated (such as molecular weight, polarity, or initial concentration) (Hu, Chen, & Wang, 2012; Suppakul, Sonneveld, Bigger, & Miltz, 2011), the chemical composition of the packaged food product (Gherardi, Becerril, Nerin, & Bosetti, 2016; Han, Castell-Perez, & Moreira, 2008), or the ambient conditions (Chalier, Ben Arfa, Guillard, & Gontard, 2009; Chen, Wang, Hu, & Wang, 2012; Han et al., 2008; Kurek, Guinault, Voilley, Galić, & Debeaufort, 2014), the polymeric/biopolymeric materials themselves play a key role in the design of novel antiviral materials.

Several factors need to be considered when designing materials with antiviral properties. The main one is the intended application of this material, as synthetic and bio-based plastics like polypropylene (PP) or polyhydroxyalkanoates (PHAs) may be used if the material is to be used as a food contact surface or food-packaging material, while natural biopolymers like polysaccharides (starch, chitosan, cellulose, etc.), proteins (soy protein, zein, etc.) and lipids (such as beeswax) with "generally recognized as safe" (GRAS) status should be selected for applications as edible coatings on fresh food products.

The most relevant factors to be considered for material selection and design can be divided into the following:

(i) Intrinsic material characteristics: these include the chemical composition and polarity (which will determine their compatibility with the active

compounds) and molecular weight (Mw), which is not usually considered but it has been reported to affect release properties (Fernández-Pan, Maté, Gardrat, & Coma, 2015; Lavin, Zhang, Furtado, Hopkins, & Mathiowitz, 2013).

(ii) Processing conditions: the processing conditions used for material development will have a direct impact on several relevant properties, such as crystallinity, thermal properties, thickness, or porosity. All these factors will affect the stability and/or release properties of the biocidal compounds incorporated although very few studies exist to date that take them into account (Efrati et al., 2014).

All the knowledge gained from the large number of existing studies on antimicrobial polymers can be leveraged for the development of antiviral materials for food applications, through the incorporation of compounds with proven antiviral properties within the polymeric/biopolymeric structures. However, it should be mentioned that the practical application of these materials as effective biocidal carriers in the food industry has been limited for many reasons, including the degradation of the bioactive agents, or their quick release from the materials (Campos, Gerschenson, & Flores, 2011). This again denotes the need to understand how the structural characteristics of the materials developed affect both the stability and release (if the substances are not immobilized) of the active compounds.

Although in the following sections specific examples about the strategies followed for the development of different types of antiviral materials are given, a general trend in this area is related to taking advantage of the inherent characteristics of different biopolymers to foster their interactions with the active compounds to control the release properties (Mascheroni, Capretti, Limbo, & Piergiovanni, 2012; Tawakkal, Cran, &

Bigger, 2016). Processing methods have also been adapted to improve biocidal activity making use of nanotechnology tools, either to protect the bioactive compounds, through micro- or nanoencapsulation (Gómez-Mascaraque, Sánchez, & Lopez-Rubio, 2016), or to develop multilayered/nanolaminate delivery systems with improved performance (Aloui & Khwaldia, 2016; Castro-Mayorga et al., 2017). In the specific case of edible coatings for fresh food products, nanoemulsions are being implemented, as they can be formulated with natural food-grade ingredients and their production process is easily scalable in the industry by high-pressure homogenization process (Donsì, Annunziata, Sessa, & Ferrari, 2011). The layer-by-layer methodology has also received great interest as a new tool to create multilayer nanocoatings to extend the shelf life of perishable foods (Fabra, Flores-López, et al., 2016; Mantilla, Castell-Perez, Gomes, & Moreira, 2013; Moreira et al., 2014; Sipahi, Castell-Perez, Moreira, Gomes, & Castillo, 2013). Recent developments in active food packaging include the use of active labels, surface modification, or incorporation of the biocide agents either included in coatings or in the adhesives of multilayer structures (Akrami et al., 2015; Gherardi et al., 2016; Han et al., 2008; Narayanan, Neera, Mallesha, & Ramana, 2013; Otero et al., 2014). These systems can be used as a starting point for the implementation of food materials with antiviral properties.

## Methodologies applied to assess the antiviral activity of polymeric and biopolymeric materials for food applications

Most studies to determine the antiviral activity of polymeric and biopolymeric materials have been performed by artificially adding a known amount of a virus to a given material, determining the reduction in the infectious titer after subjecting the spiked material to designated conditions and applying statistical procedures to determine the significance of virus decay (Fig. 1). Evidently, this implies the use of virus strains that

can be propagated in cell culture and enumerated through infectivity, thus greatly restricting the range of strains that are able to be included in these studies due to the difficulties in developing *in vitro* cultivation systems to replicate the most relevant human enteric viruses, such as HuNoV or wild-type HAV strains. Virus detection by cell culture is mainly based on the formation of cytopathic effects, followed by the quantification of the viruses by plaque assay, the most probable number, or tissue culture infectious dose 50 ($TCID_{50}$). In this sense, a promising *in vitro* cultivation system for HuNoVs using stem cell–derived human enteroids has been recently developed, but there are limitations that need to be overcome before it can be routinely used (Ettayebi et al., 2016). Therefore, the infectivity of HuNoVs has been mainly inferred through cultivable surrogates, such as feline calicivirus (FCV), murine norovirus (MNV) and, more recently, Tulane virus (TV) (Hirneisen & Kniel, 2013). Even though these animal viruses have largely been used to study the survival rate of HuNoVs exposed to different inactivation processes, the appropriateness of such surrogates as models still raises questions and need to be confirmed (Bae & Schwab, 2008; NACMCF, 2016).

Additionally, the wide range of applications of antiviral materials hampers the development of a standard methodology. To date, the absence of a specific and official regulation to evaluate the antiviral activity of active polymeric materials for food applications makes it difficult to compare the results of the assays of different studies. To overcome this lack, standard protocols developed for bacteria are often modified and adjusted to the purposes and circumstances of the antiviral assessment (Fig. 1). In fact, the antiviral experimental trials commonly apply well-established procedures aimed to assess the antimicrobial activity on plastics, and other non-porous surfaces, against bacteria and molds, such as the ISO 22196:2011 and the Japanese Industrial Standard

JIS Z 2801:2000 (Castro-Mayorga et al., 2017; Fabra, Castro-Mayorga, et al., 2016; Martínez-Abad, Ocio, Lagarón, & Sánchez, 2013). Other protocols have been also applied that differ in the inoculation, exposure, and recovery techniques adopted. For example, Amankwaah (2013) determined the virucidal activity of GTE films by placing them in the bottom of 6-well plates and filling the well with the virus suspension. After exposure, virus suspensions were recovered and titrated (Amankwaah, 2013; Haldar, An, Álvarez de Cienfuegos, Chen, & Klibanov, 2006). Similarly, Warnes and Keevil (2013) applied a previously proposed protocol optimized for bacteria (Warnes, Green, Michels, & Keevil, 2010) to assess the antiviral activity of copper coupons. In this work, virus recovery was performed with the help of glass beads, commonly used for bacteria.

