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Investigating Antimicrobial Activity and Potential Health-Related Hazards of Titanium Dioxide Nanoparticles as a Food Additive and Constitute of Food Packaging

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Background: Titanium dioxide (TiO_2) is employed in various forms, ranging from nano to macro, in food products and packaging to prolong shelf life. However, recent research has shown potential health risks associated with its use. This review investigates the health implications of TiO_2 nanoparticles (NPs) in food packaging or additives, while also examining TiO_2's antimicrobial properties and related mechanisms.
Methods: The research extensively explored TiO_2 NPs' generation methods and antimicrobial potential, especially in the context of food packaging and cosmetics. A systematic search was conducted using Google Scholar, Pub Med, and Web of Science databases to identify relevant sources. A total of 97 sources were selected from 150, without date restrictions. These references, spanning 1972 to 2023, encompass diverse full-text English materials, including reviews, original research, conferences, handbooks, and book chapters.
Results: Nanotechnology, specifically TiO_2 NPs, enhances food packaging for safety and sustainability. Innovations such as reinforced, active, and biodegradable packaging have emerged to address industry challenges, improving mechanical performance and extending shelf life. However, despite the benefits, concerns about the health and environmental implications of TiO_2 NPs have prompted regulatory reassessment.
Conclusion: Addressing concerns about TiO_2 NPs in food packaging is crucial due to potential health and environmental risks. The recent ban imposed by the European Union on TiO_2 (E171) underscores the need for ongoing research and scrutiny to ensure the safe integration of nanotechnology in food packaging.

1. Introduction

Nanotechnology is the science of building and developing materials and structures on a scale of a billionth of a meter. If a large molecule can be scaled down to nanometer size, it has the specific chemical and physical properties of the nanoparticles (NPs), which are very different from the major molecule characteristics. Despite the enormous development of nanotechnology in many areas, nanotechnology in food packaging is still at the forefront. Since a wide range of nanomaterials with their functional properties can be used to improve packaging, the future of food packaging can be attributed to this technology (Kuswandi & Moradi, 2019). The most crucial advantage of nanotechnology in the food industry is the introduction of new food packaging technology and food preservatives. The growth of nanotechnology in agriculture and the food industry has made significant progress in recent years

