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# Assessing the potential biological activities of TiO<sub>2</sub> and Cu, Ni and Cr doped TiO<sub>2</sub> nanoparticles

Shamsa Munir, <sup>a</sup> Faiza Asghar,<sup>b</sup> Faryal Younis,<sup>a</sup> Saira Tabassum,<sup>c</sup> Afzal Shah <sup>d</sup> and Sher Bahadar Khan<sup>e</sup>

Nanoparticles are like magic bullets and nanomaterials exhibit appealing properties. Their size and morphology can be switched by dopants for certain biological activities. Nanoparticles in combination with certain drugs enhance the antibiotic effects and may be valuable in combating bacterial resistance. The antimicrobial potency of nanoparticles depends upon their ability to bind to the surface of microbial cell membranes resulting in modulation of basic cell functions such as respiration. We report herein the antibacterial, antifungal and antioxidant activities of pure TiO<sub>2</sub> and TiO<sub>2</sub> doped with 4% Cu, Ni and Cr. The performance of pure and doped nanoparticles has been compared with reference compounds. A comparison of the antifungal activities of the samples doped with TiO<sub>2</sub> reveals that Cu–TiO<sub>2</sub> exhibits improved performance against *A. fumigatus* but lower antifungal activity against *Mucor* sp. and *F. solani*. Cu–TiO<sub>2</sub> and Ni–TiO<sub>2</sub> showed good antibacterial action against *B. bronchiseptica*, while Cr–TiO<sub>2</sub> nanoparticles displayed better activity against *S. typhimurium* as compared to pure TiO<sub>2</sub>. Moreover, pristine TiO<sub>2</sub> and Ni–TiO<sub>2</sub> nanoparticles were found to demonstrate maximum total antioxidant capacity.

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## 1. Introduction

Nanotechnology is an emerging technology in the modern world providing a wide variety of applications in chemistry, biology, physics, materials and health sciences. A literature survey reveals that physico-chemical and biological properties of nanoparticles depend upon their size and shape.<sup>1–4</sup> Nanoparticles exert their antimicrobial action by binding to the surface of microbial cell membranes and altering their basic cellular functions.<sup>5</sup> Moreover, nanoparticles have been reported to penetrate the microbial cells and interact with nitrogen, sulfur and phosphorus of biomolecules.<sup>6</sup> The size and morphology of nanoparticles have been found to exhibit noticeable potential for certain biological activities.<sup>7–10</sup> In fact nanoparticles are employed in combination with certain drugs to enhance the antibiotic effects and to combat bacterial resistance.<sup>6</sup>

Semiconductor oxide nanoparticles are widely synthesized by chemical as well as green routes for application in biological sciences owing to their potential as antibacterial, antifungal and antioxidant materials.<sup>11–16</sup> A recent article about the antibacterial activity of TiO<sub>2</sub> doped ZnO composite material has

reported that TiO<sub>2</sub> doping in ZnO increased the activity index.<sup>17</sup> Chitosan coated biologically synthesized TiO<sub>2</sub> nanoparticles displayed good antibacterial activities against pandrug resistant (PDR) *E. coli* strain with the prominent zone of inhibition of 23 mm.<sup>18</sup> In 2019, Islam *et al.*, reported the biological activities of gold nanoparticles functionalized with *Salix alba* synthesized via a green route which displayed good antifungal activity and also showed appreciable antinociceptive and muscle relaxant properties.<sup>19</sup> Ahamed *et al.*, prepared copper oxide nanoparticles by precipitation method and found these materials to demonstrate excellent antimicrobial potential against various bacterial strains.<sup>20</sup> Similarly Ag nanoparticles obtained through chemical and greener means have been found to demonstrate strong antimicrobial action.<sup>12,16,21–25</sup> Metal nanoparticles such as those of palladium have been considered as ecofriendly materials owing to their antifungal potential.<sup>26</sup>

TiO<sub>2</sub> nanoparticles are recognized as promising materials due to their biocompatibility, environment friendliness, stability and nontoxic nature. They exhibit strong antimicrobial and anticancer activities. It has been shown that the biological activities of TiO<sub>2</sub> nanoparticles can be significantly improved with dopants and thus doping can be employed to tune their antimicrobial properties.<sup>27,28</sup> In the present research, we have evaluated the antibacterial, antifungal and antioxidant potential of undoped TiO<sub>2</sub> and doped titania with 4% Cu, Ni and Cr synthesized by a chemical route. We found that the doped TiO<sub>2</sub> displayed appreciable antimicrobial properties compared to many previously reported studies on nanoparticles for biological activities. The excellent antimicrobial potential of doped