As a general procedure applied for antiviral polymeric materials, the evaluation considers a viral inoculation step onto the material, a waiting/contact time while the active compound in the polymeric material exerts its expected antiviral activity, and, finally, a recovery step with a neutralizer solution to stop the inhibiting action or by swabbing (Bright, Sicairos-Ruelas, Gundy, & Gerba, 2008; Martínez-Abad et al., 2013). For comparative purposes, control materials must be prepared without the active compound and tested under the same experimental conditions to rule out the intrinsic antiviral activity of the polymers/biopolymers, as described for chitosan (Amankwaah, 2013; Davis, Zivanovic, D'Souza, & Davidson, 2012). Thus, the antiviral activity of the tested polymers is estimated by comparing the number of infectious viruses on the polymers containing active compounds and the polymers without the active compound at specific experimental conditions (normally, contact time and temperature). This approach cannot be used in the case of coatings, where the gel nature of the biopolymers normally employed complicates the assessment using the procedures applied for solid

(e.g., films) materials. To overcome this limitation, our group successfully adapted the ISO 14476:2013 (ISO 14476:2013, 2013) to test the antiviral activity of polymer gels. Specifically, pieces of each edible film (25 ± 5 mg) were inoculated with virus suspensions diluted in PBS and samples were incubated overnight at 37 ºC. Then, the effect of the active polymer gels was neutralized, and viruses were titrated in the corresponding cell line (Fabra, Falcó, Randazzo, Sánchez, & López, in press).

Thus, many parameters could differ among the different procedures, and they should be reported and clearly specified in the final report displaying the results. Amongst them, the main factors to be considered are: (i) the specifications of the active compound (such as the composition and relative concentrations) and how it has been incorporated within the polymeric material, (ii) the possible cytotoxicity effect against the tested cell lines, (iii) the effect of the neutralizer solution, (iv) the effect of working conditions tested (clean or dirty conditions), (v) temperature and humidity, (vi) the contact time with the active polymeric material, and (vii) the technique adopted for the virus recovery. As an example, while dirt conditions affect the disinfectant efficiency of antiviral solutions in surfaces (Li, Baert, & Uyttendaele, 2013), for food-packaging applications this parameter loses its importance, as the food matrix characteristics are the variables to be evaluated. Indeed, the assessment of the effectiveness of the antiviral materials for a specific food application could reflect important information for its final use under real conditions. In fact, it is known that food matrices might interfere with the antiviral activity of several compounds (Li et al., 2012; Sánchez, Aznar, & Sánchez, 2015), limiting its inactivation effect. Therefore, generally, greater amounts of active compounds need to be used in real conditions to get the same effect as in the *in vitro* tests (Goyal & Cannon, 2016). In this sense, some concerns have arisen due to the correlation between such high reported log reduction in laboratory tests and the real

decrease in the risk associated with foodborne viral transmission (Goyal & Cannon, 2016). For instance, reduced antiviral activity was observed when silver nanoparticles incorporated in coupons were used in surface waters, likely due to the interaction between silver nanoparticles with nonspecific particles in the highly turbid surface waters (Park et al., 2014).

**New developments in the methodologies applied to assess the antiviral activity against HuNoVs**

Apart from using cultivable surrogates, different methodologies to assess the antiviral activity of some compounds against HuNoVs have been reported (DiCaprio, 2017) (Fig. 1), such as:

(i) Using the HuNoV's ability to bind saliva or porcine gastric mucin (PGM) (Tan & Jiang, 2005; Tang et al., 2010), which allows for the selective recovery of potentially infectious HuNoVs (Dancho, Chen, & Kingsley, 2012; DiCaprio et al., 2016). Saliva and PGM contain multiple human histo-blood group antigens that have been recognized as receptors or co-receptors for HuNoVs (Tian, Brandi, & Mandrell, 2005). Currently, PGM and saliva-binding enzyme-linked immunosorbent assays (ELISA) have been used to evaluate the antiviral activity of grape seed extract (GSE) (Li et al., 2012) and green tea extract (GTE) (Falcó et al., under review) against HuNoVs and virus-like particles (VLPs) of HuNoVs.

(ii) Using VLPs of HuNoVs, which are expressed in baculovirus-infected insect cells and have the same morphological, antigenic, and glycan-binding properties as HuNoVs. Furthermore, the protruding (P) domain of the major structural protein of HuNoV capsid VP1 forms subviral particles, the P

particles (Carmona-Vicente, Allen, Rodríguez-Díaz, Iturriza-Gómara, & Buesa, 2016; Carmona-Vicente, Vila-Vicent, et al., 2016). Both VLPs and P particles have been used to investigate the effects of GSE and GTE by ELISA and electron microscopy (Falcó et al., under review; Li et al., 2012).

(iii) Using HuNoV suspensions pretreated with nucleic acid intercalating dyes, such as conventional intercalating dyes (i.e. propidium monoazide, PMA, and ethidium monoazide, EMA) and newly developed ones (i.e., PMAxx, and PEMAX) (Elizaquível, Aznar, & Sánchez, 2014; Randazzo, López-Gálvez, et al., 2016). This approach is based on the ability of intercalating dyes to penetrate only damaged or altered capsids and intercalate covalently into a viral genome after exposure to strong visible light, thus interfering with PCR amplification. Thus far, the inactivation of HuNoV GI and GII with epigallocatechin gallate, a natural compound, has been investigated by PMAxx-Triton pretreatment (Falcó et al., 2017).

**Development of food-grade polymers and biopolymers with antiviral potential**

Antimicrobial-packaging applications are directly related to food safety as well as to shelf life extension by preventing the growth of spoilage or pathogenic microorganisms. With this aim, biopolymer matrices can serve as an excellent carrier of antimicrobial agents, as noted in the above section. In fact, several works have been carried out in the last several decades concerning the antimicrobial efficacy of essential oils, natural extracts, and bacteriocins incorporated into biopolymer matrices (Cardoso et al., 2017; Honarvar et al., 2017; Moghimi, Aliahmadi, & Rafati, 2017; Rezaeigolestani et al., 2017). Nevertheless, although their bactericide and fungicide properties have been largely studied, little information exists in the literature about how biopolymers could

act as carriers of virucide compounds and how they behave in a food package or edible coating. Thus, biopolymers can serve as an excellent vehicle of antiviral compounds in many fields within the food area, such as food packaging, food contact surfaces, and edible coatings.

Natural extracts (e.g., GTE, GSE.), essential oils, or their main compounds (e.g., carvacrol, cinnamaldehyde) and nanometals (e.g., silver, copper) with demonstrated virucidal activity can be postulated as potential candidates to develop antiviral biopolymers (D'Souza, 2014; Li et al., 2013; Ryu et al., 2015).

