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Lemon juice - mediated synthesis of titanium dioxide nanoparticles with antioxidant and anti-inflammatory activity

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ABSTRACT

Plant compounds such as flavonoids, terpenoids, polyphenols, enzymes, and alkaloids are used as reducing agents in eco-friendly titanium dioxide nanoparticle manufacturing. In the current investigation, titanium oxide was converted into titanium dioxide nanoparticles with the application of a lemon extract. Amazingly, the process was also cheap, eco-friendly, and easy to implement. Seeing the white fluid change to a pale yellowish white allowed us to visually confirm that the nanoparticles had been successfully created. Transmission electron microscopy (TEM) and ultraviolet-visible spectroscopy were employed for further characterization. Nanoparticles of titanium dioxide were measured to be between 30 and 45 nm in size. In the DPPH assay, a titanium dioxide nanoparticle concentration of 50 L was shown to be optimal for antioxidant activity. The results of the bovine serum albumin denaturation experiment validated the green produced nanoparticles' dose-dependent anti-inflammatory effect. Consequently, the green synthetic titanium dioxide nanoparticles have great potential as an anti-inflammatory and antioxidant in future medicinal applications.

Keywords: green synthesis, titanium dioxide nanoparticles, antioxidants, anti-inflammatory agents

INTRODUCTION

In both science and technology, nanotechnology is a burgeoning discipline used to create novel materials on the nanoscale [1]. Nanotechnology has led to a dramatic increase in the use of nanoparticles in numerous consumer goods, including electronics, skincare products, antimicrobials, and drug delivery systems [2,3]. Titanium is the tenth most common element in the Earth's crust and is therefore easily accessible. Titanium is often found in the crust at a quantity of 4,400 mg/kg. Titanium does not occur naturally as a metal because of its strong affinities for oxygen and other elements. Titanium can exist in any of its three oxidation states; the most frequent is +4, although the other two are also possible. Most often, metal Ti, titanium dioxide, and titanium chloride are employed as compounds in

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manufacturing. Titanium dioxide (TiO2) has the CAS number of 13463-67-7 and is a naturally occurring titanium oxide also known as titanium, titanium oxide (IV), titanium anhydride, or white titanium. The molecular weight of TiO2 is 79.9 g/mol, and its melting point is 1843 g/mol, boiling point is 2972 g/mol, and its relative density at 25 g/mol is 4.26 g/cm^3. It is non-flammable and odorless. TiO2 is commonly used in white pigments since it is a soluble pigment. TiO2 occurs in two crystal forms, anatase and rutile, with anatase being the more reactive of the two [4,5]. Due to their high stability, anticorrosion, and photocatalytic capabilities [6,7], TiO2 NPs are manufactured in large quantities and put to extensive usage. TiO2 has been allowed by the FDA for use as a food coloring additive, albeit the agency has placed a limit on its use of no more than 1% of body weight (BW). TiO2 has been designated as a "food contact substance" by the Food and Drug Administration [7], allowing it to be used in food packaging.

Solution combustion [8,9], sol-gel [9], hydrothermal [10,11], solvothermal [12], co-discharge [13], chemical vapor storage [14], and green synthesis are just a few of the ways that titanium dioxide nanoparticles can be synthesized. Green synthesis refers to the process of making titanium dioxide nanoparticles without the use of toxic or hazardous chemicals. This process involves the use of plant extracts (such as those found in leaves, flowers, seeds, and fungi), bacteria, fungi, and enzymes. Green synthesis is preferable to physical or chemical processes because it may be used on a larger scale, costs less money, and is easier to utilize. This technique does not necessitate the use of harmful ingredients, high pressures, costly machinery, or extreme temperatures [15].

