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Nurhidayatullaili Muhd Jukapli, Samira Bagheri

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Recent developments on Titania Nanoparticle as Photocatalytic Cancer Cells Treatment

Nurhidayatullaili Muhd Jukapli and Samira Bagheri
Nanotechnology and Catalysis Research Center (NANOCAT), Level 3, Block A,
Institute of Postgraduate Studies (IPS), University Malaya
50603 Kuala Lumpur, Malaysia
Corresponding author: samira_bagheri@um.edu.my

Abstract:
This review provides a background, fundamental and advanced application of titania nanoparticles (TiO₂) on the disinfection and killing of cancer cell through photocatalytic chemistry. It starts with the characteristic properties focused on the surface, light sensitivity, crystallinity and toxicology of TiO₂ as a photocatalyst. Consequently, outline and design of photocatalytic reactor has been figured out based on the target organisms, including bacteria, viruses, fungi and cancer cells. Despite a large number of studies undertaken, limited selectivity and efficacy of TiO₂ photocatalyst are still widely accepted problems. An ideal TiO₂ photocatalyst should have the combined properties of highly stable reactive oxygen species yield and a greater degree of selectivity towards cancerous cell without damaging the healthy tissues. Hybridization of TiO₂ with metal, metal oxide and carbon nano materials significantly improved both of stability and selectivity of TiO₂, whilst maintaining its high Photodynamic reactivity.

Keywords: Hypothermia; Hybrid; Cell killing; Nanomaterials; Cancer therapy
1.0 Introduction: Nanotechnology in biomedical applications

With the development of nanotechnology, nanoparticles are playing a significant role in medical applications (Table 1). Application of various types of nanoparticles, including micelles, dendrimers, nano shells, liposomes, polymer-drug conjugates, hydroxyl apatite, calcium phosphate, metallic, porous ceramic and nano polymer with size in the range of 10 to 500 nm allow overcoming some traditional therapeutic method limitation in cell killing treatments (Hleb et al. 2016). In general, it is assumed that the ideal particle size for the purpose of cell killing treatment applications that ensures vascular permeability and maximizes the accumulation in cell cancer is 100 to 150 nm. Nanoparticles greater than 200 nm is isolated in the liver, spleen and kidneys, whereas those smaller than 100 nm might leave the blood vessels through fenestration (Hu & Liu 2015; Berberidou et al 2016).

With concern to cancer therapy, nanoparticles, including gold, 1-5 eV semiconductor quantum dots, including CdSe, CdS and ZnS, composed of lipids or polymers, platinum and liposomes have gained great attention. Compared with organic nanoparticles, including liposomes or Chitosan, metal nanoparticles have the advantages as a respect to their Photodynamic characteristics, therapeutic effect and do not need encapsulation of therapeutic agents (Chinen et al. 2015; Aioub & El-Sayed 2016). Among various metal nanoparticles, TiO$_2$ has great generation property of reactive oxygen species when exposed to ultraviolet light based on particle sizes and morphology.

Recently, photo-therapy has been applied to several treatment approaches of different cancers and other diseases. This application contains the utilization of a photosensitizer, either by systemic or topical application and successive initiation of its exposure to light for production of reactive oxygen species (Figure 1). This consequently kills the cancer cells via the mechanism of apoptosis or necrosis (Raliya et al. 2016). This concept is much more beneficial as compared to conventional cancer treatment methods. The photo therapy concept is a low toxicity to normal tissue/cells in the darks and activation by light alone leads to minimize damage to these cells (Gutwein et al 2016). The combined effect of light makes the photo therapy concept as a selector to be used against cancerous or diseased tissues.
Figure 1: Photoactivation of targeted nanoparticles in cell nuclei (Yuan et al 2013)

Table 1: Application of nanotechnology for cancer treatment

<table>
<thead>
<tr>
<th>Treatment/methods</th>
<th>Advantages</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanoparticles drug delivery system</td>
<td>Provide intracellular release of the drug in order to obtain the higher intracellular concentration Minimum drug leakage Successfully penetrate inside cancer cells via endocytosis mechanism.</td>
<td>Pridgen et al. 2015</td>
</tr>
<tr>
<td>Surgery</td>
<td>Overcome biological barrier (e.g. blood barrier)</td>
<td>Liu et al 2016</td>
</tr>
<tr>
<td>Photodynamic therapy</td>
<td>Excellent intraoperative adjuvant therapy Synergistic combination of advanced physical properties Promising targeting abilities of biomolecules Multiple function of drugs and imaging payloads in one system</td>
<td>Chatterjee &amp; Zhang 2016</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>• Unique recognition capability of molecules to achieve active transport • Specific elimination</td>
<td>Petri et al. 2016</td>
</tr>
</tbody>
</table>

2.0 TiO$_2$ nano photo catalyst

The photo catalysis technique of TiO$_2$ is an emerging treatment for a variety of cancers due to its high therapeutic efficacy and less side effect for healthy tissues. TiO$_2$ has two
crystalline forms which are anatase and rutile (Liu et al 2016; Julkapli et al 2015). Anatase with a band gap of 3.2 eV has been considered as the most active form with the action spectrum. This crystalline form demonstrates a drastic decrease in the activity above about 385 nm (Amir et al 2016). Once the energy of the absorbed light is greater than TiO₂ band gap, electrons in the valence band are transferred to the conduction band, creating electron-hole pairs (Amir et al 2015). Such photo generated hole has strong oxidation and can cause various chemical reactions, including photo reduction, photo catalyst and photo organic synthesis (Melvin et al 2016).