<sup>a</sup>School of Applied Sciences and Humanities, National University of Technology (NUTECH), Islamabad, 44000, Pakistan

<sup>b</sup>Department of Chemistry, University of Wah, Quaid Avenue, Wah, Pakistan

<sup>c</sup>Department of Biotechnology, Quaid-Azam University, Islamabad, 45320, Pakistan

<sup>d</sup>Department of Chemistry, Quaid-i-Azam University, Islamabad, 45320, Pakistan. E-mail: afzals\_qau@yahoo.com

<sup>e</sup>Department of Chemistry, King Abdulaziz University, P.O. Box 80203, Jeddah 21589, Saudi Arabia


nanoparticles suggests their potential for practical applications as alternative or combinational drugs.

## 2. Materials and methods

TiO<sub>2</sub> and doped TiO<sub>2</sub> nanoparticles were synthesized *via* a sol gel method using titanium(IV)-iso-propoxide Ti[OCH(CH<sub>3</sub>)<sub>2</sub>]<sub>4</sub> precursor as described earlier.<sup>29</sup> Copper, chromium and nickel acetate were employed as precursors for doping titania with 4% Cu, Ni and Cr. Analytical grade 1-propanol and deionized water were used as media in the synthesis procedure. Characterization of nanoparticles prepared by the same method has been reported in our previous work.<sup>30</sup> The statistical analysis of antibacterial and antifungal activities was performed by using SPSS Pearson's product moment correlation coefficient method. All experiments for biological activities were performed in triplicate.

### 2.1. Biological activities protocols

The potential of the material against bacterial strains was evaluated according to literature reported procedure.<sup>31</sup> Samples to be tested (5 µL of 4 mg per mL DMSO; 100 µg per disc) were pervaded on 6 mm discs of sterile filter paper put on seeded nutrient agar plate Cefixime-USP (20 µg per disc) and DMSO impregnated discs were employed as +ve and -ve controls, respectively.<sup>31,32</sup> Clear zones of inhibition were determined after 24 hours of incubation time. Fungal strains were bought from fungal culture bank of Pakistan and antifungal activity was determined according to procedures described earlier.<sup>31</sup> 100 µL of harvested spores of each type were placed on plates containing 25 mL sterilized Sabouraud dextrose agar (SDA). 5 µL of each sample to be tested (4 mg per mL DMSO; 100 µg per disc) and standard drug (50 µg per disc) were pervaded in filter paper discs. Samples were incubated for 24–48 h at 28 °C. Afterwards, clear inhibition zones were measured employing a vernier caliper.

Total antioxidant activity of extracts was evaluated by method with a little modification as described elsewhere.<sup>33</sup> A 4 mg per mL of each sample was dissolved in DMSO solvent. A 100 µL volume of each sample solution was then combined with 900 µL of solutions prepared using H<sub>2</sub>SO<sub>4</sub> (0.6 M), NH<sub>4</sub>MoO<sub>4</sub> (4 mM) and Na<sub>3</sub>PO<sub>4</sub> (28 mM). Incubation of the reaction mixtures was done for about 90 min at 95 °C, followed by cooling to room temperature. Then, the absorbance was determined at the wavelength of 695 nm.<sup>32</sup> A 100 µL of DMSO was used as a standard. Moreover, ascorbic acid was employed as positive standard for calibration curve with a concentration of 4 mg mL<sup>-1</sup>. The total antioxidant capacity (TAC) was indicated in µg ascorbic acid equivalent (µg AAE) per mg dry weight.