The development of new packaging functionalities (i.e., antiviral) is possible because the processing equipment and conditions are the same as those currently being used (casting, melt-compounding) for other applications. Nonetheless, the effectiveness of the antiviral compounds could even be increased by developing multilayer structures (Fabra, Castro-Mayorga, et al., 2016), encapsulating the active compound (Gómez-Mascaraque et al., 2016) with potential application on shellfish depuration (McLeod et al., 2017), or even modifying the biopolymer surface to increase the antiviral activity. More detailed information about the potential and specific areas of interest will be detailed below (Fig. 2).

**Antiviral materials for food contact surfaces**

Even if human enteric viruses are primarily transmitted through direct contact person-to-person, or through contaminated water or food (de Graaf, van Beek, & Koopmans, 2016; Sánchez, 2015), an increasing number of outbreaks in developed countries originated from cross-contaminated surfaces (fomites). In fact, their low infectious dose (Teunis et al., 2008), prolonged stability in the environment, and resistance to chemical inactivation (Cheesbrough, Green, Gallimore, Wright, & Brown, 2000; Kuusi et al., 2002), make human enteric viruses highly transmissible through environmental fomites,

409 including food contact surfaces. Common areas and facilities, e.g., hospitals, cruise
410 ships, restaurants, and communal kitchens, represent exposure sites with a high health
411 risk associated with viral outbreaks (EFSA, 2016; Hall et al., 2014; Hedlund, Rubilar-
412 Abreu, & Svensson, 2000). Both non-porous (aluminum, china, glazed tile, glass, latex,
413 plastic, polystyrene, and stainless steel) and porous (cloth, different types of papers, and
414 cotton cloth) surfaces have been reported to harbor enteric viruses (Abad et al., 2001;
415 Boone & Gerba, 2007). Thus, different guidelines have been proposed to limit and
416 control the occurrence of pathogens on food products by increasing hygienic measures
417 along the entire food chain (Codex Alimentarius, 2012; WHO, 2015). Specifically, for
418 food industries and food handling services, it is extremely important to control the viral
419 contamination of surfaces, both in food-processing lines and in manipulation counters.
420 For food contact surfaces, the ideal material should exert its antiviral activity
421 throughout its use. Therefore, the polymeric material should act by direct contact and
422 not by migration of the active compounds, as is normally the case for most natural
423 compounds. Another aspect to consider when selecting the material to be used is that it
424 must be nontoxic and designed to withstand the environment of their intended use and
425 the action of food. Moreover, a smooth and non-porous surface is preferable to avoid
426 the presence of bacterial and/or viral reservoir niches. Additional features should be the
427 material's ease of cleaning and washing and its resistance to chemical detergents.
428 The first attempt to develop antiviral materials for food contact surfaces was
429 successfully carried out by Martínez-Abad and collaborators (Martínez-Abad et al.,
430 2013). Specifically, the authors applied silver-infused polylactide films for the
431 inactivation of FCV and tested their antiviral performance in food application. The
432 active renewable food- packaging material based on polylactic acid (PLA) incorporating
433 silver ions (from 0.1 to 10 g/Kg) was obtained by a solvent casting technique, and its

antimicrobial efficacy was evaluated by using the JIS Z 2801 standard (Japanese Standards Association, 2012). The antiviral activity of silver-PLA films was dose-dependent, where increasing concentrations of silver showed increased reduction in viral titers. FCV, often reported as the most sensitive HuNoV surrogate compared to others, such as MNV or Tulane virus, was less susceptible than *Salmonella*, suggesting a higher resistance of viruses to antimicrobial compounds than bacteria (Russell, 2003). In particular, reductions of approximately 2 and more than 4.4 log $TCID_{50}$/mL were shown by 0.1 and 1% of silver-PLA films after 24 h contact, respectively, while for *Salmonella*, reductions of more than 6 log CFU/mL were reported under the same experimental conditions (Martínez-Abad et al., 2013). The authors also demonstrated that after consecutive washings of the silver-PLA material, it efficiently kept its antiviral activity, thus providing a long-lasting antiviral effect, highlighting its suitability for use as food contact surfaces.

Another attempt to develop antiviral surfaces was made by Park et al. (2014), who developed a novel micrometer-sized magnetic hybrid colloid (MHC) activated with variously sized AgNPs and evaluated its efficacy for inactivating bacteriophage φX174, MNV, and adenovirus serotype 2 (AdV2). The infectivity of phage φX174 and MNV was reduced by more than 2 log after exposure to $4.6\times10^{9}$Ag30-MHCs/mL (silver content 400 ppm) for 1 h at 25 °C while in a previous study *Escherichia coli* reductions of more than 6 log CFU/mL were reported (Park, Park, Ko, & Woo, 2013).

Since it is of particular interest to develop active surfaces with enhanced virucidal activity at lower loadings due to legislative restrictions, Castro-Mayorga et al. (2017) have recently developed novel routes to guarantee the dispersion and stability of silver nanoparticles (AgNPs) in biopolymer matrices. Furthermore, the effect that the stabilized AgNPs had on transparency and mechanical properties was negligible due to

459 the low AgNPs loadings. Concretely, they applied poly (3-hydroxybutyrate-co-3-
460 hydroxyvalerate) (PHBV) materials enriched with AgNP to inactivate HuNoV
461 surrogates, FCV and MNV. Interestingly, the active surface was obtained by depositing
462 a coating of thermally post-processed electrospun PHBV18 (18% mol valerate)/AgNP
463 fiber mats over compression molded PHBV3 (3% mol valerate) films, showing
464 excellent antimicrobial properties even at 0.027%. Moreover, the homogeneous
465 distribution of AgNP into the coating and onto the PHBV3/PHBV18 layer was
466 confirmed by scanning electron microscopy (SEM) and energy dispersive analysis of X-
467 rays (EDAX) analysis. The antiviral activity of AgNP materials, tested by adapting the
468 ISO 22196:2011 norm (ISO 22196:2011), showed complete inactivation for FCV only,
469 following 24 h exposure at 37 °C and 100% RH. In the same conditions, MNV
470 infectivity was reduced by only 0.86 log (Castro-Mayorga et al., 2017) and no viable
471 counts of *Salmonella enterica* and *Listeria monocytogenes* were recorded (Castro-
472 Mayorga, Fabra, & Lagaron, 2016).
473 A different antiviral material (plastic coupons based on zeolites containing silver/copper
474 ions) was evaluated by Bright et al. (2008), who reported its effectiveness against feline
475 infectious peritonitis virus and FCV. Zeolites (sodium aluminosilicate) are porous
476 minerals that can be activated with metal ions, exchanging those for other cations
477 present in the environment, finally resulting in an interesting progressive release of the
478 active compounds. The antiviral effectiveness of zeolites activated with silver/copper
479 ions and incorporated into plastic coupons was evaluated by recovering the target virus
480 from the active surface by a swabbing procedure. Bright et al. (2008) reported more
481 than a 5 log reduction for FCV infectivity after 24 h at 23 °C on plastic coupons
482 impregnated with 10% zeolite powder containing 6.5% copper and 3.5% silver ions.
483 The silver amount into these coupons was approximately 3.5 ppm, and excluding the