2.1 TiO₂ nano photocatalyst: Photocatalytic properties

Once the TiO₂ illuminated by UV light with wavelength of less than 385 nm, photo-induced electron and hole is subsequently created. These photo-induced electron and holes could further react with hydroxyl ions or H₂O to form powerful oxidative radicals, which capable of destroying the structure and components of cancer cells (Chen & Lin 2016). The cell killing properties of TiO₂ photo catalyst have been reported (Table 2). The reactive oxygen species may disrupt or damage various cells or viral structure (Figure 2). The photocatalytic chemistry studies revealed that the hydroxyl radical created by holes transfer does not diffuse from the surface of TiO₂ (Blanchet et al 2004). For the cell or virus which are located on TiO₂ surface, there could exist direct electron/hole transfer to the organism or one of its components. In nano sized, TiO₂ may penetrate into the cell and this process may take place in the interior (Lopez et al 2011). Orientation and distance are highly influenced by microbes which have similar size with aggregates of TiO₂ nanoparticles.

Table 2: Series of TiO₂ nanoparticles with killing cancer cell properties

<table>
<thead>
<tr>
<th>Types of TiO₂</th>
<th>Killing cell properties</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiO₂-Pt</td>
<td>The existence of TiO₂-Pt catalyst caused by illumination with near UV light for 1-2 hours can result in death of microbial cells in water</td>
<td>Lu et al 2003</td>
</tr>
</tbody>
</table>
| TiO₂-acetylcellulose membrane | E-coli suspension flowing through was completely killed  
Create new avenues for sterilization, disinfecting drinking water and eliminating bio aerosols from indoor environments | Braydich-Stolle et al 2009 |
| TiO₂                   | Killing of polyunsaturated phospholipids as integral component of the bacterial cell membrane | Onuma et al 2009   |
| TiO₂ nanoparticle      | Lipid peroxidation reaction                                                             | Hu et al 2007      |
| TiO₂                   | The surviving fraction of S. mutans cells up to 58 % under white fluorescent light  
The analysis based on second order kinetics with     | Xu et al 2012      |
Ultra-fine TiO$_2$ can cause plasmid DNA breakage at the concentration range of 0.05 to 0.15 mg/mL after incubation for 8 hours at 37°C (Yoo et al. 2012).

**Figure 2:** Photodynamic antitumor treatment that is based on the photosensitizers inhibiting cancer cells by yielding reactive oxygen species after irradiation of light with specific wavelengths (Hou et al. 2015).

TiO$_2$ nanoparticles have been applied in the phototherapy of malignant cell and have potential for the photo degradation of cell cancer treatment because of its high stability and irradiation-induced photo toxicity (Zhang & Sun 2004). Indeed, the series of cellular cells, including carbohydrates. Lipids, proteins and nucleic acids can be damaged and afterward cause cell death under irradiated TiO$_2$. TiO$_2$ also demonstrated a noticeable activity in the adsorption of basic L-amino acids, including L-lysine and L-arginine in an aqueous solution (Seo et al. 2007). TiO$_2$ is capable of absorbing and inactivating various bacteriocin from culture supernatant. TiO$_2$ photo degradation of DNA and RNA bases has been proved by the formation of nitrite, carbon dioxide and ammonia. Synthetic supercoiled plasmid DNA has been utilized as free radical at TiO$_2$ surface (Kalbacova et al. 2008). It has been figured out that cellular RNA seems to be more susceptible to oxidative damage caused by irradiated TiO$_2$ as compared to DNA due to the compartmentalization of DNA within the cell nucleus (Cai et al. 1992) (Figure 3).
2.2 TiO$_2$ nano photocatalyst: Structural properties

The metal core-TiO$_2$ outer shell semiconductor is considered as a superb catalyst for its unique photocatalytic properties including photo induced band gap excitation, charge separation, and charge equilibrium at the Fermi level as well as core-shell structure (Yang et al. 2016). TiO$_2$ has higher surface-to-volume ratio as compared to other nanoparticles with single crystalline features. Greater surface-to-volume ratio and crystallinity could enhance the photocatalytic efficiency by augmenting the number of catalytic sites and delocalization of carriers to lessen electron-hole pair recombination (Wang et al. 2013; Lu et al. 2013). The mechanical property of TiO$_2$ is conferred by a layer of oxide present on its surface. The high refractive index of TiO$_2$ has advantages in sensor properties based on the optical detection method (Hu et al. 2014). Besides, the remarkable characteristics of TiO$_2$ have demonstrated its potential application in air/water purification and energy storage offering enhanced prospects for commercial and industrial purposes.