The reduction potential was investigated according to procedure described earlier.<sup>33</sup> A 4 mg per mL of each sample was dissolved in DMSO solvent. A 100 µL volume of each sample solution was then combined with 200 µL of 0.2 M phosphate buffer and 250 µL of 1% w/v potassium ferricyanide. Incubation of the mixtures was done for 20 min at a temperature of 50 °C. Following this a 200 µL of 10% w/v trichloroacetic acid was added to the mixture for acidification. The resulting mixtures were centrifuged at the rate of 3000 rpm for about 10 min. The

150 µL of the supernatant layer was mixed with 50 µL of 0.1% w/v FeCl<sub>3</sub> solution and optical density was measured at 630 nm using microplate reader.<sup>32</sup> The results were expressed as µg AAE per mg dry weight using ascorbic acid as positive standard.

For estimating free radical scavenging potential, we used 2,2-diphenyl-1-picryl hydrazyl (DPPH). The mixture of 10 µL of extract (4 mg per mL) and 190 µL of DPPH (0.004% w/v) in methanol was incubated for 1 h in the dark. The optical density was similarly determined at the wavelength of 515 nm through microplate reader. Samples to be evaluated were first tested at a concentration of 200 µg per mL and those exhibiting good quenching activity (*i.e.* ≥50%) were tested at smaller concentration (200, 66.6, 22.2, 7.41 µg per mL) to find IC<sub>50</sub> values. Following formula was employed to calculate the percent inhibition:

$$\% \text{ Inhibition of the sample} = \% \text{ of scavenging activity} \\ = (1 - \text{Ab}_s/\text{Ab}_c) \times 100.$$

where, the absorbance of the DPPH solution along with sample is represented by Ab<sub>s</sub> and absorbance of the negative standard (*i.e.*, reagent and solvent) is represented by Ab<sub>c</sub>. IC<sub>50</sub> was evaluated by using Table curve software 2D version 4.

## 3. Results and discussion

### 3.1. Biological activities

The synthesized nanoparticles were examined for the evaluation of their antifungal, antibacterial and antioxidant potential. The antifungal activities of TiO<sub>2</sub> and doped TiO<sub>2</sub> analyzed against *A. fumigatus*, *Mucor* sp. and *F. solani* in comparison with the standard drug terbinafine can be seen in Fig. 1. Although the synthesized compounds demonstrate lower activity than the reference drug used against the fungal strains, but a comparison of the activities of the doped samples with pristine TiO<sub>2</sub> reveals improved performance of Cu-TiO<sub>2</sub> against *A. fumigatus* but a lower activity against *Mucor* sp. and *F. solani* as depicted from the zone of inhibition values of 18, 15 and 10 mm, respectively. A recent article indicate that TiO<sub>2</sub> nanoparticles synthesized *via* green route exhibit no activity against *A. fumigatus* at concentrations of 10, 20 and 30 mg mL<sup>-1</sup>.<sup>34</sup> In another report, biologically synthesized ZrO<sub>2</sub> nanoparticles displayed a zone of inhibition of 34 ± 1 mm at a concentration of 15 mg mL<sup>-1</sup>.<sup>35</sup> Similarly 15% Zr doped CeO<sub>2</sub> nanoparticles employed against *A. fumigatus* have been reported to have a maximum zone of inhibition of 10 mm.<sup>36</sup>

Ag nanoparticles are widely investigated for antimicrobial action. According to the recent literature Ag nanoparticles show no significant activity towards *Mucor* sp.<sup>37</sup> Cu, Ni and Cr doped TiO<sub>2</sub> indicated reduced activity against *F. solani* than that of the pure TiO<sub>2</sub> nanoparticles. Moreover, literature survey reveals few reports using metal nanoparticles as antifungal agents against *F. solani*.<sup>38</sup> One report manifested the reduction of the growth of *F. solani* to 1.42% (as compared to 93% of the control), at a concentration of 100 mg mL<sup>-1</sup> for TiO<sub>2</sub> nanoparticles prepared *via* a greener route.<sup>39</sup> Direct comparison is difficult to make due to different experimental conditions and concentrations of the samples.