484 additional antiviral effect of copper (Warnes & Keevil, 2013), such concentration
485 resulted in a greater inactivation in comparison with the AgNP-containing material
486 tested by Castro-Mayorga et al. (2017). However, although the reduction rates reported
487 for FCV by Martínez-Abad et al. (2013) using silver-PLA materials (>4.4 log) were
488 greater than those reported by Castro-Mayorga et al. (2017) using AgNP-PHBV
489 materials (1.42 log) under the same experimental conditions (24 h at 25±1 °C, 100%
490 RH), the silver concentration within the polymer matrices was significantly different, 10
491 ppm and 0.27 ppm, respectively. Nevertheless, the specific surface of nanoparticles as
492 well as the dispersion and stability of AgNPs in the polymer are key aspects that
493 determine the antiviral activity of the active surfaces. However, although it could then
494 be inferred that PHBV3/PHBV18/AgNP may have higher antiviral activity against FCV
495 than the above-mentioned publications, further studies should evaluate the efficacy of
496 such system in experiments mimicking real application conditions.
497 Studies evaluating copper antiviral activity incorporated into surfaces have been
498 reported for several viruses. For example, Noyce, Michels, and Keevil (2007) reported
499 that influenza A virus particles inoculated onto copper surfaces showed nearly a 4 log
500 decrease following 6 h of incubation at 22 °C at 50 to 60% relative humidity. Using a
501 surrogate of HuNoV (Warnes & Keevil, 2013; Warnes, Summersgill, & Keevil, 2015),
502 reported rapid MNV inactivation on dry copper and copper alloy (60-80% Cu) surfaces,
503 demonstrating that it was due to the loss of viral capsid integrity. Similarly, Manuel,
504 Moore, and Jaykus (2015) evaluated the reduction of HuNoV genogroup II.4 exposed
505 for 60 min to pure copper surface as 4 log units by RT-qPCR, observing, in addition, a
506 proportional reduction effect related to the percentage of copper in the alloys.
507 The antiviral effect of polymeric matrices containing copper has been also reported by
508 Borkow and Gabbay (2004), who evaluated the antiviral efficacy of latex gloves

509 containing copper that reduced human immunodeficiency virus (HIV-1) infectivity in a
510 dose-dependent manner (Borkow & Gabbay, 2004).
511 The antiviral activity of glass coated with thin films of titanium dioxide ($TiO_2$), copper
512 oxide (CuO), and hybrid $CuO/TiO_2$ prepared by atmospheric chemical vapour
513 deposition (Ap-CVD) was investigated by Ditta et al. (2008) using the inactivation of
514 bacteriophage T4 as a model for inactivation of enteric viruses. The inactivation rates
515 were reported to be higher by CuO and $CuO/TiO_2$, suggesting that photocatalysis and
516 toxicity of copper acted synergistically to inactivate bacteriophage T4.
517 Castro-Mayorga, Fabra Rovira, Cabedo Mas, Sánchez Moragas, and Lagarón Cabello
518 (2018) recently developed and characterized two active copper-based systems
519 performing interesting antiviral activity. In their study, the antiviral activity of
520 biodegradable PHBV melt mixed nanocomposites containing 0.1 and 0.05% of CuO
521 was compared to bilayer structures consisting of a bottom layer of compression molded
522 PHBV3 (3% mol valerate) coated with an active electrospun fibers layer made with
523 microbial mixed culture-derived PHBV18 (18% valerate) and CuO nanoparticles
524 (0.05%). Remarkably, the antiviral assay carried out with MNV adapting the ISO
525 22196:2011 showed 1.83 and 3.19 log $TCID_{50}$/mL reductions for 0.1 and 0.05% neat
526 PHBVs films, respectively, while no infectious viruses were recovered when in contact
527 with the coated structure for the same experimental conditions (24 h at 25 °C, 100%
528 RH). Therefore, it was demonstrated that by incorporating CuO into an electrospun
529 coating, the CuO loading could be reduced.
530 As reported for other antimicrobial materials, higher antibacterial activity against
531 *Salmonella enterica* and *Listeria monocytogenes* was recorded under the same
532 experimental conditions (Castro-Mayorga et al., 2018).

533 Even if evidence of zinc virucidal activity has been reported against rhinoviruses
534 (Hulisz, 2004), respiratory syncytial virus (Suara & Crowe, 2004), vaccinia virus (Katz
535 & Margalith, 1981), herpes simplex virus (HSV) (Arens & Travis, 2000), and HIV-1
536 (Haraguchi, Sakurai, Hussain, Anner, & Hoshino, 1999), it has been scarcely
537 investigated against human enteric viruses either in suspension or applied into
538 materials. Some inference regarding its antiviral activity has been drawn for brass (zinc-
539 copper alloy) using MNV (Warnes et al., 2013). In particular, Warnes and Keevil
540 (2013) suggested that zinc did have some antiviral effect, which was synergistic with
541 copper and resulted in an increased efficacy of brasses with lower percentages of
542 copper.
543 To date, the antiviral activity of gold-based surfaces has not been reported, and the
544 elevated cost of this metal limits its application in food contact surfaces. Nevertheless,
545 Broglie et al. (2015) reported the rapid inactivation of HuNoV due to Au/CuS core/shell
546 NPs evaluated on HuNoV GI.1 VLPs as a model viral system and using an absorbance
547 based ELISA.
548 *Regulatory issues*
549 Interestingly, the use of metal nanoparticles has attracted considerable attention, even
550 though nanotechnology is still out of most legislation frames. In this context, the
551 application of nanostructured materials demonstrated enhanced antimicrobial activity at
552 low concentrations due to the high surface-to-volume ratio, thus representing a
553 promising tool to improve the functionality of polymers used in antimicrobial food
554 antimicrobial food contact surfaces. In the last years, nanoparticles composed of metals,
555 metal oxides, metal salts, and metal hydroxides have been developed, the metal
556 nanoparticles of zinc oxide and silver being the most promising against both foodborne