The current investigation utilized a reducing and stabilizing reagent, lemon juice extract, to create titanium dioxide nanoparticles. *Rutaceae* family member Citrus limon (L.) Burm is indigenous to Asia. Commercial cultivation takes place in warm temperate, tropical, and semitropical climates, especially the Mediterranean. Long grown in Southeast Asia and China, C. limon was introduced to the Mediterranean during the Roman era and the New World in the sixteenth century [16,17]. Lemon trees can grow to be 6 meters tall and have incredibly sturdy spines. Fruit has several applications outside its primary role as a food and beverage ingredient. They are commonly used to keep fresh fruits from becoming brown by protecting them from oxidation. Lemons are regarded as a nutritious food choice for a variety of reasons, including the high levels of vitamin C and citric acid they contain, as well as the fact that they contain a number of other useful components. Lemons have a diverse range of nutrients, including phenolic compounds, vitamins, minerals, dietary fibers, essential oils, organic acids, and carotenoids [18,19]. This makes them an intriguing fruit to study in terms of nutrition.

The use of an extract made from lemon juice is effective in capping and stabilizing nanoparticles of titanium dioxide. Transmission electron microscopy (TEM) was employed, together with a UV-Visible spectrophotometer, in order to investigate the nanoparticles. The DPPH assay and the Bovine Serum Albumin Denaturation Assay were used, respectively, to determine whether or not the nanoparticles possessed antioxidant or anti-inflammatory capabilities.

MATERIALS AND METHODS

Extraction of lemon juice extract

The local grocer got a fresh supply of lemons from a local supplier, Poonamallee. The fresh lemons were halved, filtered, and used to create an extract with a volume of 50 milliliters. Titanium dioxide nanoparticles were synthesized with the help of freshly collected lemon juice extract, which served as a reducing and stabilizing agent.

Green synthesis of Lemon juice mediated titanium dioxide nanoparticles

Dissolving 0.395g of titanium oxide in 50 mL of purified water. The next step was to add 50 mL of filtered lemon juice extract. The reaction mixture was then placed on a magnetic stirrer and continued spinning at 600 rpm for 48 hours. The formation of titanium dioxide nanoparticles was monitored by UV-Visible spectroscopy in the meantime. After centrifuging at 8000 rpm for 10 minutes, the supernatant was collected and the particle was discarded. The pellet was stored in an airtight Eppendorff tube for further characterization and biological uses, while the supernatant was discarded.

Characterization

Using a double beam spectrophotometer (ESICO), the eco-friendly titanium dioxide nanoparticles were characterized at set intervals of time. Titanium dioxide nanoparticle morphology, including size and shape, was examined using transmission electron microscopy (TEM).

Antioxidant activity:

DPPH METHOD

The DPPH test was utilized in order to investigate the effect that lemon juice had on the antioxidant capacity of nanoparticles composed of titanium dioxide. Titanium dioxide nanoparticles (10 mL, 20 mL, 30 mL, 40 mL, and 50 mL) were mediated by lemon juice extract, and they were combined with 450 mL of 50 mM Tris HCl buffer (pH 7.4) and then allowed to incubate for 30 minutes. After that, we measured the degree to which DPPH free radicals were neutralized by utilizing the absorbance at 517 nm. The inactive substance butylated hydroxy toluene was administered as a placebo. In the study, ascorbic acid acted as a placebo for participants. To determine what proportion of inhibition there was, we utilized the following equation:

% inhibition = [(Absorbance of control – Absorbance of test sample)/Absorbance of control] × 100

Anti-inflammatory activity:

ALBUMIN DENATURATION ASSAY:

Researchers investigated the potential for biosynthesized titanium dioxide nanoparticles to inhibit inflammation by using an albumin denaturation assay. An aqueous solution containing 1% bovine serum albumin was combined with 0.05 milliliters of titanium dioxide nanoparticles having different degrees of fixation. A minute quantity of 1N hydrochloric acid was added in order to bring the pH down to 6.3. These samples were heated to 55°C in a water bath for thirty minutes after having been incubated at room temperature for twenty minutes. After the samples had been allowed to cool, spectrophotometry was utilized to determine the absorbance at 660 nm. The group serving as the control was given diclofenac sodium. In the research, dimethyl sulfoxide, also known as DMSO, served as the benchmark. The following formula was utilized in the process of determining the level of protein denaturation:

% inhibition = [(Absorbance of control – Absorbance of sample)/Absorbance of control] × 100

RESULT AND DISCUSSION

Visual observation

Eye inspection is the method that has the best chance of detecting the creation of nanoparticles in the very first instance [20]. The hue of the reaction mixture changed from white to a tint that could be described as light yellowish white after the addition of lemon juice extract. The solution that contained titanium oxide as a precursor had been white. After 24 hours, the color of the solution was examined; nevertheless, after 48 hours, the brilliant golden white remained unaltered. The UV-visible spectra of the green titanium dioxide nanoparticles that were synthesized are displayed in Figure 1.