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(Dasguptaal et al., 2015). In this regard, NPs can be used to increase the shelf life and improve the final quality of food due to their specific properties, including the ability to regulate the release of antioxidants, antibacterial agents, flavors, and enzymes (Daneshniya et al., 2020a). Nanocomposites, which are made from a combination of conventional food packaging materials with nanomaterials, have received significant attention due to their excellent mechanical performance, good antibacterial properties, and high resistance. According to different studies, the incorporation of TiO_2 into food packaging has formed three closely related categories of food packaging, namely, enhanced nanoparticle packaging, active and intelligent packaging, and biodegradable nanocomposite packaging (Daneshniya et al., 2021a; Latifi et al., 2021). Packaging of reinforced NPs can increase the surface area, which significantly improves mechanical performance such as flexibility, reduced gas permeability, temperature stability, moisture resistance, light and flame, and the use of NPs can be associated with the inclusion of antimicrobial properties for packaging materials (Latifi et al., 2021). In the section on active and intelligent packaging, "active" is a type of packaging that can eliminate undesirable flavor and improve the color and aroma of packaged materials, and "intelligent" means that relevant information monitors the quality of packaged food. Some of the bio-nanocomposites used in food packaging are active, releasing antimicrobial and antioxidant compounds by eliminating undesirable factors such as oxygen and water vapor to increase products' shelf life (Latifi et al., 2021; Abdolmaleki et al., 2023). This new branch of food packaging has played a pivotal role in extending the shelf life of various food products. his innovative packaging approach is particularly significant due to its impact on optimizing food packaging materials and offering highly biodegradable packaging solutions. Currently, most of the materials used in food packaging are plastic polymers that are non-biodegradable and cause irreparable damage to the environment. These non-biodegradable plastics pose a serious threat to humans and the environment (Kirwan & Strawbridge, 2003). The time required to decompose different types of plastics varies. This timeframe can be anywhere from 15 years to never. In such circumstances, the importance of using biodegradable materials in food packaging becomes more pronounced. These include edible and biodegradable films made from recyclable materials (Tharanathan, 2003; Kuswandi, 2017). The use of nanocomposite packaging is increasing day by day, with the number of food products using nanocomposite packaging going from less than 40 in 2002 to over 400 in 2006. In the next decade, nanotechnology is expected to affect 25 % of the food packaging market, which is currently estimated at 100 billion dollars. This suggests that in the coming decade, about 500 food products will be marketed with nanotechnology packaging (Latifi et al., 2021). The reason for this increase in market share is people's perception of the safety of fixed NPs and their inability to affect the quality of food; however, monitoring and strict surveillance of NPs incorporation in food packaging have created a major concern for nanotechnology research and development in the food industry. Different experiments have shown that nanoparticles such as titanium dioxide (TiO_2) NPs used in packaging tend to have the potential to migrate to food and that consumption of these foods may pose a risk to consumers' health (Daneshniya et al., 2020a). However, TiO_2 has been recognized as non-toxic and safe by the American Food and Drug Administration (FDA) for human food, drugs, cosmetics, and food contact materials. The natural source of oxidized titanium is titanium oxide, also known as titanium (IV) oxide or titanium (Thiruvenkatachari et al., 2008; Emamifar, 2011). Food preservation possesses a critical importance for the food industry. In the development of new antimicrobial agents and addressing food safety concerns, it is essential to reduce the occurrence and economic impact of foodborne illnesses (Carvalho, 2017; Nie et al., 2017; Myszka et al., 2019). There is currently significant interest in the self-disinfecting characteristic of TiO_2 for meeting hygienic design demands in food processing and packaging surfaces. Even though the bactericidal and fungicidal effects of TiO_2 on *Escherichia coli*, *Salmonella choleraesuis, Vibrio parahaemolyticus*, *Listeria monocytogenes*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Diaporthe actinidiae*, and *Penicillium expansum* have been approved; its photocatalytic disinfection application for drinking water production was investigated as well (Thiruvenkatachari et al., 2008). The output of various microorganisms such as *Lactobacillus Plantarum*, *Escherichia coli*, *Staphylococcus aureus*, *Salmonella*, *Alicyclobacillus acidoterrestris*, and aerobic psychrotrophic, molds, and leaves can be minimized with the utilization of nanomaterials in food packaging (Emamifar et al., 2010; Fernández et al., 2009; Jin & Gurtler, 2011; Nobile et al., 2004; An et al., 2008). TiO_2 is also being applied directly to foods. This metal oxide is a white, odorless, and tasteless compound widely used as a food additive to enhance the visual appeal of various products. Commonly identified by the E number E171, TiO_2 is employed in a variety of food items, including confectionery, baked goods, sauces, and dairy products, primarily due to its ability to impart a bright white color (Jovanović, 2015). One of the primary functions of titanium dioxide in the food industry is its role as a whitening agent. It imparts a clean and bright appearance to food products, making them more visually appealing to consumers. This is especially crucial in candies, icing, and certain dairy products. TiO_2's ability to provide opacity and coverage is exploited in applications such as coatings and fillings. It helps create a uniform color and prevents the transparency of certain food items, ensuring a consistent visual experience (Boutillier et al., 2021). Regarding its regulation, In the European Union (EU), no specific maximum level for E171 has been stipulated (Winkler et al., 2018). The Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives refrained from establishing an acceptable daily intake (ADI) for TiO_2, citing its minimal oral absorption rate, which does not exceed 0.1 %. In the United States, the utilization of the food additive TiO_2 dates back to 1966, with the Food and Drug

Administration (FDA) generally recommending concentrations below 1 % by weight of the food. Nevertheless, increasing apprehension has emerged concerning the safety of titanium dioxide as a food additive (Kamat, 2011). Recently, there has been growing concern over the safety of TiO_2 in different scales, from macro to nano. Studies have shown that nano-sized titanium dioxide particles can pass through the intestinal barrier and accumulate in various organs, including the liver, spleen, and brain. Moreover, studies on animals have shown that exposure to titanium dioxide can lead to inflammation, oxidative stress, and DNA damage (Catalano et al., 2020). Hence, we aimed to review recent progress in the utilization of TiO_2 with a focus on their antimicrobial activity and potential health-treating hazards regarding their utilization as food additives and in food packaging.

2. Materials and Methods

To ensure a comprehensive exploration of complex subjects, such as the generation methodologies of TiO_2 NPs, their antimicrobial potential (including induction approaches and underlying mechanisms), and the health-related issues associated with their application in packaging or direct use in cosmetic and food products, this study relied on a robust research methodology. The primary research tool employed was Google Scholar, along with Pub Med and Web of Science databases. The search strategy involved the integration of keywords such as "food packaging," "food additive," "shelf life extension," "antimicrobial," "hazards," and "regulations" with "Titanium Dioxide Nanoparticles" to retrieve pertinent literature on the designated subject matter. This inquiry yielded a total of 150 sources. To streamline the references, the authors meticulously selected 97 sources. Notably, the selection process did not impose additional criteria, including publication dates. Consequently, the chosen articles span from 1972 to 2023. It is important to highlight that all selected references are accessible with full text in English and include all types of papers, including reviews, original research, conferences, as well as other resources like handbooks, and book chapters.