2.3 TiO$_2$ nano photocatalyst: Surface properties

Surface properties of TiO$_2$ have shown some effect on its cell-particle interaction, including cell uptake, activity inside the cell, membrane binding and internalization of nanoparticles (Habisreutinger et al. 2013). In vivo researches have been revealed that TiO$_2$ can travel in the bloodstream via binding to plasma protein, through the lymphatic system after phagocytosis by macrophages, or to the bone marrow via monocytes. TiO$_2$ particles has a great opportunity to react with cell membrane proteins and contribute to cell particle interaction (Lee et al. 2012; D’Agata et al. 2014). The cell interaction with difference surface functionalities of TiO$_2$ could affect the pH, charge, integrity and function of cell membrane (Rao et al. 2016). Surface functional groups might have a toxicity extent depending on the
interaction between the certain surface chemical group and the properties of a particular cancer cell’s membrane (Gerloff et al 2012). Review of literature has shown that TiO$_2$ particles have a net negative charge at pH 7 and also bind favorably to amino acids containing –OH, -NH and –NH$_2$ in their side chains (Figure 4). The positively charged of –NH$_2$ group leads to an adverse effect on the negatively charged membrane of the cells (Jimeno-Romero et al 2016). It appears that the positive surface charge may improve particle accumulation on cell membrane and then particle uptake by cells. In case of negative charge surface, quite a lot of numbers of researches have demonstrated a promising serum protein interaction with-COOH surfaces as well as favorable particle uptake. The –COOH group might provide simple uptake and processing of the particles into intracellular compartments, which can avoid aggregation and undesired reactions with the cell membrane and so diminish damage to the cell membrane (Tilly et al 2014).

Figure 4: Adhesion of Müssel Foot Protein-3 to TiO$_2$ Surfaces: the Effect of pH (Yu et al 2013)

2.4 TiO$_2$ nano photocatalyst: Toxicological properties

It has been demonstrated that when TiO$_2$ particles are exposed to UV light they create electron and holes causing subsequent to the production of reactive oxygen species, including hydrogen peroxide, hydroxyl radicals and superoxide (George et al 2014) (Figure 5). TiO$_2$ particles have been demonstrated to trigger reactive oxygen species generated by alveolar macrophages, phagocytes and microglial cells upon interaction with the cell membranes (Sokwong et al 2016). Additionally, in vivo experiments or oral uptake of TiO$_2$ have reported their existence in the blood circulation, influencing both liver and kidney damage. These oxidative reactions impact on cell rigidity and chemical arrangements of surface structures, affecting cell toxicity.

Analysis on toxicology of TiO$_2$ towards different types of cell reported that, TiO$_2$ nanoparticles have low cytotoxicity comparing with B16F10 and B16F1 melanoma cells and
3T3 fibroblasts. Different sizes and concentration of TiO$_2$ particles have been verified to be non-toxic in cell monolayer uptake model in vitro (Pansare et al 2016), in vivo and inhalation models (Kocbek et al 2010). Though, in the case of the JHU prostate tumor cells and LLC cells, there are noticeable differences in the level of TiO$_2$ particles’ viability at a concentration of 1 mg/mL for LLC cells ad 0.1 mg/mL for JHU prostate tumor cells (Thevenot et al 2008). A single oral utilization of TiO$_2$ nanoparticles in rats resulted in nanoparticle distribution and accumulation in several tissues including the brain. Also, intranasal exposure of TiO$_2$ nanoparticles revealed higher accumulation of the nanoparticles in different regions of the brain tissue damage. A cell dependent effect due to exposure to TiO$_2$ nanoparticles wherein BV2 microglia cell lines have a faster decrease in viability compared to N27 neuronal cell lines suggesting that microglia are more susceptible to TiO$_2$ nanoparticles. Thus, TiO$_2$ particles possess cell specific toxicity, depending on its concentrations and surface functionality (Johnston et al 2009).

![Figure 5: Schematic Illustration of proposed TiO2 NP induced toxicity mechanisms under light and dark conditions (Dalai et al 2012)](image)

2.5 TiO$_2$ nano particles: Cell killing properties

The UV light employed in the cancer cell killing method can transfer an electron from a valence band to a conductance band in the TiO$_2$ semiconductor by creating a hole in the valence band. This electron-hole pairs are competing constantly with trapping processes (Chalew & Schwab 2013).