A double beam spectrophotometer was utilized in order to investigate and analyze the green synthetic titanium dioxide nanoparticles' optical properties. At predetermined intervals, readings across the wavelength range of the UV-Visible spectrum, from 250 to 650 nm, were collected. After 24 hours, the peak Surface Plasmon resonance wavelength of the eco-friendly Tio2 NPs was found to be 360 nm. This was determined using spectroscopy. After swirling for a total of 48 hours using a magnetic stirrer, the largest 375 nm absorption peak was found [21]. Images taken by a transmission electron microscope (TEM) of titanium dioxide nanoparticles that have been changed by lemon extract are presented in (Figure 2).

Nanoparticles of titanium dioxide were created by reacting lemon juice with titanium dioxide, and a transmission electron microscope was used to investigate the particles' sizes and shapes. Figure 2 displays a TEM picture that was acquired at a mag-

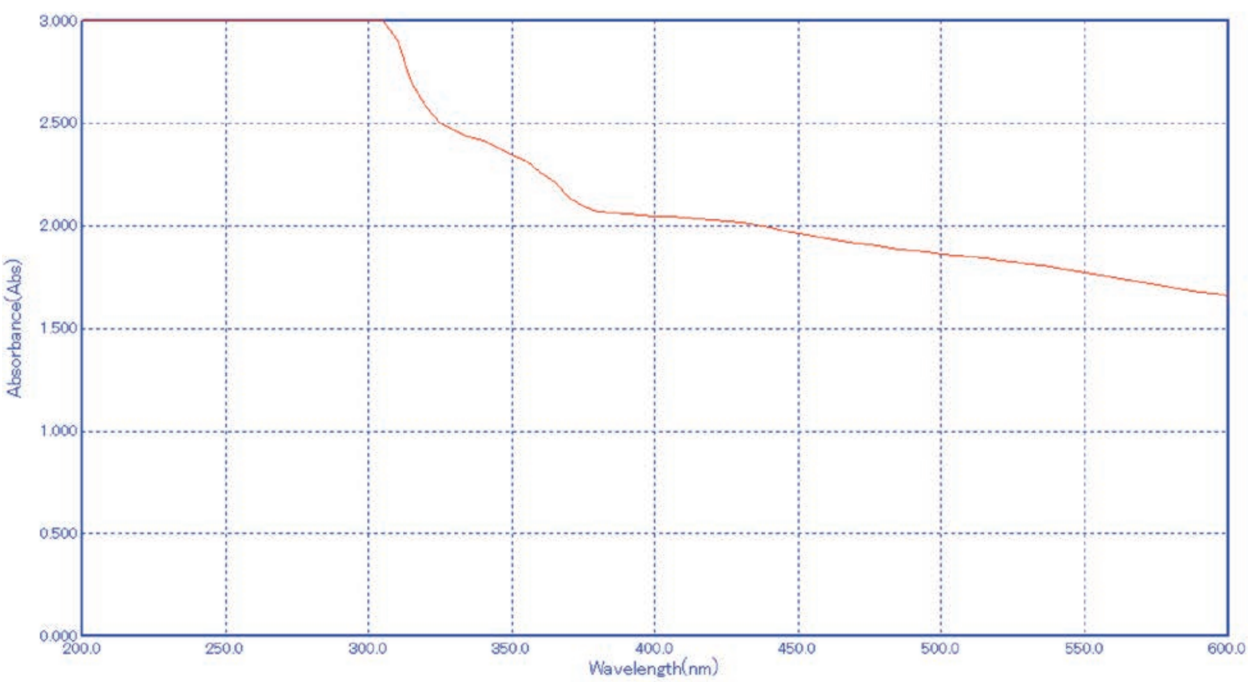

FIGURE 1. UV-Visible spectra of the green synthesized titanium di oxide nanoparticles