557 bacteria (Mauriello, 2016; Moritz & Geszke-Moritz, 2013) and human enteric viruses
558 (Castro-Mayorga et al., 2017).
559 In the US, and especially in Japan, the use of silver zeolites and silver zirconium
560 phosphate resins is well established with several commercial brands incorporating silver
561 in textiles or as coatings in different products (Appendini & Hotchkiss, 2002;
562 Quintavalla & Vicini, 2002) with a maximum silver content of 3%. However, in the
563 food area, only silver nitrate is regulated with a maximum limit of 0.017 mg/kg in
564 foodstuffs and 0.1 mg/kg for drinking waters (FDA, 2010). As far as nanosilver is
565 concerned, colloidal solutions are accepted in the US and commercialized as nutrition
566 supplements. In the EU, the EFSA provisionally accepts the use of silver in food contact
567 materials with a maximum of 5% silver in the form of silver zeolites or silver
568 zirconium phosphate glasses, and silver migration is restricted to a maximum 0.05
569 mg/kg in food (EFSA, 2006) while 5 mg Cu/Kg food is the permitted migration limit
570 established by the current EU regulation (European Commission, 2011) for a
571 hypothetical package surface of 6 $dm^2$/Kg food, although there is not a specific
572 regulation for NPs. As of now, the EU legislation requires a market authorization of
573 nanomaterial applications in foods based on a safety assessment by the EFSA of the
574 potential health risks that may be associated with nanomaterials in foods (EFSA,
575 2011b).
576
577 **Antiviral food packaging materials**
578 Currently, the increasing consumers' demand for fresh, minimally processed, and ready-
579 to-eat (RTE) products has challenged industries to extend the shelf life of food products
580 together with guaranteeing their safety. Furthermore, the changes in food production
581 (i.e., global trade) and food processing (i.e., cross-contamination) have posed novel

582 risks that need to be controlled. As a result, food-packaging materials have been
583 developed with the aim of controlling pathogenic and spoilage bacteria, yeast, and
584 molds in food, exerting an inhibition of their growth (bacteriostatic activity) or a killing
585 effect (bactericidal activity) (Yildirim et al., 2018). In this sense, the physicochemical
586 properties of the polymer constituting the selective barrier to gas transport together with
587 the antimicrobial properties of different active compounds have been pointed out as key
588 factors of a hurdle technology applied to extend foods' commercial shelf life. The use of
589 biopolymers as food-packaging materials is of high interest given their excellent film-
590 forming, non-toxic, odorless, tasteless, biodegradable, and edible properties. In the case
591 of food-packaging materials with antiviral activity, the main goal is the inactivation of
592 human enteric viruses that may be present in the food due to contamination from both
593 raw materials or during processing procedures.
594 To date, limited information is available concerning food-packaging materials
595 specifically developed to control human enteric viruses (Table 1 and Fig. 2), and just
596 one study evaluated its efficacy in food products (Martínez-Abad et al., 2013). In this
597 study, a silver-infused PLA material with antiviral activity was successfully
598 manufactured and evaluated on lettuce and paprika (Martínez-Abad et al., 2013).
599 Generally, the authors reported lower FCV inactivation when films were applied on
600 food samples compared to food-contact surfaces, also showing variable results
601 depending on the food type. In fact, 1% silver-PLA films eliminated the infectivity of
602 FCV in lettuce. Less silver amount (0.1%) progressively reduced the FCV infectivity,
603 achieving the complete inactivation only at the end of the storage time (6 days). On the
604 contrary, silver-PLA films did not affect FCV infectivity on paprika, suggesting an
605 interfering effect dependent on the food matrix. Additionally, silver-PLA films applied
606 to food showed higher inactivation on *Salmonella* compared to FCV.

607 The use of ions incorporated into packaging materials showed some drawbacks, as
608 physical or chemical factors may alter their properties resulting in compounds without
609 antimicrobial activity (Castro-Mayorga et al., 2016; Ilg & Kreyenschmidt, 2011). For
610 instance, sulphides or other silver complexes may occur due to the exposure of silver
611 ions to mid-high temperature, light, or UV, not only losing the antimicrobial activity,
612 but also producing a strong brownish or blackish coloration of the material (Kasuga,
613 Yoshikawa, Sakai, & Nomiya, 2012), which finally limits its application for food
614 packaging applications.
615 Apart from metals, several plant extracts have been incorporated into polymers with the
616 idea of developing antiviral-packaging materials, even though these materials have not
617 been evaluated in food matrices. For example, a pioneering study by Fabra, Castro-
618 Mayorga, et al. (2016) evaluated the antiviral activity of a multilayer structure based on
619 polyhydroxybutyrate (as outer layers) interlayed with electrospun zein fibers activated
620 with cinnamaldehyde. In particular, the electrospinning process produced biodegradable
621 multilayer structures by the application of electrostatic forces that draw polymer
622 solutions or melts into ultrathin fibers, thus depositing them as mats of micro- or nano-
623 scale fibers (Fabra, Busolo, Lopez-Rubio, & Lagaron, 2013). This process overcomes
624 the main drawback of typical technologies where high temperatures are needed to mold
625 biodegradable polymers, a factor that limits their application for producing food-
626 packaging materials activated with thermally-sensitive compounds. This proof-of-
627 concept study developed a multilayer system activated with cinnamaldehyde (2.60
628 mg/cm$^2$) with antiviral activity against norovirus surrogates, but not for HAV. In
629 particular, adapting the ISO 22196:2011, 2.75 log $TCID_{50}$/mL reductions and complete
630 inhibitions (>2.48 log $TCID_{50}$/mL) were reported for MNV and FCV after overnight
631 treatment at 37 °C and 100% RH, respectively. Changes in temperature conditions

632 resulted in significant reduced effectiveness of cinnamaldehyde multilayer systems,
633 indicating that temperature is a major factor influencing the release or effectiveness of
634 cinnamaldehyde, as previously reported for other natural compounds (Su & D'Souza,
635 2011).
636 Among the natural polysaccharides, chitosan showed strong antimicrobial, antifungal
637 and antioxidative activities (Friedman & Juneja, 2010; Seyfarth, Schliemann, Elsner, &
638 Hipler, 2008), together with excellent film- and coating-forming properties. As an
639 example, the reduction or control of foodborne pathogenic bacteria could be enhanced
640 by the addition to chitosan coating and films of natural active compounds, as essential
641 oils (Randazzo, Jiménez-Belenguer, et al., 2016; Yuan, Chen, & Li, 2016) or propolis
642 (Torlak & Sert, 2013) that act synergistically.
643 Although recently the antiviral properties of chitosan have been reported for virus
644 suspensions (Chirkov, 2002; Davis et al., 2012; Davis, Zivanovic, Davidson, &
645 D'Souza, 2015; Su, Zivanovic, & D'Souza, 2009), its antiviral activity when
646 incorporated in food packaging remains poorly investigated. In Amankwaah's study
647 (2013), chitosan did not enhance the antiviral activity of GTE and GSE in film-forming
648 solutions (FFS) of either film. GTE and GSE were incorporated into chitosan films and
649 tested against norovirus surrogates. Specifically, 1.60 and 4.50 log PFU/mL reductions
650 of MNV were obtained after 24 h contact with 5% and 10% GTE films, respectively.
651 The film with the highest GTE concentration tested (15%) reduced MNV infectivity to
652 undetectable levels (Amankwaah, 2013). Similarly, MNV infectivity was reduced by
653 0.92, 1.89, and 2.27 log PFU/mL after 4 h at 23 °C in contact with films with 5, 10, and
654 15% GSE, respectively. Higher reductions were recorded after 24 h; the 15% GSE film
655 completely inactivated MNV (more than 4 log) (Amankwaah, 2013).
656 *Promising developments*

Although many other natural compounds have shown antiviral activity when tested *in vitro,* their application into packaging materials to inactivate human enteric viruses still remains unexplored. In fact, many of such compounds have been successfully tested against food pathogenic bacteria and demonstrated antimicrobial activity also when incorporated into food-packaging materials.