2.5.1 TiO$_2$ Nanoparticle in cancer cell treatment

The photo generated holes on the TiO$_2$ surface can react with water to generate powerful oxidative radicals (Xu et al 2013). The highly reactive radicals are expected to be toxic to the
cell cancer and damage them depending on the particle location upon excitation (Table 3). Various cell cancer lines demonstrated significantly different degrees of toxicity towards TiO₂. For example, the survival of the LLC cell line drops sharply up to 75% with increasing of the TiO₂ concentration of 10 mg/mL (Thevenot et al 2008). The cell killing properties of 10 mg/mL of TiO₂ towards B16F10 and JHU cell was intermediate between that of B16F1 and LLC cells, being at 75% and 50%, respectively. The photocatalytic activity of TiO₂ has been improved by retarding the electron hole recombination.

Table 3: Several mechanisms of cell killing properties of TiO₂

<table>
<thead>
<tr>
<th>Model of compounds</th>
<th>Cell killing mechanism</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidation Coenzyme A (CoA) in <em>S.cerevisiae</em> yeast</td>
<td>Loss of intracellular CoA level for the reduction in respiratory activities which lead to cell death. Direct contact between cells and TiO₂ is extremely required for cell killing. Incorporation of catalase failed to decrease the killing effect. Oxidative species, including H₂O₂ and free radicals formed during the photocatalytic process are not responsible for the bactericidal effect.</td>
<td>Irradiation of metal halide lamp for 120 min resulted more than 97% of intracellular CoA content was loaded as compared to a 42% loss without TiO₂.</td>
<td>Maness et al 1999; Zhang et al. 2013</td>
</tr>
<tr>
<td>Endotoxin from <em>E.coli</em></td>
<td>TiO₂ photo catalysis cause the demolition of the outer membrane of <em>E. coli</em> cell, followed by the degradation of toxic compounds subsequently released from dead cells.</td>
<td>Mineralization of <em>E.coli</em></td>
<td>Ireland et al 1993; Cho et al 2004</td>
</tr>
<tr>
<td><em>E.coli</em> suspension</td>
<td>Addition of catalase quenched the killing significantly. Addition of PTFF membrane separates the <em>E. coli</em> suspension from TiO₂ film.</td>
<td>H₂O₂ rather than hydroxyl radicals act as long range bactericidal effect. Level of H₂O₂ detected was lower than usually required to kill bacteria.</td>
<td>Sunada et al 1998; Matsunaga, &amp; Okochi 1995</td>
</tr>
<tr>
<td>Organic compounds</td>
<td>DNA converted to the relaxed form and linear form proceeds withstand breakage. Hydroxyl radical is responsible for the damage and not the</td>
<td>Detrimental effect on DNA and RNA</td>
<td>Weon &amp; Choi 2016</td>
</tr>
<tr>
<td>Human skin fibroblast cells</td>
<td>Higher oxidative damage to RNA as opposed to DNA. The DNA molecules in procaryotic cells are attached directly onto the cell membrane and more susceptible to oxidative damage than eukaryotic cells.</td>
<td>Administration of TiO₂ and UV A light caused 85% cytotoxicity to human skin.</td>
<td>Yang et al 2013; Cunningham et al 2016</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Purine or pyrimidine bases</td>
<td>Formation of NO and NH ion species. The transient formation of unidentified peroxide species along with phosphate and carbon dioxide.</td>
<td>DNA decomposition within 1 to 3 hours.</td>
<td>Wang et al 2015</td>
</tr>
<tr>
<td>Human malignant cell</td>
<td>TiO₂ particles were distributed at the outer surface of cell membranes and in the cytoplasm. Induced process of phagocytosis “cell eating”.</td>
<td>At second stage leakage, major rupture of the cell membrane and decomposition of essential intracellular components including organelles occurred.</td>
<td>Zhang et al 2012; Yuan et al 2013</td>
</tr>
<tr>
<td>Sarcoma cell culture, platelet aggregation and lipoxygenase enzyme</td>
<td>TiO₂ irradiated with UV C able to inhibit proliferation of sarcoma cells while it was found had no effect when applied to the normal fibroblast cell line. Inhibition of platelet aggregation. Hinder the expression of lipoxygenase.</td>
<td>Only 50% of the cell population survived on 24 hours of irradiation while at 48 hours no cell survived.</td>
<td>Noujaim et al 2016; Pandurangan et al 2015</td>
</tr>
<tr>
<td>Carcinoma cells</td>
<td>Rapture of cell membranes and decomposition of essential intracellular components, thus speeding up cell death.</td>
<td>At a concentration of TiO₂ above than 20µg/mL a significant decrease in survival ratio under UV A irradiation for 30 min.</td>
<td>Nejad et al 2016; De Angelis et al 2013</td>
</tr>
<tr>
<td>Streptococcus sobrinus AHT</td>
<td>Disruption of the cell wall, cell membrane and leakage of cell content. Leakage of many acidic cellular components.</td>
<td>Rapid leakage of potassium ions within 3 min upon illumination of TiO₂. With illumination up.</td>
<td>Zhukova 2016</td>
</tr>
</tbody>
</table>
3.0 **Configurations of photo-reactor**

In many photo reactor designed for photo catalyst process of TiO$_2$, the light has to travel and penetrate through the cancer media or gas containing reagent to ensure that all light adsorption data has been captured and properly analyzed. There are four configuration systems based on reactor design for TiO$_2$ photo catalyst with the respective configuration and work phase (Table 4).