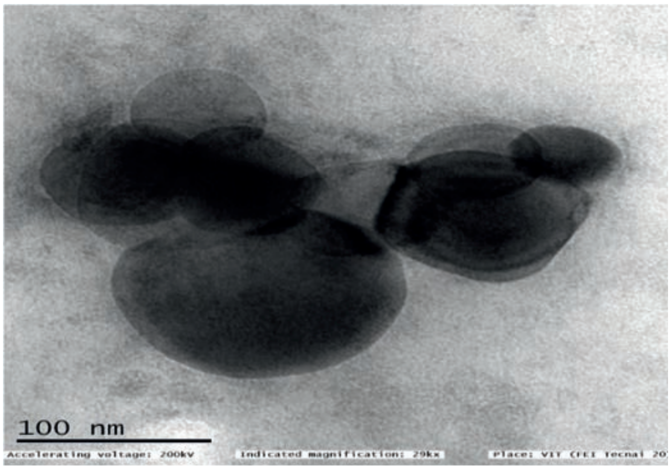

FIGURE 2. TEM image of lemon extract mediated titanium di oxide nanoparticles

nification of 29Kx and an acceleration voltage of 200Kv. According to the image obtained from the TEM, the nanoparticles of titanium dioxide that were formed had a mean particle size of approximately 30-45 nm and appear to have a spherical shape. It has been demonstrated that nanoparticles of titanium dioxide with a spherical shape and a more uniform size distribution have an enhanced surface area as well as an increased number of active sites. Titanium dioxide nanoparticles that had a smaller negative influence on the environment were initially created by Thakur and colleagues. The amount of *Azadirachta indica* found in the environment decreased before reaching a point where it was stable. Using transmission electron microscopy (TEM), the morphological characteristics were analyzed, and it was found that the shape was spherical, and the size ranged from 15 to 50 nm [22]. Previous research [23] had revealed that the size of the titanium dioxide nanoparticles that were mediated by the *Trigonella foenum graecum* extract was 25 nm (Figure 3). Lemon juice has the ability to activate antioxidant capabilities that are already present in titanium dioxide nanoparticles.

By consuming foods rich in antioxidants, you can reduce the amount of oxidative acidity in your diet [24,25]. Antioxidants work by destroying the free radicals that are created during the oxidation process. As a result of metabolism and other activities, oxygen-reactive species, also known as free radicals, are created. In addition, the natural antioxidant capacity of the body adds to the oxidative stress that can occur [26]. Oxidative stress has been shown to play a role in a variety of diseases, including cancer, cardiovascular illness, neurological disease, and even the aging process [27]. The ability of the biosynthesized titanium dioxide nanoparticles to remove the coloring from DPPH free radicals provided evidence that the titanium dioxide nanoparticles possessed antioxidant characteristics. In a dose-dependent manner, DPPH was scavenged at concentrations ranging from 10 to 50 liters per liter, and the results were plotted in (Figure 3). The responses ranged from 72.61-92.06%. The free radical scavenging activity of phytosynthesized TiO2 at 50 liters was practically comparable to that of conventional ascorbic acid, reaching up to 92%. This was determined by comparing the concentrations of both compounds. When compared to the activity indicated by the standard, which was 70.2%, TiO2 NPs were found to have 64% antioxidant activity at the lowest concentration tested, which was 10 L. According to the results of the DPPH experiment, the most recent generation of titanium dioxide nanoparticles from *Coleus aromaticus* extract by Anupong et al. 2023 [28] demonstrated a peak free radical scavenging efficacy of 89% at 100 g/mL^{-1}. Titanium dioxide nanoparticles were created by Akinola et al. in the year 2020 utilizing extract from *Cola nitida.* The DPPH scavenging rate of these nanoparticles was measured to be between 51.19 and 60.08% [29].