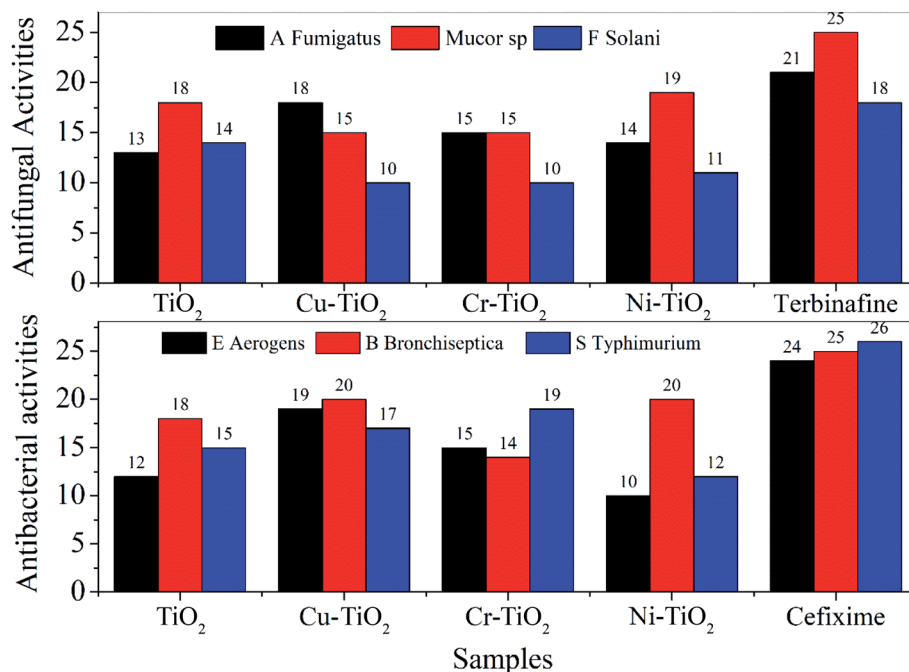


Fig. 1 Comparative analysis of antifungal and antibacterial activities of TiO<sub>2</sub> and doped TiO<sub>2</sub> nanoparticles with reference drugs.

Antibacterial activities were also determined for TiO<sub>2</sub> and doped TiO<sub>2</sub> nanoparticles and compared with the reference drug cefixime. The result of antibacterial activity against *E. aerogens*, *B. bronchiseptica* and *S. typhimurium* has been displayed in Fig. 1. Although TiO<sub>2</sub> and doped TiO<sub>2</sub> displayed lower antibacterial action than that of the reference drug, but demonstrated enhanced performance compared to many reported studies employing nanoparticles as antibacterial agents. For instance, a study of the antibacterial action of chemically synthesized TiO<sub>2</sub> encapsulated into zeolite and SiO<sub>2</sub>-TiO<sub>2</sub> composite nanoparticles displayed no activity against *E. aerogenes*<sup>40</sup> compared to our data of 12, 19, 15 and 10 mm for TiO<sub>2</sub>, Cu-TiO<sub>2</sub>, Cr-TiO<sub>2</sub> and Ni-TiO<sub>2</sub>, respectively. Recent literature also showed that the Ag nanoparticles possess zone of inhibition of 7.1,<sup>41</sup> 24 (ref. 42) and 11 mm<sup>43</sup> against *E. aerogens* at various concentrations of Ag nanoparticles. Similarly, MnO nanoparticles prepared *via* a green route displayed 9 mm zone of inhibition<sup>44</sup> against *B. bronchiseptica*. Antibacterial action of nanoparticles against *S. typhimurium* has been reported for Ag,<sup>45</sup> Se,<sup>46</sup> Au<sup>47</sup> and ZnO<sup>48</sup> employing other methods and sample concentrations. Cu nanoparticles capped with 1% gum arabic<sup>49</sup> displayed a higher zone of inhibition of 27 mm. Phosphorous and fluorine co-doped TiO<sub>2</sub> are also reported against *S. typhimurium* (approximately 10<sup>6</sup> CFU mL<sup>-1</sup>) under day light.<sup>50</sup> However, comparison of the results cannot be made with literature data due to different conditions of measurements and concentrations of the samples.