<table>
<thead>
<tr>
<th>Reactor type</th>
<th>Configuration</th>
<th>Work phase</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid-solid-moveable bed reactor</td>
<td>Slurries of TiO$_2$ suspended in the liquid to be treated. The concentration of TiO$_2$ (0.05 to 1 wt%)</td>
<td>The catalyst flows into and out of the reactor with liquid being treated. Natural or artificial irradiation sources are external to the system. Photons are transmitted through UV transparent parts. Separation step is necessary to remove the TiO$_2$ from treated water.</td>
<td>Dong et al 2015; Cheng et al 2012</td>
</tr>
<tr>
<td>Liquid-solid-fixed bed reactor</td>
<td>Lower reaction rate</td>
<td>Relatively low extent of contact between the catalyst and molecules to be oxidized. Mass transport limitation</td>
<td>Piskun et al 2016</td>
</tr>
<tr>
<td>Gas-solid-moveable bed reactor</td>
<td>Destruction of chemicals in air. Catalyst particles are not entrained in the air stream. Catalyst is contained in the irradiated reactor vessel.</td>
<td>An entrained bed system is envisioned. Separation of catalyst particles from the air stream is easier than separation from a water slurry. Moveable bed reactor may benefit from the light dark phenomena.</td>
<td>Wang et al 2014; Li et al 2013</td>
</tr>
<tr>
<td>Gas-solid fixed bed reactor</td>
<td>Occupied with an inner annulus, which is the</td>
<td>The annular region can be filled with Ti4 crystal or</td>
<td>Faria et al 2014; Sannino</td>
</tr>
</tbody>
</table>
light source may transparent sheath around light source Inside surface of the outer annulus is often coated with TiO$_2$ leading to illumination coated surface substrates coated with TiO$_2$. Powder layer reactors are supported on a frit Fluid to be treated flows normally, through the powder and frit External illumination is provided through a UV transparent window UV transparent tubes, filled with catalyst particles or coated with catalyst illuminated with both natural and artificial light et al 2013

3.1 Bacteria as target organisms

The reactor design for bacteria killing has been covered under irradiation from a germicidal lamp with wavelength of 2 to 54 nm. The irradiation would result in the formation of free radicals, including chlorine atom or hydroxyl radical. This consequently results in DNA strand breakage or initiate autoxidation of cell components (Barnes et al 2013). The ozone or singlet oxygen can attack molecular structures found in cell components with some selectivity. Bacteria have some developments in terms of defense and repair mechanisms to prevail over photochemical and oxidative damage that make them to live in an aerobic environment and to deal with the low level of irradiation (Rengifo-Herrera et al 2013). Thus, the selection of light source and reactor type are decidedly variable. Some pilot experiment results showed that TiO$_2$ suspended in water has no noteworthy impacts on survival of bacteria in the dark, and the effect of light with TiO$_2$ is greater than that of light alone (Leyland et al 2016; Schlur et al 2014; Bonetta et al 2013). The lamp with about 41 % of output below than 315 nm demonstrated greater killing mechanism with or without TiO$_2$ as compared to the ones with only 4 % of its output (Figure 6). Researches employing light sources with fluxes in the range of about 100 to 2000 pE/mzs reported 100% deactivation in _E.coli_ in 7 to 120 min.
3.2 Viruses as target organism

The virus contains a group of heterogeneous with the sized range of 0.01 to 0.3 nm. One important key process to inactivate viruses is through the control of their surface structure, specifically their bind in sites (Etacheri et al 2013). By doing that, they would not be able to detect the receptor locations on the host cells. In this condition, the photocatalytic process of TiO$_2$ may attack effectively on the cell surface and disinfect viruses through modification of their surface structure (Nakona et al 2013).

3.3 Fungi as target organisms

Fungi are eukaryotic organism with genetic material which are located in a nucleus enclosed by a membrane. Fungi are recognized to stay alive in critical stressful conditions owing to their tougher cell wall structure. They are able to stand an extensive range of pH and extract water from solutions with high concentration of salt/sugar (Dhanalakshmi et al 2013).

3.4 Cancer cells as target organism

The cancer cells are generally categorized depending on their desire to spread, including benign or malignant cells. Usually, normal cell cultures are similar to the cell from which they are derived and likely to keep their differentiation that distinguish them from cells obtained from other tissues (Huang et al 2014). It found that, without UV irradiation the surviving fraction of the HeLa cells treated with TiO$_2$ up to 200g/ml was not less than 90%. However,
once the TiO₂ has been exposed to the radiation of UV lamp A, the cell survival rate was reduced dramatically (Abdulla-Al-Mamun et al 2016).