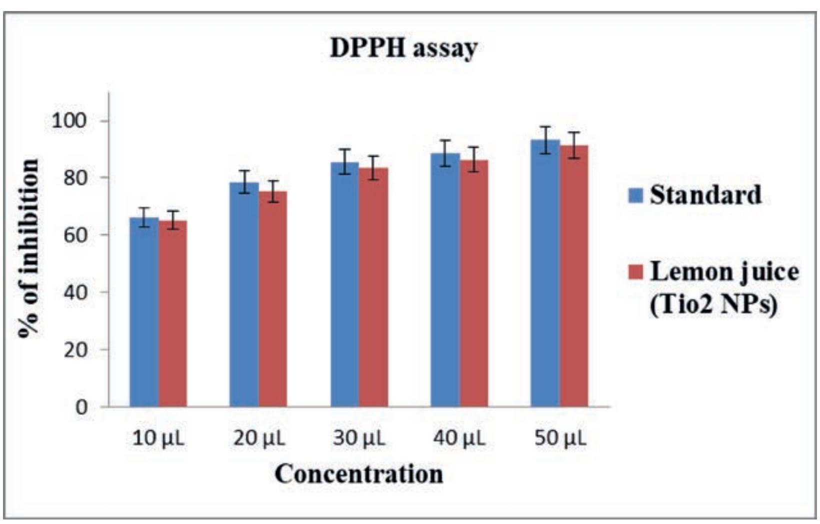

FIGURE 3. Antioxidant activity of lemon juice mediated titanium dioxide nanoparticles

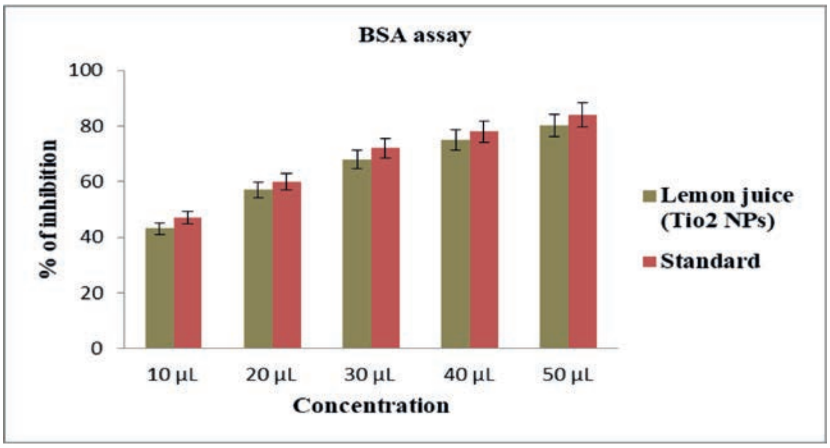

FIGURE 4. Anti-inflammatory activity of Green synthesized titanium dioxide nanoparticles

In a different piece of research, TiO2 nanoparticles were manufactured with the use of an aqueous extract of *P. guajava* leaf. According to the findings, the synthesized TiO2 nanoparticles were far more effective at quelling the effects of free radicals than the aqueous leaf extract was. It was established that the DPPH activity of the nanoparticles grew dose-dependently, and that they were capable of attaining a maximal DPPH scavenging activity of over 85%. Therefore, the custom-tailored TiO2 nanoparticles hold potential as a new type of antioxidant. The development of the Internet has resulted in the emergence of cutting-edge technologies that have the potential to bring about significant shifts in the way that we live our lives. In this particular investigation, lemon extract played the role of a mediator, elevating the level of antioxidant activity exhibited by TiO2 nanoparticles. It's possible that the nanoparticles' reactive surface sites are to blame for this effect; these sites can react with free radicals [30].