We further evaluated the antioxidant activities of the pure TiO<sub>2</sub> as well as doped TiO<sub>2</sub>. Total antioxidant capacity (TAC) values were found to be highest for Ni-TiO<sub>2</sub> followed by pristine TiO<sub>2</sub> nanoparticles (see Fig. 2 & Table 1) whereas; minimum TAC values were obtained for Cu-TiO<sub>2</sub> nanoparticles. Literature

survey on the cytotoxic effects of TiO<sub>2</sub> shows no significant cytotoxic effects on lung epithelial cells at a concentration of 0.1 mg mL<sup>-1</sup> titania.<sup>51</sup> Another article on the cytotoxicity studies of TiO<sub>2</sub> and doped TiO<sub>2</sub> on human cells demonstrates high oxidative stress mediated cytotoxicity on lung epithelial cells at a concentration of 2-200 µg mL<sup>-1</sup> (ref. 52) which can be greatly reduced by the antioxidant *N*-acetyl cysteine.<sup>53</sup> Mg and Cu co-doped TiO<sub>2</sub> display high antibacterial potential against *E. coli* and *S. aureus* with exceptional cytocompatibility.<sup>54</sup> The *in vitro* release kinetic study of co-doped TiO<sub>2</sub> reveals that Cu ions at a concentration greater than 9 mg L<sup>-1</sup> is cytotoxic to MC3T3-E1 cells, however maximum single day release is 2.29 mg L<sup>-1</sup>.<sup>54</sup> A recent study has reported the cytotoxicity of Ni (1%) and Pt

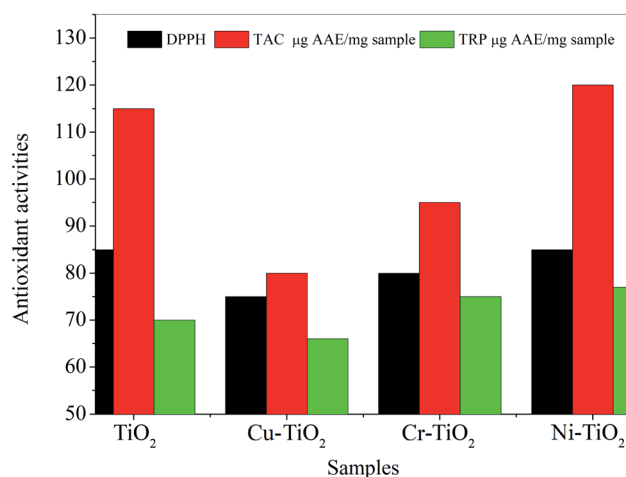


Fig. 2 Comparative analysis of total antioxidant capacity (TAC) and total reducing power (TRP) of TiO<sub>2</sub> and doped TiO<sub>2</sub> nanoparticles using bar graph.



**Table 1** Summary of the antifungal, antibacterial and antioxidant activities of TiO<sub>2</sub> and doped TiO<sub>2</sub> nanoparticles prepared by sol–gel method

Activity	TiO <sub>2</sub>	4% Cu doped TiO <sub>2</sub>	4% Cr doped TiO <sub>2</sub>	4% Ni doped TiO <sub>2</sub>	Ref. drugs
Antifungal					<b>Terbinafine</b>
<i>A. fumigatus</i>	13 ± 1.91	18 ± 1.81	15 ± 1.23	14 ± 1.14	21 ± 1.46
<i>Mucor</i> sp.	18 ± 1.49	15 ± 1.41	15 ± 1.34	19 ± 1.27	25 ± 0.26
<i>F. solani</i>	14 ± 1.32	10 ± 0.19	10 ± 0.149	11 ± 0.707	18 ± 0.808
Antibacterial					<b>Cefixime</b>
<i>E. aerogenes</i>	12 ± 1.51	19 ± 1.477	15 ± 1.473	10 ± 1.41	24 ± 1.11
<i>B. bronchiseptica</i>	18 ± 1.81	20 ± 1.23	14 ± 1.14	20 ± 1.46	25 ± 1.44
<i>S. typhimurium</i>	15 ± 1.41	17 ± 1.34	19 ± 1.27	12 ± 1.21	26 ± 1.12
Antioxidant					
DPPH	85	75	80	85	—
TAC µg AAE per mg sample	115 ± 1.11	80 ± 0.21	95 ± 0.21	120 ± 0.21	—
TRP µg AAE per mg sample	70 ± 0.77	66 ± 0.75	75 ± 1.41	77 ± 0.88	—