4.0 TiO₂ nano photocatalyst: Challenges and limitation cancer cell treatment

Despite of promising outcomes in killing cancer cells, TiO₂ photo catalyst treatment would be challenging in terms of clinical settings. The UV light used for excitation is not able to penetrate profoundly into human tissues, therefore restricting this approach to superficial tumors. Additionally, UV-mediated production of reactive oxygen species has a short life span and so could not offer nonstop prolonged cancer killing effect (Zhang et al 2014; Jang et al 2015). Charge recombination or the grain boundary of TiO₂ also limits the efficiency of light energy conversion (Tang et al 2013). Therefore, the hybridization of TiO₂ with metal, metal oxide and nano carbon materials has found interest among the researchers to re-engineering the band gap energy and increase stability of TiO₂.

5.0 TiO₂ hybrid photo catalysis: Cancer Cell Treatment

The majority of pristine TiO₂ nanoparticles are active under UV light excitation, due to their large band gap energy. However, UL light induces damage to biological components and its penetration into biological tissue is very limited (He et al 2015; Meng et al 2015). This frequently makes UV light to not reach the cancer cells situated far away from the tissue surface. Thus, UV sensitive TiO₂ nanoparticles are not suitable for effective in vivo, which requires long-wavelength visible light or near infra-red irradiation. Thus, the hybrid of TiO₂ with metal/metal oxide/nano carbon materials has proved to narrow its band gap energies and in turn improve its photocatalytic under visible light excitation (Ouyang et al 2016).

5.1 TiO₂/metal oxide hybrid photo catalyst

The metal oxide plays crucial role in the photocatalytic activities of TiO₂ by changing the distribution of electrons due to its higher work function than TiO₂. As TiO₂ and metal oxide are in contact with the Fermi levels, electrons have given rise to the metal oxide flow from TiO₂. The reduction in electron density within TiO₂ causes a rise in the hydroxyl group acidity which impacts on the photocatalytic process of TiO₂ surface.

5.1.1 TiO₂/SiO₂ hybrid photo catalyst

Incorporation of silica oxide (SiO₂) into TiO₂ induces higher toxicity toward cancerous cells. Findings demonstrate that the folic acid conjugated silica-TiO2 nanoparticles can be used as
an effective photosensitizing agent for active targeting of cancer cells. Addition of folic acid improves the cell proliferation, add essential vitamin B elements and promote the cell growth (Mungondori et al 2015; Li & Zhao 2013; Yu et al 2012). The observed relative surviving fraction of the cancer cells were 100%, 96 %, 99% and 90 % with folic acid conjugated silica-TiO₂ at 10 min, 20 min, 45 min and 60 min of UV irradiation, respectively. The surviving fraction of cells was reduced from 100% for the control to 93%, 78% and 82% in the presence of 12.5 g ml⁻¹ of folic acid conjugated silica-TiO₂. The viability of cancerous cells was further reduced to 57% when the folic acid silica-TiO₂ concentration was increased to 100 gml⁻¹.

5.2 TiO₂/Metal hybrid photo catalyst

Hybridization of metal nanoparticles significantly affects the improvement of photocatalytic activities of TiO₂ semiconductor. Metal nanoparticles deposited to TiO₂ nanostructures undergo Fermi level equilibration following the UV excitation and improve the efficiency of charge transfer processes (Fan et al 2014; Yang et al 2014). The TiO₂/metal hybrid can suppress the charge recombination and improve the energy conversion efficiency. In the TiO₂/metal nano hybrid, metal nanoparticles are dispersed on oxide surfaces (Hou et al 2015). The photo generated electrons of TiO₂ are capable to reduce the metal nanoparticles, depending on reactants and surrounding media. There are two major factors contribute to photocatalytic efficacy of TiO₂/metal (i) the dielectric properties of the medium and (ii) the density of electrons of the metal cluster (Zhang et al 2016). Corrosion or dissolution of the noble metal particles during the photocatalytic reaction is likely to limit the use of metal nanoparticles. The oxidation by photo generated holes and oxidizing radicals at the TiO₂-metal interface is a chief procedure to determine the overall photocatalytic efficiency of the hybrid system (Feng et al 2013; Tang et al 2013). A superior synthetic design can meaningfully enhance the catalytic performance of TiO₂/metal hybrid photo catalyst.