Of interest for future investigation to develop active antiviral materials are, for instance, clove, oregano, and zataria essential oils, as they have demonstrated interesting antiviral activity against norovirus surrogates (MNV and FCV) and HAV, as well as some main essential oil compounds, such as thymol and carvacrol (Elizaquível, Azizkhani, Aznar, & Sánchez, 2013; Sánchez et al., 2015; Sánchez & Aznar, 2015). Moreover, essential oils have demonstrated antimicrobial properties when incorporated into packaging films (Kashiri et al., 2017; Maisanaba et al., 2017; Randazzo, Jiménez-Belenguer, et al., 2016; Requena, Jiménez, Vargas, & Chiralt, 2016) and antifungal activities (Mateo et al., 2017). Therefore, taking into account such encouraging findings, future research should investigate the antiviral performances of packaging films enriched with essential oils.

Furthermore, other natural plant-derived substances, such as aloe vera and Eriobotryae folium extracts, showed antiviral activity against MNV (Ng et al., 2017) and could be incorporated into food packaging materials in future studies.

In the last years, many algal-derived products have been investigated, and some of the algal polysaccharides, like carrageenan, fucan, laminaran, and naviculan, are candidates as natural antiviral agents in agricultural, biomedical, food, and pharmaceutical applications (Ahmadi, Zorofchian Moghadamtousi, Abubakar, & Zandi, 2015). For instance, HIV, papillomavirus, HSV, and influenza A virus have been successfully inactivated *in vitro* by carrageenan, a phycocolloid extracted from different red seaweed species (Pangestuti & Kim, 2014). Moreover, recent studies developed active food-

682 packaging films with antibacterial activity by including marine algal compounds (Luzi
683 et al., 2017; Rodríguez-Martínez et al., 2016).

684 **Antiviral food coatings**

685 The growing consumer demand for minimally processed, easily prepared, and ready-to-
686 eat "fresh" food products with minimal chemical preservatives pose major challenges
687 for food safety and quality. Different methods have been evaluated to eliminate or
688 reduce human enteric viruses in food products, but many of the effective food-
689 processing technologies cause physicochemical changes in foodstuffs (Sánchez, 2015).
690 In contrast, edible films and coatings have been postulated as an emerging technology
691 because their efficiency is based on the controlled release of the antimicrobials retained
692 in the biopolymer matrix by optimizing and restricting additive doses. Edible films and
693 coatings can be defined as food-grade emulsions based on polysaccharides, proteins,
694 and lipids, which can be applied to most foodstuffs by spraying, spreading, or dipping,
695 to enhance food quality, stability, and safety. The use of antimicrobial (bactericide,
696 fungicide, and virucide) agents into edible films and coatings present several
697 advantages, such as the dosage adjustment, cost reductions, and greater product
698 adherences on the foodstuffs (Aloui & Khwaldia, 2016; Dehghani, Hosseini, &
699 Regenstein, 2018).

700 There are many antimicrobial natural compounds with recognized bactericide,
701 fungicide, or virucide activity than can be incorporated into edible films and coatings to
702 reduce the risk of foodborne contamination and inhibit the development of spoilage
703 microorganisms. The incorporation of natural extracts (i.e., polyphenol compounds) or
704 essential oils having antimicrobial properties in edible films and coatings represent a
705 new route to control microorganisms and foodborne pathogens transmitted through food
706 to consumers. When selecting the active agent to be incorporated in an edible coating,

not only its effectiveness against the target microorganism should be taken into account, but also its potential interactions with the hydrocolloid matrices and with the food components over which it will act (Sánchez-González, Cháfer, Hernández, Chiralt, & González-Martínez, 2011).

There are several works in the literature reporting on the bactericide and fungicide properties of natural compounds incorporated into edible films and coatings (Bermudez-Oria, Rodriguez-Gutierrez, Vioque, Rubio-Senent, & Fernandez-Bolanos, 2017; Bosquez-Molina, Jesús, Bautista-Baños, Verde-Calvo, & Morales-López, 2010; Guo, Yadav, & Jin, 2017; Umagiliyage, Becerra-Mora, Kohli, Fisher, & Choudhary, 2017; Umaraw & Verma, 2017). However, to the best of our knowledge, there is no information about antiviral edible films and coatings. This new aspect could be of great interest, for instance, in minimally processed fruits and vegetables, which are obtaining increasing recognition as important vehicles for the transmission of human pathogens, including foodborne viruses (Lynch, Tauxe, & Hedberg, 2009). Therefore, there is a need to develop new strategies, such as the development of edible coatings to improve the virological safety of these products.

In this regard, potential natural compounds with demonstrated antiviral activity, such as carvacrol (Sánchez et al., 2015), cinnamaldehyde (Fabra, Castro-Mayorga, et al., 2016), GTE (Falcó et al., 2018; Randazzo, Falcó, Aznar, & Sánchez, 2017), and GSE (Joshi, Su, & D'Souza, 2015; Su & D'Souza, 2011; Su & D'Souza, 2013), can be added to hydrocolloid matrices to confer them antiviral activity. In fact, Fabra et al. (in press) have recently reported, for the first time, the antiviral properties of alginate-lipid edible films containing GTE or GSE against MNV and HAV, GTE being more efficient than GSE (Fig. 1 and 2).

It is worth mentioning that, in this particular case of antiviral edible coatings in which the coating can be eaten, the dose is the most restrictive aspect since even though most of the antimicrobial agents are GRAS, there are some limiting doses to avoid toxicity, which is the case of essential oils (Bakkali, Averbeck, Averbeck, & Idaomar, 2008).

According to EU legislation, edible coatings are included in the regulations for food additives, which says "in order to protect human health, the safety of additives for use in foods for human consumption must be assessed before they are placed on the community market" so in the development of edible films and coatings, only additives that appear in the community list of authorized substances can be used (EC 1331/208). In addition, the ingredients used should not mislead consumers and sufficient information (i.e., toxicity assays) is needed to confirm that the additive used is safe for consumers (EU 234/2011).

In the US, edible coatings are considered a part of the food; as a consequence, their ingredients must be declared on a label under the Food and Drug Administration (FDA). In fact, the FDA provides a list that must be used as part of the coatings and emulsions. This regulation permits the use of the listed components (mainly GRAS substances and other safe ingredients) at certain concentrations (Aguirre-Joya et al., 2018; Franssen & Krochta, 2003). These authorized substances appear in the Title 21 "Food and Drugs," Chapter I "Food and Drug Administration, Department of Health and Human Services" in part 175 "Indirect Food Additives: Adhesives and Components of Coatings" (FDA, 2017). Furthermore, the US regulation also indicates that in the case of fruits and vegetables, consumers must be informed about the food product composition (including the coating ingredients).