3. Results and Discussion

3.1 Generation of TiO_2 NPs

Heat or mass transfer, nanoscale reaction engineering, nanobiotechnology, and molecular synthesis are used as the methods of nano-food packaging preparations. Generated nanocomposite polymers can be used in food packaging to enhance packaging's barrier properties, including ceasing the penetration of carbon dioxide, moisture, and oxygen into the packaging. Furthermore, these polymers can be utilized in active packaging aiming at delaying or restraining microbial growth and the spoilage of food. Intelligent packaging is another sort of packaging in which nanocomposites can be used to monitor food health. Degradable biopolymers are another area in which nanocomposites can be used for Improvements in biopolymers' physical and chemical consistency (Mei & Wang, 2020; Kim et al., 2022; Pirsa & Shamusi, 2019; Ding et al., 2020; Kraśniewska et al., 2020; Sun et al., 2020; Daneshniya et al., 2020a). As mentioned in Table 1, different methods can be utilized to generate TiO_2 NPs. Due to strong ultraviolet-blocking efficiency, TiO_2 is a widely studied semiconductor as it can effectively absorb short-wavelength light with considerable photostability. The integration of TiO_2 NPs into food packaging polymer films contributes to retaining high transparency and prevents the harmful impact of ultraviolet irradiation on food components (Emamhadi et al., 2020; Duncan, 2011). According to Figure 1, structural construction from atom to cluster to NPs is a bottom-up or efficient method. The most widely used method for handling NPs has been sol-gel, and recent biosynthesis has attracted the attention of the scientific community (Chaudhary et al., 2020).

Table 1. Different methods to prepare NPs (Chaudhary et al., 2020)

Bottom-up approach		Top-down approach	
Method	*NPs*	*Method*	*NPs*
Sol-gel method	Carbon, metal, and metal oxide-based	Thermal decomposition method	Carbon and metal oxide-based
Chemical vapor deposition (CVD) method	Carbon and metal oxide-based	Nanolithograph y method	Metal-based
Spinning method	Organic polymers	Mechanical milling method	Metal, oxide, and polymer-based
Pyrolysis method	Carbon and metal oxide-based	Sputtering method	Metal oxide-based
Biosynthesis method	Organic polymers and metal-based	Laser ablation method	Carbon and metal oxide-based

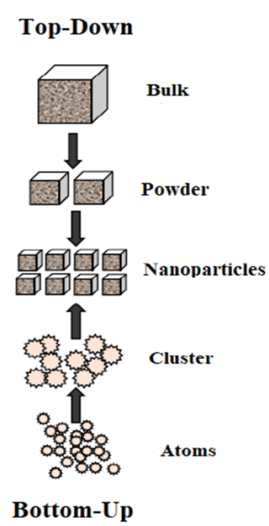

Figure 1. Top-down and Bottom-up approaches (Daneshniya et al., 2020b)

3.2 Antimicrobial activity of TiO_2 NPs

According to Figure 2, the antimicrobial activity of metal NPs may be related to several mechanisms. The NPs can directly interact with the microbial cells or, as the precedent, interrupt transmembrane electron transfer, disrupt/ penetrate the cell envelope, oxidize cell components, or produce secondary products such as reactive oxygen species (ROS) or dissolved heavy metal ions cause damage (Li et al., 2008; Daneshniya et al., 2020b).

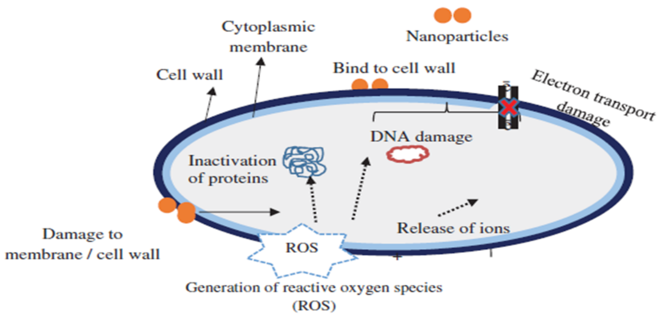

Figure 2. Microbial inactivation in microbial cells through metal NPs (Hoseinnejad et al., 2018)

The mechanism of antimicrobial action of TiO_2, shown in Figure 2, is based on the decay of the microorganism by hydroxyl radicals and ROS produced through a light reaction in water media. Hydroxyl radicals inactivate microorganisms by oxidizing their unsaturated phospholipids parts of the plasma membrane. According to Figure 3, the initial step for TiO_2 to induce its antimicrobial activity is to be exposed to ultraviolet light, where excitation with energy beyond the corresponding band gap (approximately 3.2 eV), forms energy-rich electron-hole pairs. At the exterior of the material, such charge carriers interact with microorganisms in a biocide manner (Hoseinnejad et al., 2018; Hrnjak-Murgic, 2015).