5.2.1 TiO₂/Au hybrid photo catalyst

Gold (Au) nanoparticles have been effectively applied in treatment of canceling cells by photothermal in vitro technique. The efficiency of this treatment approach arises from the synergistic effect of photo thermal and photocatalytic killing of Plasmon excited metal nanoparticles with excitation of electron-hole pairs in TiO₂ (Zhang et al 2014). The experimental investigations show that the photocatalytic inactivation efficiency on human colon LoVo cancer cells can be significantly improved almost 100% by the modification of Au on TiO₂ nanoparticles at 2wt% at 100 minutes of irradiation time (Tang et al 2013). However, as the composition of Au increased to 4 wt%, the photocatalytic killing effect reduced to 75%. This could be attributed to light shadowing by the deposited when excessive Au nanoparticles covered the surface of TiO₂ particles.
5.2.2 TiO$_2$/Fe$_3$O$_4$ hybrid photo catalyst

TiO$_2$/Fe$_3$O$_4$ has many advantages than that of native TiO$_2$ as concerned with thermal-photocatalytic cancer cell killing efficiency. Addition of Fe$_3$O$_4$ into TiO$_2$ system has been approved to increase the cytotoxicity under combined magnetic field induction and photoirradiation (Yu et al 2012). It suggested that, the cell killing process occurs at the cellular level that is mostly caused by the heat-induced malfunction of repair processes after radiation induced DNA damage (Lu et al 2013). Thus, the procedures of cell killing can be attributed to the cumulative effects of hyperthermia and photocatalytic cell killing. HeLa cells demonstrate 100 % of killing efficiency by using a dose of 150µg/mL of TiO$_2$/Fe$_3$O$_4$ for 10 min induction and irradiation (Meng et al 2015; Yuan et al 2013).

In many cases, stability of TiO$_2$/Fe$_3$O$_4$ becomes significant consideration. For that, Fe$_3$O$_4$ has been used as a core and TiO$_2$ was used a shell. The super-paramagnetic properties brought by Fe$_3$O$_4$ acted as an efficient photo thermal mediator (Chalasani & Vasudevan 2013). The reactive oxygen species, including hydroxyl radicals and hydrogen peroxide are formed on photo-excited surface of Fe$_3$O$_4$-TiO$_2$. These highly oxidizing OH radicals and H$_2$O$_2$ can be expected to be toxic to cells. Moreover, the photo-generated hole reacts with a water molecule and being toxic to cells (Xu et al 2014; Dong et al 2013).

In advance, surface functionality of TiO$_2$/Fe$_3$O$_4$ has been carried out to increase the selectivity towards a specific type of cell cancer. Folic acid has been immobilized on the super-paramagnetic TiO$_2$/Fe$_3$O$_4$ to increase the selectivity of the photocatalyst system (Huang et al 2014). The conjugation occurs by the interaction of the carboxylate group of folic acid and OH group of TiO$_2$. As each folic acid molecule comprises of two carboxylate groups, there may be some free carboxylate groups of bound folic acid molecules that attributed in negatively charged of TiO$_2$/Fe$_3$O$_4$ photo catalyst (Ma et al 2012). It has been suggested that the folic acid-modified TiO$_2$/Fe$_3$O$_4$ is partially beneficial in cancer therapy due to the great amount of folic acid in cancer cell surface. The surface functionalization of folic acid on TiO$_2$/Fe$_3$O$_4$ with a ratio smaller than one could result in severe cell damage under UV irradiation (Hu et al 2013). The improvement of cytotoxicity was because of the greater amount of TiO$_2$ uptake by cells via the recognition of folic acid to the cell surface. However, the greater amount of folic acid attached on TiO$_2$/Fe$_3$O$_4$, the smaller the photocatalytic efficiency since the presence of folic acid could shield the illumination of UV light. In another study, TiO$_2$/Fe$_3$O$_4$ has been chemically modified with (3-aminopropyl)-trimethoxysilane to introduce NH$_2$ groups on their surface before forming a conjugate with protein compounds via covalent linkage.

5.2.2 TiO$_2$/Ag hybrid photo catalyst
Ag nanoparticles are chemically very reactive can be oxidized in direct contact with TiO$_2$ to produce silver oxide (Ag$_2$O)/ TiO$_2$/Ag has been effectively applied to improve the photocatalytic decomposition of organic compounds and photo killing bacteria. The Ag core in the TiO$_2$/Ag hybrid system enables to decelerate the electron-hole recombination at the surface of TiO$_2$ particles (Abdulla-Al-Mamun et al 2016). As a result the trapped electron in the conduction band and the trapped hole in valence band become a free charge carrier in the conduction and valence bands. Indeed, the Ag core can charge electron under UV irradiation and discharge them in the dark on demand (Daghrir et al 2013). Charging and discharging process of the TiO$_2$/Ag hybrid system is variable based on the amount of Ag. Once the photo-induced excitation of TiO$_2$/Ag is carried out in the presence of an electron acceptor and allow the photo-generated electron are scavenged by the acceptor molecules.