**Table 2** Correlation coefficients of antifungal activities of nanoparticles obtained by statistical analysis

	TiO <sub>2</sub>	Cu–TiO <sub>2</sub>	Cr–TiO <sub>2</sub>	Ni–TiO <sub>2</sub>	Terbinafine
TiO <sub>2</sub>	1				
Cu–TiO <sub>2</sub>	−0.047 (0.970)	1			
Cr–TiO <sub>2</sub>	0.327 (0.788)	0.929 (0.242)	1		
Ni–TiO <sub>2</sub>	0.807 (0.402)	0.5 (0.667)	0.786 (0.425)	1	
Terbinafine	0.807 (0.402)	0.552 (0.628)	0.822 (0.386)	0.998 (0.039)	1

(0.2%) doped TiO<sub>2</sub> in ARP-19 cells and dermal cells of balb/c mice where the ARP-9 cells have been found more susceptible to Pt doped TiO<sub>2</sub> and less susceptible to Ni doped TiO<sub>2</sub>.<sup>55</sup> Hence, to establish the toxicological effects of TiO<sub>2</sub> and doped TiO<sub>2</sub> nanoparticles further concentration based cytotoxicity studies are required.

Total reducing power (TRP) was highest for Ni–TiO<sub>2</sub> followed by Cr–TiO<sub>2</sub> and TiO<sub>2</sub> nanoparticles. The values of TAC and TRP coincided well with percent inhibition of DPPH as well (see Table 1).

**3.1.1. Statistical analysis.** Statistical analysis of antibacterial and antifungal activities was performed by using SPSS, where TiO<sub>2</sub>, Cu–TiO<sub>2</sub>, Cr–TiO<sub>2</sub> and Ni–TiO<sub>2</sub> were taken as variables to find out the correlation of antifungal/antibacterial activities between the reference drug and the nanoparticles.

The correlation data between nanoparticles and the reference drug for antifungal activities as presented in the Table 2, is positive and moderate to strong ( $r = 0.807$ ,  $r = 0.552$ ,  $r = 0.822$ ,  $r = 0.998$ ). Data show the strongest correlation of reference drug with Ni–TiO<sub>2</sub>, Cr–TiO<sub>2</sub> and TiO<sub>2</sub> as seen from the correlation value of 0.998, 0.822 and 0.807, respectively. Although the antifungal activities against all the fungal strains are not much significant for Ni–TiO<sub>2</sub>, however the statistical analysis is

representing the overall correlation of doped samples against all three strains with reference drug and is complementing our results of antifungal activities. In addition to the correlation of reference drug with doped samples, the correlation of TiO<sub>2</sub> with doped samples can be seen from statistical data listed in Table 2. TiO<sub>2</sub> has non-significant weak negative correlation with Cu ( $r = -0.047$ ,  $p = 0.97$ ) which indicates less correlation between TiO<sub>2</sub> and Cu–TiO<sub>2</sub> antifungal activities as manifested in our values. Similarly, moderate positive correlation with Cr–TiO<sub>2</sub> ( $r = 0.327$ ,  $p = 0.788$ ), strong positive correlation of Ni–TiO<sub>2</sub> ( $r = 0.842$ ,  $p = 0.363$ ) with pristine TiO<sub>2</sub> is in accordance with our results. Correlations are all non-significant *i.e.*, the  $p$  values are greater than 0.05 due to small sample size ( $n = 3$ ). The large  $p$  values do not manifest invalid results rather it is a consequence of small data set.<sup>56</sup>

Similarly for antibacterial activities TiO<sub>2</sub> has non-significant positive correlation with Cu–TiO<sub>2</sub> ( $r = 0.327$ ,  $p = 0.788$ ), weak negative correlation with Cr–TiO<sub>2</sub> ( $r = -0.189$ ,  $p = 0.879$ ), strong positive correlation with Ni–TiO<sub>2</sub> ( $r = 0.945$ ,  $p = 0.212$ ) (see Table 3). These complement the antibacterial activities given in Table 1. The negative values correspond to the pattern (increasing or decreasing) with the reference. Again, non-significant  $p$  values are due to small data set. Cefixime has