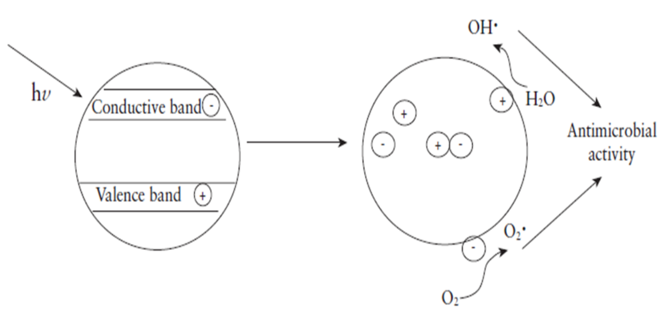

Figure 3. Antimicrobial impact of TiO_2 (Hrnjak-Murgic, 2015)

Silver (Ag), gold (Au), zinc oxide (ZnO), silica (SiO_2), titanium dioxide (TiO_2), alumina (Al_2O_3), and iron oxides (Fe_3O_4, Fe_2O_3) are metal and metal oxide nanomaterials widely used as antimicrobial agents. Nano-zinc oxide and magnesium oxide have recently been discovered to have antimicrobial effects. Zinc oxide and TiO_2 NPs are expected to offer a more affordable and secure food packaging option in the future compared with silver NPs (Chaudhry et al., 2008). TiO_2 NPs are highly regarded due to their low production cost, chemical stability, photocatalytic activity, and favorable antimicrobial effect. Non-toxic and antimicrobial activity against various microbes has led to the use of TiO_2 as a suitable component in food packaging. The FDA has endorsed the utilization of TiO_2 in medicines, cosmetics, and food contact surfaces (Bodaghi et al., 2013). Regarding the antimicrobial activity of TiO_2, two model bacterial strains, Gram-negative *Escherichia coli,* and Gram-positive *Bacillus subtilis,* were used to examine the toxic effects associated with TiO_2 water suspensions. It was concluded that in the presence of light, the antibacterial activity of TiO_2 against Gram-negative and Gram-positive bacterial organisms was substantially higher compared to the dark, and cell death by TiO_2 in the darkness was less pronounced (Adams et al., 2006). To research the antimicrobial effects on *Escherichia coli in vitro* in a real food system, TiO_2-coated polymer films were made. The findings revealed that with the utilization of 20 W black-light illumination, the film coated with TiO_2 powder has a higher antimicrobial activity with a 3 CFU/mL reduction of *Escherichia coli* compared to uncoated film (only 1 log CFU/mL reduction after three h of illumination) (Chawengkijwanich & Hayata, 2008). Polyethylene films produced utilizing blown film extruders with and without incorporated TiO_2 showed that the blank film did not have antibacterial activity. In contrast, the polyethylene film with incorporated TiO_2 showed the following antibacterial activity with ultraviolet light for an hour, eliminating 89.3 % of *Escherichia coli*, and 95.2 % of *Staphylococcus aureus* (Xing et al., 2012). Using blown film extrusion, the low-density polyethylene/TiO_2 film was generated and tested on *Pseudomonas spp.* and *Rhodotorula mucilaginosa*, which revealed vigorous antimicrobial activity in the films. These findings show that extrusion-prepared plastic films with embedded TiO_2 NPs could be successfully used in food packaging applications (Bodaghi et al., 2013). TiO_2-coated films can reduce the microbial contamination of food products on the surface and reduce the risk of microbial growth in fresh products (Chawengkijwanich & Hayata, 2008). The addition of silver to TiO_2 can also boost the antibacterial properties of polypropylene nanocomposites. It was concluded that silver particles were filled with TiO_2 and that the composition of TiO_2 had no crystalline alteration. These nanocomposites have been found to have a high bactericidal effect since almost 98 % of *Staphylococcus* bacteria areas were eliminated after 10 min on antibacterial polypropylene relative to neat polypropylene, where only 10 % of the bacteria were killed during the same period. This composite's bactericidal effect is substantial, and such composites are a potential candidate for many applications where a bactericidal effect is needed (Ahmadi et al., 2009). Investigation of polypropylene nanocomposite antibacterial operation with silver/TiO_2 with varying filler proportions (0-1 % by weight) indicated that with a composite packed with 0.75 % of particles, the optimal bacterial behavior was seen (Dastjerdi et al., 2008).

3.2.1 Interaction of TiO_2 NPs under ultraviolet and photocatalytic activity

Due to its desirable characteristics, TiO_2 is one of the most tested oxide NPs for ultraviolet blocking and is very desirable in practical applications. TiO_2, widely used as a filler and pigment, may also usually be effective as an absorber that selectively absorbs and re-emits ultraviolet light at a less damaging wavelength, predominantly as heat. This TiO_2 behavior has been depicted in Figure 4. In order to satisfy the reduced ultraviolet percentage transmission criteria for the particular application, the polymer form, the ultraviolet absorber type, the thickness of the plastic component, and the concentration of the ultraviolet absorber need to be addressed in each application (Hrnjak-Murgic, 2015; Cheremisinoff, 1997; Frank et al., 2002).