The plausible mechanism of TiO$_2$/Ag photocatalytic against the cancer cell start with the formation of penetration of photo-excited electrons with quick transformation through TiO$_2$ shell into the Ag nano core until the Fermi level charge equilibrium is attained between shell and core systems (Abdulla-Al-Mamun et al 2012). As a promising Fermi level is accomplished, electrons are enabled to rapidly transfer from excited TiO$_2$, starting the redox reactions at the interface of TiO$_2$ shell and suspension. The reactive oxygen species, including hydroxyl radicals and hydrogen peroxide are generated on the photo excited TiO$_2$/Ag hybrid system. The highly oxidizable hydroxyl and hydrogen peroxide species are expected to be toxic to the cells (Hou et al 2012). The photo-induced electron transfer to the interfacial surface of excited TiO$_2$ before transferred to the Ag core until the Fermi level equilibrium will be attained. Some electrons can be transferred to the TiO$_2$ surface and reduce the dissolve O$_2$ easily, because dissolved oxygen is also one of the good electron acceptor. The Ag core act as a Schottky barrier of TiO$_2$ excited electrons and protects the electron-hole recombination (Khanna & Shetty 2014). Thus, the photo-induced solid-liquid interfacial charge-transfer processes are promoted and photocatalytic cell killing than TiO$_2$ alone is improved.

It demonstrated that the photocatalytic cytotoxicity of TiO$_2$/Ag required only one-fourth the irradiation time required by single TiO$_2$ (Chang et al 2015; Hosseinnia et al 2014). The killing efficiency of TiO$_2$/Ag is more than three times greater than that of TiO$_2$ alone at the same volume. For the HeLa cell killing study, the photo-luminescence intensities of TiO$_2$ and TiO$_2$/Ag hybrid demonstrated that the TiO2/Ag fluorescence intensity is much larger than TiO$_2$ alone.

In advanced, TiO$_2$/Ag hybrid has been prepared by citrate reduction. The citrate can cap the Ag nanoparticles and hydrolysis of titanium (IV) (triethanolamine) isopropoxide can condense quickly in boiling temperature on the Ag nanoparticles surface under N$_2$ purge and UV irradiation in solution to give the Ag metal core-TiO$_2$ shell structure (Abdulla-Al-Mamun et al 2016).
5.3 TiO$_2$ doped

One of the important characteristics for maximum light penetration is determining the appropriate size and morphologies of TiO$_2$. Thus, the doping materials such as carbon, nitrogen and sulfur have been approved to reduce aggregation and develop longer wavelength visible light of TiO$_2$ (Giordano et al 2016). Doping element’s toxicity possibly has unfavorable impacts on biomolecules. The doped TiO$_2$ absorbs only a short range of visible light (400-600 nm). This consequently limits the penetration distance in the tissue (Jang et al 2015). The near infrared (700 to 1000 nm) light demonstrates the maximum penetration of light into the tissue.

5.4 TiO$_2$/gambogic acid

Gambogic acid is a major active component from Garcinia hanburyi tree in Southeast Asia. The synergistic effect with TiO$_2$ and gambogic acid has been used for targeting cells of HepG2 cancer cell (Li et al 2014; Xu et al 2015). Owing to interesting properties of this photosensitizer, the TiO$_2$ particles blending with gambogic acid are able to improve the use of relevant anticancer agents and provide prospective application for therapeutic alliance in multi-mode cancer treatment (Yue et al 2016). Moreover, TiO$_2$/gambogic acid has a higher pH sensitivity of efficient cancer cell killing process as compared to parent TiO$_2$. This also indicates the efficiency of TiO$_2$/gambogic acid to promote reduction in side effects of relevant drugs to the normal cells/tissues in the blood circulation (Orecchioni et al 2015).

6.1 Photoluminescence detection of hydroxyl radical

The creation of hydroxyl radicals on the surface of UV-visible irradiated TiO$_2$ photo catalyst can be analyzed by photoluminescence (PL) method using a robe molecule (terephthalic acid). Terephthalic acid reacts with hydroxyl radicals to create a highly fluorescent product which is 2-hydroxyterephthalic acid during the irradiation time. The intensity of PL peak of 2-hydroxyterephthalic acid is proportional to the amount of OH radicals produced in water.

Conclusion

The worldwide prevalence of cancer leads an increase in attempts which are aiming for the development of innovative and effective photo-catalyst for treatments of cancer cells. Comparing with different oxide semiconductor photo-catalyst, TiO$_2$ has demonstrated to be the most appropriate materials for cancer cell treatment due to its cost effectiveness, biological and chemical inertness, and long term stability against corrosion, and strong oxidizing power. Nanostructured TiO$_2$ exhibit greater photocatalytic activity than
conventional bulk materials for its high surface area. Under UV radiation exposure, TiO$_2$ particles generate active free radicals that are in charge of decomposing organics on the particle surface. Thus, several researches have been reported utilization of TiO$_2$ photo catalyst for disinfection and killing of fungi, bacteria, viruses, and cancer cells under various killing approaches.

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Conflict of Interest Statement

Hereby, I confirm there is no Conflict of Interest Statement between the authors.
Highlights

Titania can kill cancer cell through photocatalytic chemistry

Titania has stable reactive oxygen species and great selectivity towards cancer cell

Titania photocatalyst can kill cancer cells without damaging healthy tissues

Titania hybrid improves stability and selectivity whilst maintains photodynamic reactivity