**Encapsulation of antiviral compounds**

As previously mentioned, shellfish represents one of the most common food vehicles of viral contamination. Shellfish depuration is a commercial processing technology used worldwide, where shellfish are placed in tanks containing clean seawater and allowed to purge the contaminants for several days. Shellfish depuration rapidly removes bacterial pathogens, however the scientific community agrees on the inadequacy of commercial shellfish depuration processes for enteric viruses (McLeod et al., 2017). In this specific case, the incorporation of antiviral compounds within the water tanks is envisaged as the most promising approach. However, many natural antimicrobial compounds are sensitive molecules which can be affected by food processing conditions or interaction with food components, resulting in reduced antimicrobial effect. Micro- and nanoencapsulation processes, in which a compound is embedded within a protective matrix, have attracted increasing research interest for the protection of these sensitive compounds (Gómez-Mascaraque, Ambrosio-Martín, Fabra, Pérez-Masiá, & López-Rubio; Gómez-Mascaraque & Lopez-Rubio, 2016; Pérez-Masiá, Lagaron, & López-Rubio, 2014). Many studies have focused on the development of micro- or nanoparticle-based systems for increased antimicrobial stability and activity but, to date, information about their potential use in food products is rather limited (Castro-Rosas et al., 2017). For instance, encapsulation of antimicrobial compounds has demonstrated to enhance their stability during food-processing treatments, such as electron beam irradiation (Gomes, Moreira, & Castell-Perez, 2011), and the usefulness of these techniques to generate natural additives (Ko, Kim, & Park, 2012) or to formulate antibacterial disinfectants (Krogsgard Nielsen et al., 2017). Similarly, encapsulation of antivirals for food applications has been scarcely explored. Recent developments in encapsulation of antiviral compounds include the use of chitosan to enhance the protection for (–)-epigallocatechin gallate (EGCG, a green tea polyphenol) (Gómez-Mascaraque et al.,

2016) which was previously reported to be a very effective antiviral compound, reducing the titers of HAV and MNV in a dose-dependent manner at neutral pH. Microencapsulated EGCG showed the potential to prolong the antiviral activity of EGCG against MNV via gradual bioactive release combined with its protection against degradation in simulated physiological conditions. Therefore, these results highlight the potential of encapsulated natural antiviral compounds to be used in food applications. For example, GSE and GTE have been successfully used as natural sanitizers of fresh produce and food contact surfaces (Falcó et al., 2018; Li et al., 2012; Randazzo et al., 2017; Su & D'Souza, 2013), and encapsulation of these antiviral compounds may provide enhanced and prolonged antiviral activity as a consequence of the protection and more gradual release provided by the biopolymeric encapsulating matrices. In fact, different studies demonstrated the efficacy of alginate-based delivery particles to target shellfish tissues (Darmody et al., 2015; Prado-Alvarez et al., 2015), suggesting that encapsulation could represent a viable tool for the transport and delivery of antiviral compounds directly to the shellfish tissues.

## Final remarks

Food contamination by human enteric viruses is a serious health and economic problem. Currently, food manufacturing processes that may inactivate human enteric viruses cannot be applied without adversely affecting food quality. Therefore, the effective prevention of contamination, new food-processing strategies, new sanitation approaches, and consumer education could reduce enteric virus numbers and thereby decrease consumer risks of enteric virus infections. Among these strategies, one promising technology is the use of polymers and biopolymers with antiviral activity.

To evaluate the potential of polymers or biopolymers with antiviral activity, some publications have explored their efficacy against HAV and HuNoV, mainly using

HuNoV surrogates. The use of different virus titers, inoculum-suspending matrices, and virus-recovery procedures complicates comparisons among studies, as documented in this review. Additionally, antiviral polymers have been mainly applied in *in vitro* experiments with different levels of success.

The use of metals or metal nanoparticles to render antimicrobial polymeric materials has significant potential applications. This is particularly the case in food contact and packaging applications. However, there are still a number of issues, such as regulatory issues and effectivity at low dosages that need to be better addressed and resolved for this interesting technology to be widely used in industrial applications. The most promising research is oriented toward the mastering of nanoparticles, which seems to offer better stability, efficacy, and cost effectiveness.

Although there is increasing interest in the use of antimicrobial packaging and edible coatings, motivated by the increasing consumer demand for safe and stable foods, little information is available in the literature about how biopolymers could act as carriers of antiviral compounds in real food samples. Therefore, the development of biopolymers with antiviral activity and their applications in the food area is today an open field of research that needs to be fully addressed.

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**Author Contributions**

Randazzo and Falcó researched prior studies, interpreted the results and drafted the manuscript. Fabra compiled data and drafted the manuscript. López-Rubio and Sánchez conceived the original idea and drafted the manuscript. All authors contributed to the final manuscript.

Table 1. Active packaging and food contact surfaces with virucidal activity.

| (Potential) Application | Active compound | Type of polymer or biopolymer | Virus | Concentration of the active compound | Test conditions | Inactivation (log reduction) | Reference |
|---|---|---|---|---|---|---|---|
| Active packaging | Green seed extract | Chitosan | MNV | 5; 10; 15% | 23 ºC, 24 h | 1.9; 3.2; >4.0 | (Amankwaah, 2013) |
| | Green tea extract | Chitosan | MNV | 5; 10; 15% | 23 ºC, 24 h | 1.6; 4.5; >4.5 | (Amankwaah, 2013) |
| | Cinnamaldehyde | PHB | MNV | 2.60 mg/cm$^2$ | 37 ºC, ON, 100% RH | 2.7 | (Fabra, Castro-Mayorga, et al., 2016) |
| | | | FCV | | | <LOD | |
| Active packaging and food contact surfaces | Silver ions | PLA | FCV | 0.1; 1% | 24 °C, 24 h | 2; >4.4 | (Martínez-Abad et al., 2013) |
| | Silver nanoparticles | PHBV | MNV | 0.027% | 37 °C, 24 h | 0.86 | (Castro-Mayorga et al., 2017) |
| | | | FCV | | | <LOD | |
| Food contact surfaces | Silver ions | Plastic coupons impregnated with zeolite powder | FCV | 0.00035% | 23 °C, 24 h | 5 | (Bright et al., 2008) |
| | Silver nanoparticles | Magnetic hybrid colloid | φX174 | 0.04% | 25 °C, 1 h | >2 | (Park et al., 2014) |
| | | | MNV | | | >2 | |
| | Copper | PHBV[1] | MNV | 0.05% | 25 °C, 24h, 100% RH | 3.19 | (Castro-Mayorga et al., 2018) |
| | Copper | Copper surfaces | MNV | 89% | RT, 30 min | 5 | (Warnes et al., 2015) |
| | Copper | | HuNoV GII.4 | 100% | RT, 1 h | 4 | (Manuel et al., 2015) |

Abbreviation: PHB, Polyhydroxybutyrate; PHBV, 3-hydroxybutyrate-co-3-hydroxyvalerate; PLA, Polylactide; LOD, limit of detection.