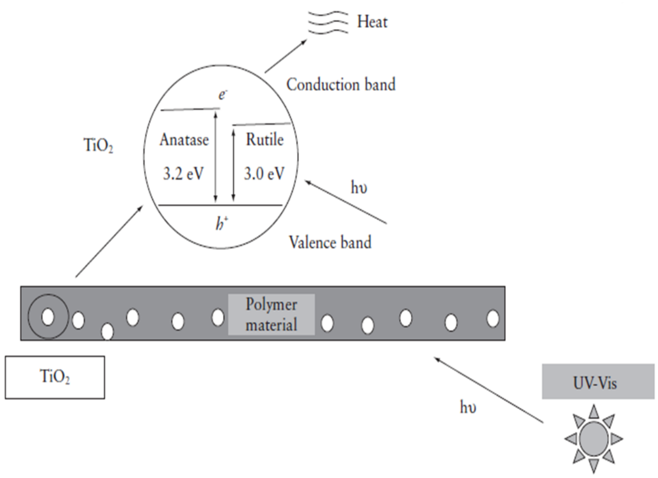

Figure 4. TiO_2 behavior under ultraviolet light. ultraviolet-visible (Hrnjak-Murgic, 2015)

Ilmenite was found in 1791 with TiO_2. In 1929, TiO_2's photoactivity was first reported when it was used in buildings as white pigments. Many TiO_2 polymorphs exist; anatase, rutile, and brookite, which were found in 1801, 1803, and 1825, are the recognized phases of TiO_2. The metastable forms of anatase and brookite can be irreversibly converted by heating to stable rutile, the naturally occurring TiO_2 state (Hanaor & Sorrell, 2011). The photodegradation of a broad range of environmental pollutants is the most promising field of TiO_2 photocatalysis; complex organic compounds and inorganic products, for example, are converted into CO_2 and innocuous inorganic anions. As a photocatalyst, TiO_2 has demonstrated tremendous promise for wastewater detoxification or remediation. During the decontamination process, TiO_2 NPs may be freely suspended in wastewater or deposited on substrates (Philippopoulos & Nikolaki, 2010; Sawunyama et al., 1997), which can, in turn, play a critical role in treating the wastewater in the food industry and other sectors, aiming at reaching sustainable food production. To provide an effective health care system, hazardous chemical, and microbial pollutants should be inhibited from developing. Consequently, the process of manufacturing and employing effective materials rendering both photocatalytic and antimicrobial features is critical. With their higher wavelength ultraviolet absorption (UV-A 320-400 nm), semiconductors like TiO_2, SnO_2, and ZnO are extremely active under ultraviolet light irradiation. There are numerous fields in which TiO_2 NPs' photocatalytic behavior has been studied, such as in photocatalytic water splitting, photocatalytic self-cleaning, wastewater purification, photo-induced super hydrophilicity, photovoltaics, photosynthesis gap, and antibacterial/antimicrobial activity (Daneshniya et al., 2021b; Fujishima & Honda, 1972; Fujishima et al., 2000; Ni et al., 2007; Hashimoto et al., 2005; Pozzo et al., 1997; Konstantinou & Albanis 2004; Carp et al., 2004; Grätzel, 2005; Umadevi et al., 2013; Yu et al., 2013). TiO_2 NPs received much attention in active food packaging, the main reason for which can be related to the remarkable antimicrobial properties of these particles. Due to their photocatalytic activity, these particles can have high oxidizing properties after exposure to ultraviolet rays and effectively destroy the microorganism's cell structure's organic compounds. Photocatalytic activity is usually an expected performance of semiconductor NPs, which has been investigated for many NPs. According to Figure 5, when a semiconductor surface is exposed to ultraviolet light, a specific wavelength is absorbed, which eventually transmits electrons from the Valance Band (VB) surface to the Conduction band (CB) (Daneshniya et al., 2021b; Jain & Vaya, 2017). These two levels are present in all semiconductors, and the energy difference between these two levels is called the band gap. After the electron is transferred between the two surfaces, the electron-hole pair remains in the valence band. These holes create a high reduction and oxidation potential for the metal (Nabika & Unoura, 2016). Figure 6 shows the mechanism of photocatalytic activity.

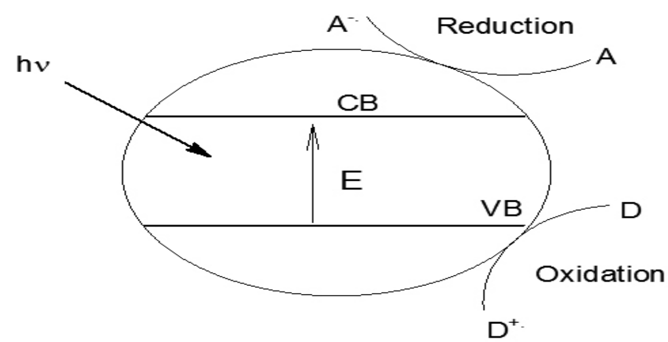

Figure 5. Mechanism of Photocatalytic Activity (Nabika & Unoura, 2016)