Protein denaturation is the traditional starting point for the investigation of inflammation. After an injury to a living tissue, inflammation is believed to emerge as an effect of the results. This illness is characterized by a number of symptoms, including pain, inflammation, redness, heat, and loss of function. It does this by destroying the hydrogen bonds, sulfur bonds, and electrostatic charges that are present in the protein [31,32]. Denaturation, also known as the loss of protein form and function, is caused by the activation of a large number of enzymes, as well as the release of mediators, cell migration, cell death, and tissue repair. Substances that can block these modifications and minimize protein denaturation as a result of heat or heat have the potential to have applications in the field of therapeutics [33].

The bovine serum albumin denaturation assay was utilized in order to determine whether or not bovine titanium dioxide nanoparticles (TiO2 NPs) had an anti-inflammatory effect. Diclofenac sodium, a common anti-inflammatory medicine, was tested for its anti-inflammatory effects at five different doses ranging from 10 to 50 liters per container. Finding out which proteins can be held in place by nanoparticles of titanium dioxide is the ultimate objective of this investigation. The percentage of patients who experienced an anti-inflammatory effect ranged from 42.6 percent to 78.1 percent. It was discovered that the anti-inflammatory effects of TiO2 NPs were at their highest level at a concentration of 50 L, reaching 78.02 percent. It has been established that sustainably manufactured TiO2 nanoparticles have excellent anti-inflammatory properties that are concentration dependent. The effectiveness of the medicine diclofenac sodium, which is widely prescribed, ranged anywhere from 45.03 to 79.80 percent. This reveals that the effect exerted by TiO2 NPs is orders of magnitude more than that of drugs which exist naturally. Recent research conducted by Chahardoli et al. 2022 looked at the effects of quercetin-coated titanium dioxide nanoparticles on the denatured state of bovine serum albumin as well as the stability of membranes. The findings showed remarkable membrane stabilization action and anti-inflammatory potential, comparable to that of a reference medicine [34].

Because of the lowering and stabilizing effects that caffeic acid (CA) possesses, it was utilized in a different study as a means of producing titanium dioxide nanoparticles (TiO2NPs). In testing of the biocompatibility and biological activity of the produced CA-TiO2NPs, a good activity for membrane stabilization was found, and there were no hemolytic effects seen. Because of these properties, CA-TiO2NPs might be able to reduce inflammation in the body. The fact that CA-TiO2NPs were just as efficient as the gold standard in preventing the denaturation of proteins demonstrates that they contain properties that are anti-inflammatory. The level of inflammation can be brought under control by lowering the quantity of protein denaturation that occurs within cells and tissues [35]. In a more recent investigation, anti-inflammatory effects comparable to those of diclofenac sodium were observed, which is consistent with the findings of the current analysis.

CONCLUSION

In general, the utilization of lemon extract both as a reducing and capping agent allows the production of titanium dioxide nanoparticles a straightforward, risk-free, and straightforward one-step process. The fact that the bioprocess does not require the use of any chemical reagents or surfactants, two typical types of pollutants, is one of the many benefits of the bioprocess. Using transmission electron microscopy (TEM), the researchers were able to establish that the nanoparticles were spherical in shape and ranged in size from 30 to 45 nanometers. Nanoparticles that have been artificially produced can function as an antioxidant in a manner analogous to that of ascorbic acid. It has been demonstrated that nanoparticles of titanium dioxide possess an anti-inflammatory effect that is significant and dose-dependent, very similar to that of the over-the-counter medication diclofenac sodium. This shows that nanoparticles derived from plants have the potential to be useful therapeutic agents in the treatment of diseases caused by free radicals.

The anti-inflammatory properties of these nanoparticles are dose-dependent, which makes them a potentially useful choice for developing new therapeutic methods. In addition to this, as an alternative to more traditional methods of synthesis, their plant-mediated synthesis is a more environmentally friendly and risk-free option. Titanium dioxide nanoparticles were discovered to be effective at scavenging free radicals, which suggests that they may have therapeutic utility for treating diseases that are caused by free radicals. It is necessary to conduct additional research on their anti-inflammatory activities, as well as their safety and effectiveness in clinical settings, in order to gain a deeper comprehension of the processes that are at work.

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