**Figure 1.** Diagram of the methods used for assessing the antiviral activity of food-grade polymers or biopolymers.

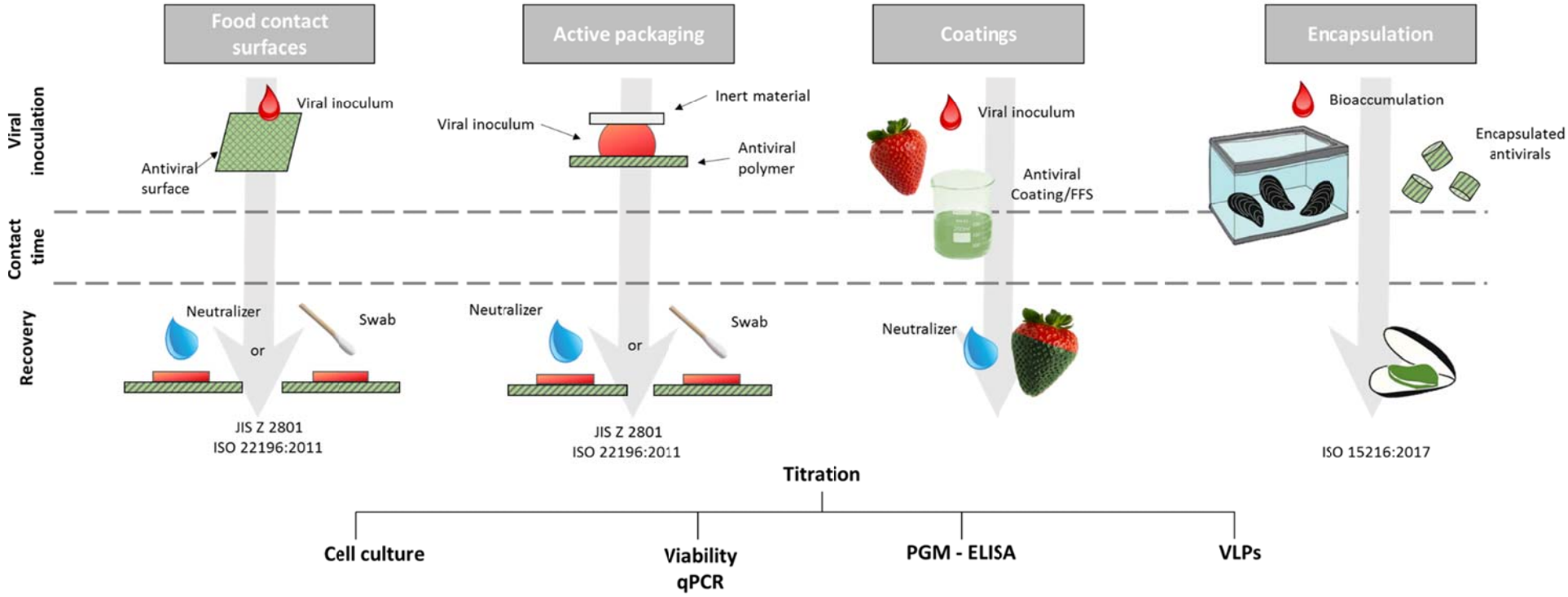
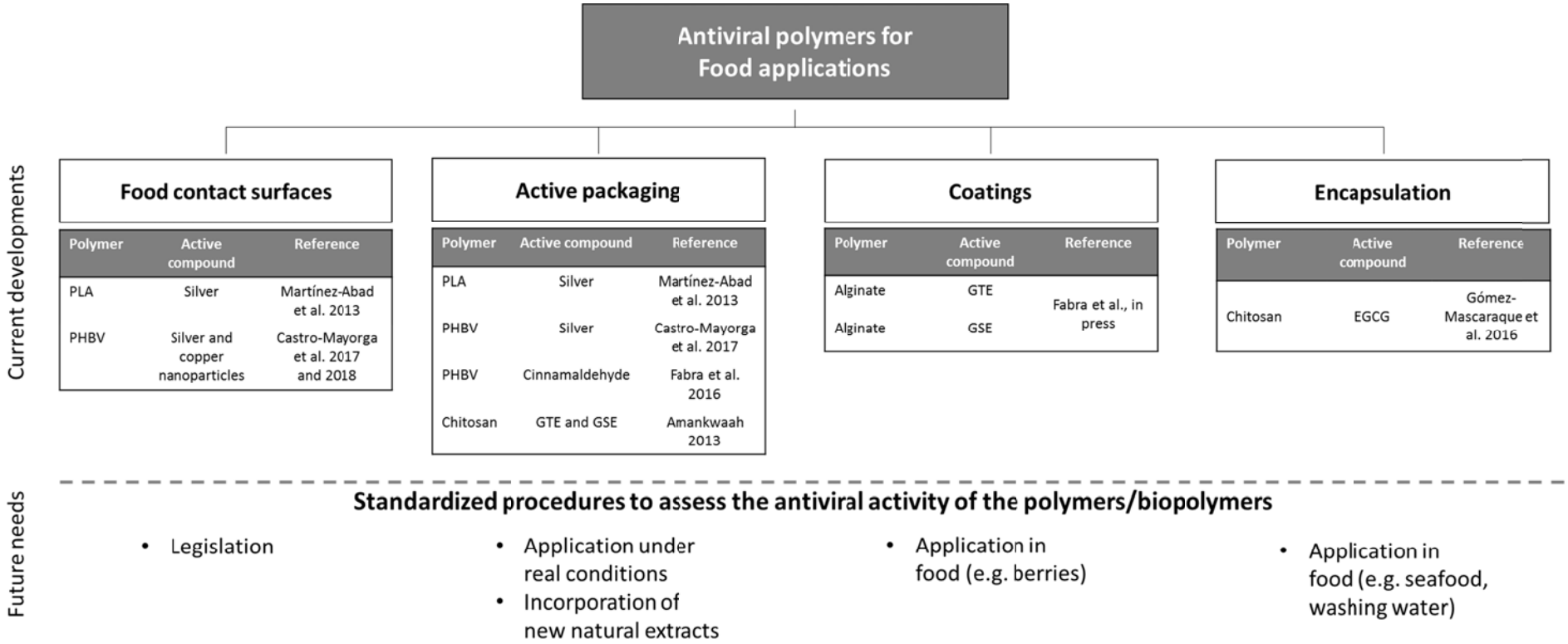


**Figure 2.** Food application of polymers and biopolymers with antiviral activity.



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