TiO_2 is expected to be in three forms, namely anatase, rutile, and brookite. Anatase has high photochemical activity and, under the action of ultraviolet light, can dissolve organic compounds. As it is stable only at low temperatures, brookite has no great functional importance, while rutile has some intriguing features. Rutile implies ultraviolet light absorption up to visible light wavelength proximity and transparency at visible light wavelengths. As a result, rutile-containing polymer nanocomposites can be of considerable use both in the manufacture of visually transparent ultraviolet films and in coatings for ultraviolet-sensitive materials (Maleki & Daneshniya, 2021). Rutile TiO_2 has photocatalytic activity only under ultraviolet irradiation, which usually limits its visible light use (Li et al., 2019). A successful way to minimize band-gap energy and increase the photocatalytic function of TiO_2 under visible light is the insertion of an Ag nanoparticle into TiO_2 (Lungu et al., 2014). Anatase and rutile have a band difference of 3.2 and 3.0 eV, respectively. Among these two groups, anatase is considered the most active form; as shown in Figure 6, a sharp decrease in activity is evident given the action spectrum of anatase roughly above 385nm (Fronzi et al., 2016; Kaplan et al., 2016). The greater surface area of anatase at moderate temperatures in the metastable state is often useful as reaction enhancers in photocatalysis and catalysis (Reidy et al., 2006; Dastjerdi & Montazer, 2010). Chemical reactions in anatase particles can produce highly reactive species during the photocatalytic process. An electron-hole pair is created due to the transmission of an electron from the valence to the conduction band whenever TiO_2 NPs are irradiated with photons at wavelength ~ 385 nm. The energy/band gap is defined as the energy disparity between the unfilled conduction band's low-energy electrons and the high valence band's filled energy (Dworniczek et al., 2016).

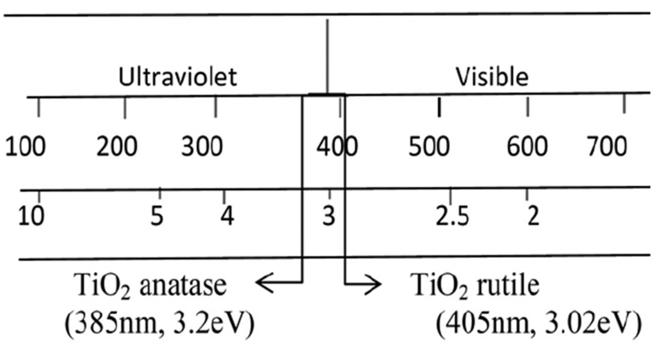

Figure 6. Ultraviolet area for TiO_2 photoactivity (Nabika & Unoura, 2016)

On the surface of TiO_2, as it is exposed to ultraviolet radiation, two genres of photochemical reactions can be observed; redox reaction excited by photons occurring in the adsorbed compounds and hydrophilic alteration by photons of TiO_2 itself. Concerning the first reaction, water and oxygen react with photogenerated holes and electrons, and then, along with other ROS comprising hyperoxide anions (O^{-2}) and hydrogen peroxide (H_2O_2), extremely reactive hydroxyl (·OH) radical groups are formed. Hence, TiO_2 can both kill bacteria and simultaneously disintegrate toxins that are produced by bacteria. This process can be divided into five distinct stages (Hou et al., 2015; Pleskova et al., 2016; Rincón & Pulgarin, 2007; Zou & Zhu, 2007; Zhang et al., 2009):

1. Absorption of photons by TiO_2, which is needed for reactions (hv ≤ EG = 3.2e).

$$(TiO_2) + hv \longrightarrow e^-_{CB} + h^+_{VB}$$

2. Oxygen ionosorption process, which modifies the degree of oxidation of oxygen.

$$(O_2)_{ads} + e^-_{CB} \longrightarrow O^{\cdot -}_2$$

3. OH functional groups are neutralized by photo holes, and ultimately, OH radicals are yielded.

$$(H2O) \rightleftharpoons H^+ + OH^-_{ads} + h^+_{VB} \longrightarrow h^+ + \cdot OH$$

4. $^-$OH radicals successively bombard the organic-based reactant, and thus oxidation occurs.