**Table 3** Correlation coefficients of antibacterial activities of nanoparticles obtained by statistical analysis

	TiO <sub>2</sub>	Cu–TiO <sub>2</sub>	Cr–TiO <sub>2</sub>	Ni–TiO <sub>2</sub>	Cefixime
TiO <sub>2</sub>	1				
Cu–TiO <sub>2</sub>	0.327 (0.788)	1			
Cr–TiO <sub>2</sub>	−0.189 (0.879)	−0.990 (0.091)	1		
Ni–TiO <sub>2</sub>	0.945 (0.212)	0.619 (0.575)	−0.500 (0.667)	1	
Cefixime	0.500 (0.667)	−0.655 (0.546)	0.756 (0.454)	0.189 (0.879)	1





non-significant positive correlation with TiO<sub>2</sub> ( $r = 0.500$ ,  $p = 0.667$ ), good negative correlation with Cu-TiO<sub>2</sub> ( $r = -0.655$ ,  $p = 0.546$ ), good positive correlation with Cr-TiO<sub>2</sub> ( $r = 0.756$ ,  $p = 0.454$ ) and weak positive correlation with Ni-TiO<sub>2</sub> ( $r = 0.189$ ,  $p = 0.879$ ).

## 4. Mechanism of action of nanoparticles

The nanoparticles are known to have antimicrobial action (a) due to binding with the cell membrane and thus altering their basic cell functions such as respiration and (b) by penetration of the nanoparticles inside the cell and interaction with sulfur and phosphorous containing compounds, particularly DNA. The cell walls of microbes are composed of metal binding ligands which can reduce the metal ions by donating electrons and thus allowing metals to penetrate inside the cell.<sup>57</sup> The accumulated metal ions can further penetrate into the cell components and damage the cell depending upon the cell's resistance for that metal. The severity of cell damage depends on various factors such as composition of cell wall, the sorption site, and the chemical interaction of the metal ions. Thus titanium ions can enter into the cell membrane and bind with DNA *via* direct bonding<sup>58</sup> thus disrupting their normal function. This in turn prevents the cell replication and ultimately results in the death of the microorganisms.<sup>59</sup> Doping of TiO<sub>2</sub> resulted in the substitution of Ti<sup>4+</sup> ions by the dopant metal (*i.e.* Cu<sup>2+</sup>, Cu<sup>+</sup>, Ni<sup>2+</sup>, Ni<sup>3+</sup> or Cr<sup>3+</sup> in our case) depicted by XPS. We have seen that Cu, Cr and Ni doped TiO<sub>2</sub> have shown better antifungal and antibacterial activities in general as compared to the undoped TiO<sub>2</sub> and similarly reported data for other nanoparticles, indicating stronger interaction and sorption of Cu, Cr and Ni doped TiO<sub>2</sub> into the microbial cells.

## 5. Conclusions

TiO<sub>2</sub> nanoparticles were synthesized and doped with 4% Cu, Ni and Cr *via* sol-gel chemical method and evaluated for their antibacterial, antifungal and antioxidant potential. A comparison of the activities of the doped samples with pristine TiO<sub>2</sub> reveals better performance of Cu-TiO<sub>2</sub> against *A. fumigatus* but lower antifungal activity against *Mucor* sp. and *F. solani*. The antibacterial action of TiO<sub>2</sub> and doped TiO<sub>2</sub> was found lower than the reference drug but better than many reported studies employing nanoparticles as antibacterial agents. Statistical analysis provided an overall comparison of antibacterial/antifungal activities of doped samples with pristine TiO<sub>2</sub> as well as reference drugs. Strong to moderate correlations were predicted from data of antimicrobial activities, however, correlations were non-significant (*i.e.*,  $p > 0.05$ ) due to small sample size. The total antioxidant capacity (TAC) values were found to be the highest for pristine TiO<sub>2</sub> and Ni-TiO<sub>2</sub> nanoparticles. Cu, Ni and Cr led to alteration of the antimicrobial action of TiO<sub>2</sub> nanoparticles due to stronger chemical interaction and sorption of these metals into the microbial cells that led to cell death. The results of the biological assay demonstrated

promising potential of doped TiO<sub>2</sub> as alternative or combination drug for practical applications.

## Author contributions

Dr Shamsa Munir synthesized and characterized the nanoparticles, Dr Faiza Asghar analyzed the data. Dr Saira Tabassum carried out the biological activities of the samples. Dr Faryal Younis performed the statistical analysis of the results. Dr Afzal Shah and Dr Sher Bahadar Khan helped in writing of the manuscript.

## Conflicts of interest

The authors declare no conflict of interest.

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