$$R + \cdot OH \longrightarrow R^\cdot + H_2O$$

5. The functional group is oxidated directly as it reacts with holes.

$$R + h^+ \longrightarrow R^{\cdot +} \longrightarrow \text{degraded output}$$

3.3 TiO_2 NPs health-threatening hazards

Nanomaterials have been used in many industries, such as the food industry, because of their unique properties. However, some of these properties, such as high chemical reactivity and good bioavailability, have increased their potential for toxicity so that a similar volume of a substance in the nano-sized state has greater toxicity potential than in the case of larger particles (Kirwan & Strawbridge, 2003; Tharanathan, 2003; Maleki & Daneshniya, 2021). Research in different regions like China, South Korea, Japan, the European Union, and the United States has shown that NPs can be toxic to humans and the environment due to various physico-chemical properties such as size, morphology, and surface properties (Han et al., 2011). The migration of NPs from food packaging to beverages or food is commonly cited as the primary concern. Research has shown that the smaller the NPs and the lower the density, the higher the likelihood of these particles being transferred to the food and causing health problems for the consumer (OECD, 2009). According to the European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC), inhalation, skin contact, and oral administration are the main ways in which humans are exposed to NPs (Borm et al., 2006). It also has been proved by several studies that ingestion, pulmonary absorption (mostly by inhalation), epidermal exposure, and injection are the four primary mechanisms of exposure to TiO_2 NPs in humans. Ingestion, inhalation, and injection of TiO_2 NPs all result in systemic disposal, according to researchers. However, when it comes to epidermal exposure, the findings are inconsistent (Shakeel et al., 2016). The NPs enter the lungs when inhaled and can enter the bloodstream. In skin contact with NPs, these substances can enter the cell in three ways, intracellular, intercellular, and follicular penetration (Zaiter et al., 2022). If the NPs are transported to the food, the NPs are digested and accumulate in the digestive tract. They are then absorbed through the intestinal epithelium and can pass to other parts. Previous research has shown that smaller NPs are usually faster than larger adsorbed particles and more easily dispersed by anionic NPs through the epithelial surface (Han et al., 2011). Cationic NPs are typically trapped due to the negative charge of mucus (Szentkuti, 1997). Hence, the increasing use of TiO_2 NPs in food packaging as well as in the formulation of food and cosmetic products has raised concerns about potential hazards to human health and the environment, some of which have been mentioned in Table 2. TiO_2 has also been used as an ingredient in the food industry to improve the white color of some items, such as desserts and dairy products (Jovanović, 2015). Besides the migration of the packaging to the food, other issues mentioned in Table 3 are also related to the TiO_2 NPs utilized as additives. Normalized to the titanium per serving, chewing gums, sweets, powdered sugar toppings, and items with white icing possess the highest titanium content, according to a study that measured and analyzed the quantity of titanium in typical food products (Musial et al., 2020). In the United States, the difference in TiO_2 consumption between men and women was minimal. However, there was a considerable variation in intake between children and adults. Children may ingest up to four times the amount of TiO_2 per kilogram of body weight (kgbw) in comparison to an adult. This may be explained simply by their consumer preferences, which are mostly oriented on the flavor of sweet snacks, many of which include E171. As a result, eating choices have a role in TiO_2 exposure (Weir et al., 2012; Dudefoi et al., 2018). Since daily exposure to E171 can reach many hundreds of milligrams, with a significant portion (approximately 36 %) appearing in the nano range, there are suspicions that long-term exposure to this compound could have detrimental effects on the human body (Jovanović et al., 2018). The European Food Safety Authority (EFSA) published a 're-evaluation of TiO_2 (E171) as a food additive' in response to this growing public health concern, based on documentation on TiO_2 usage levels and safety provided by various international associations, councils, and committees. The EFSA panel determined that orally given micro-and nano-TiO_2 had limited absorption and bioavailability. Except for a small quantity (less than 0.1 %) that is absorbed by gut-associated lymphoid tissue and transported to various organs, the majority of the TiO_2 eaten dosage is excreted unaltered in the feces. The panel concluded that in vivo, micro-and nano-sized particles are unlikely to pose a genotoxic risk (Geiss et al., 2020; EFSA, 2016). A year later, research found that orally delivered food-grade TiO_2 nanoscale particles impair immunological homeostasis and cause cancer in rats. The French ANSES (Agency for Food, Environmental, and Occupational Health) released an opinion on TiO_2 NPs based on this paper, emphasizing the importance of completing rigorous research into the potential hazards associated with the use of E171. Because of the potential detrimental impacts on individuals and a lack of scientific data to prove its safety, France is the first country to prohibit the use of the E171 food additive. The limitations went into effect in 2020 (Bettini et al., 2017; ANSES, 2017; Arrêté, 2020).

Table 2. Issues associated with the utilization of the TiO_2 NPs as food additives and constitute a packaging

Area of use	Related-challenge	Reference
Specific to TiO_2 NPs in the packaging	Migration of NPs	One of the primary concerns regarding TiO_2 NPs in food packaging is their potential to migrate from the packaging materials into the food products they come into contact with. The small size of NPs can facilitate their movement through packaging barriers, especially in cases of fatty or oily foods or foods with a high water content. Studies have demonstrated that TiO_2 NPs can indeed migrate into food, leading to possible human exposure through ingestion (Wang et al., 2016).
Common between the TiO_2 NPs additive and its utilization in food packaging	Toxicity and Health Risks	Upon ingestion, TiO_2 NPs can interact with cells and tissues in the human body, leading to concerns about their potential toxicity. While the exact mechanisms of nanoparticle toxicity are still being studied, research has shown that TiO_2NPs can induce oxidative stress, inflammation, and cellular damage. These adverse effects could potentially impact various organs and systems in the body (Sharma et al., 2019).
	Gastrointestinal Effects	Studies on animals have shown that TiO_2 NPs can accumulate in the gastrointestinal tract after ingestion. This accumulation has raised concerns about potential gastrointestinal effects, such as alterations in gut microbiota and intestinal barrier function. Moreover, the possibility of TiO_2 NPs reaching the systemic circulation through the gut lining has raised questions about their impact on organs beyond the gastrointestinal tract (Gao et al., 2021).
	Immunotoxicity	Research has indicated that TiO_2 NPs can modulate the immune response, leading to immunotoxic effects. These NPs can interact with immune cells and influence their activity, potentially impairing immune system function. Prolonged exposure to TiO_2 NPs may increase the risk of immune-related disorders and infections (Bettini et al., 2017).
	Genotoxicity and Carcinogenicity	Concerns have been raised regarding the genotoxicity and carcinogenicity of TiO_2 NPs. Some studies have suggested that TiO_2 NPs can cause DNA damage and initiate preneoplastic lesions, leading to the promotion of aberrant cell growth and tumor development. However, further research is needed to establish a definitive link between TiO_2 nanoparticle exposure and cancer (Bettini et al., 2017).
	Environmental Impact	In addition to human health concerns, the environmental impact of TiO_2 NPs is also an area of interest. During the manufacturing, use, and disposal of food packaging materials containing TiO_2 NPs, there is a possibility of nanoparticle release into the environment. These NPs could accumulate in soil and water bodies, potentially affecting aquatic organisms and soil microorganisms (Wojcieszeket al., 2020).

Finally, in a report No. E42022-0011, The European Commission has declared a prohibition on using E171 as a food additive in the EU, beginning on February 7, 2022, with a six-month phase-out period until August 7, 2022, after which a full ban would apply. Annex II and III to Regulation (EC) No 1333/2008 on food additives will be changed as a result of the publishing of Commission Regulation (EU) 2022/63 in the EU's Official Journal (OJ) on January 18, 2022. The Regulation also contains a determination to assess the need to keep E171 on the EU list of food additives for sole use as a color in medical goods or to remove it. The Commission previously issued Commission Implementing Regulation (EU) 2021/2090 in the OJ of the European Union on November 30, 2021, refusing the licensing of TiO_2 (E171) as a feed supplement for all animal species (EU, 2022). On the whole, the ultimate conclusions of the safety-related threats of TiO_2 NPs can be seen in Table 3. Various studies have already demonstrated that E171 has a genotoxic potential. In a study wherein an in vitro model with human Caco-2 and HCT116 cells was used to research the potentially toxic effects of E171, which contains fractions of micro-and NPs (MPs and NPs, respectively), it was discovered that E171-defined as a mixture of 39 % TiO_2 NPs and 61 % MPs-had the highest capability to induce ROS generation in a cell-free environment, followed by NPs and MPs. However, only MPs demonstrated the ability to generate ROS in a cellular environment, which may result in a pro-inflammatory response. Nevertheless, the NPs did not promote the development of ROS, which was accounted for by the fact that, after internalization, they interact with cellular components that prevent the formation of ROS. This study also showed that all E171, NPs, and MPs caused single-strand DNA breakage in Caco-2 cells. The study authors hypothesized that compared to NPs or MPs alone, E171 was more hazardous to Caco-2 cells (Proquin et al., 2017). In another study, food-grade particle size distribution was used in a repeated 3-week oral administration of E171 to mice (E171 suspension dripping into the mouth of mice, 5 mg/kgbw for three days per week); results were related to both toxic outcomes, such as an inflammatory response and increased superoxide production in the digestive tract, and the deposition of TiO_2 in the internal organs, particularly in the liver and large intestine, where a three-fold increase in TiO_2 NPs was noted (Talamini et al., 2019).

Table 3. Safety-related TiO_2 NPs conclusions based on previous studies (Musial et al., 2020)

Type of Usage/Application of TiO_2 NPs	Conclusions	
Food additive E171	The absorption of TiO_2 from the digestive tract	Generally considered extremely low
	Safety of long-term dietary exposure to TiO_2 NPs	Still uncertain: potential toxic effects may concern the absorption, distribution, and accumulation of TiO_2 NPs
	Potential risks caused by TiO_2 NPs	Genotoxicity, inflammatory response, carcinogenesis
	Lack of established, acceptable daily intake limits.	

Authors' Contributions

Mohammad Hossein Maleki: data collection. Milad Daneshniya: study design; writing manuscript. Farzaneh Abdolmaleki: supervision of study; result validation.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Ethical considerations

There were no ethical considerations to be considered in this research.

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