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RESEARCH PAPER

Antifungal and Antibacterial Properties of Graphene-based Nanomaterials: A Mini-review

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ABSTRACT

In recent years, the availability and use of various antibiotics and antimicrobial agents have resulted in increase of drug resistant pathogens. Therefore, scientist's attention has been diverted to find a suitable replacement for antimicrobial treatment. Graphene (G), as a two-dimensional (2D) carbon-based nanomaterials (CBNs) has a unique physicochemical properties including thermal, optical and electrically conductive activities along with high surface-to-volume ratio and mechanical strength. Also, they have gained significant attention in biomedical application, such as regenerative medicine and drug delivery carriers. With the emergent of nanomaterials over the past decades, there has been a growing interest in using GBNs to develop new antifungal and antimicrobial nanomaterials due to their diverse antifungal and bactericidal mechanisms and relatively low cytotoxicity towards mammalian cells. Numerous reviews on GBNs are available with different perspective. In this review, we summarized the latest progresses towards an understanding of the antifungal and antibacterial properties of GBNs for developing a new antifungal and antibacterial materials

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INTRODUCTION

Currently, the prevalence of antibiotic-resistant bacteria and costs of treatment has become public health concern [1]. Microorganisms (e.g. fungi and bacteria) can easily attach to the surfaces of medical apparatus and colonize on their surfaces. These contaminations are threat to human health and might lead to economic losses [2]. The advances in the field of nanotechnology has created good opportunities to solve these issues. Consequently, synthesis and application of new material to overcome these threats are highly desirable. In recent years, Nano materials have paved the way to create novel antimicrobial agents with exclusive chemical and physical properties [3-5]. Many nanomaterials including silver (Ag) [6, 7], zinc oxide (ZnO) [8], titanium dioxide (TiO_2) [9], iron oxide (Fe_3O_4) [10], copper oxide (CuO) [11], magnesium oxide (MgO) [12], nitric oxide (NO) nanoparticles[13] have been shown to have good antibacterial properties. Thus, expansion of such nanoparticles to combat microbial agents can be an important component for the decontamination process in the near future.

Another kind of nanomaterials that has been investigated widely, are carbon-based nanomaterials. Graphene-based nanomaterials (GBNs) as an important member of this family has been investigated in last decade due to its unique properties, such as large surface-to-volume ratio, mechanical flexibility and thermal stability [14-17]. GBNs are a promising candidate in polymeric

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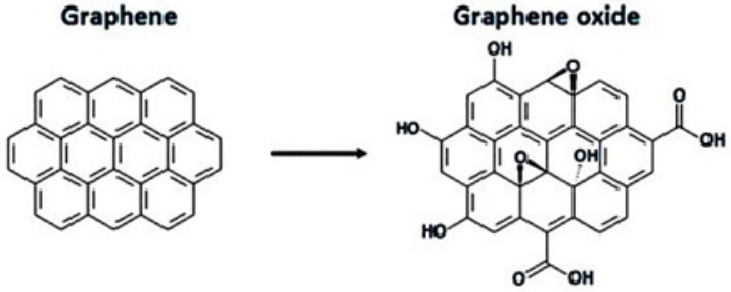

Fig. 1. Graphene (G) and Geraphene oxide (GO) structures [44].

nanocomposite synthesis [18, 19], catalysis [20-23], solar cells [24], biosensors [25], drug delivery and gene delivery [26, 27], imaging [28-30], photothermal therapy [31, 32], tissue engineering [33, 34], and stem cell technology [35, 36].

Moreover, GBNs have established to have antibacterial activities. Graphene oxide (GO) and reduced graphene oxide (rGO) are toxic to both Gram-positive and Gram-negative bacteria [37, 38]. The antifungal and antibacterial applications of GBNs are still relatively novel. In the last decade attention to GBNs has increased exponentially. Numerous reviews on GBNs are available with different perspective [39-42]. In this review, we summarized the latest progresses towards an understanding of the antifungal and antibacterial properties of GBNs. In the first section, we introduced GBNs, and the approaches to their fabrication. The second part briefly looks at their main antifungal and antibacterial mechanism. The last part include several examples of GBNs application as an antifungal and antibacterial nanomaterial.

The GBN family and their fabrication

GBNs can be defined and classified according to their features including morphology and composition, the average of lateral dimension and the number of G layers, which is determined by the atomic carbon/oxygen ratio, material's size and degree of deformability, thickness, specific surface area, and the bending elasticity of the material properties [43] [44]. The morphological and compositional based classification is essential when working with GBNs. Depending on the synthetic methods, G can be prepared in various morphologies for example sheets, platelets, ribbons and quantum dots (QDs). According to this family of nanomaterials, there are various nanostructures including graphene (G), graphene oxide (GO), reduced graphene (rGO), ultrafine graphite that are between 5 to 10 sheets and below 100 nm in thickness, as well as graphene ribbons, graphene quantum dots (GQDs), and pristine graphene (pG) [45-48]. G is a single monolayer of sp^2-bonded carbon with a single atom thick of 2D-model graphite carbon material, which can be fabricated from graphite by scotch-tape technique,[49] chemical exfoliation [50], chemical vapor deposition [51], arc discharge [52], and decomposition of carbide phases [53]. GO structure consists of single-atom-thick carbon sheets with carboxylate groups on the periphery, where they provide pH dependent negative surface charge and colloidal stability. GO is a single layer that can be produced via reaction of crystalline graphite with a mixture of oxidizing agents and sonication or other dispersion methods, (Fig. 1) shows G and GO [44].

Also, it consists of epoxy, hydroxyl and carboxylic acid groups on its surface and edges. rGO is a single layer that can be fabricated from GO through under reducing condition, consisting of high-temperature thermal treatment and chemical treatments with hydrazine (N_2H_4) or other reducing agents [54]. GQDs are small pieces of G with a 2D lateral size less than 100 nm, which have been synthesized by oxidative cleavage [55], hydrothermal or solvothermal method [56-58], macrowave-assisted / ultrasonic-assisted process [59], electrochemical oxidation [60], and carbonization [61]. pG is an apolar and hydrophobic member of GBNs that its dispersibility in aqueous media is improved by oxidizing. Due to unique arrangement of sp^2 bonded carbon atoms, each GBNs can exhibit remarkable different physical, morphological and chemical properties (Fig. 2)

GBNS antifungal and antibacterial mechanisms

The antimicrobial mechanisms responsible for

Fig. 2. GBNs classification

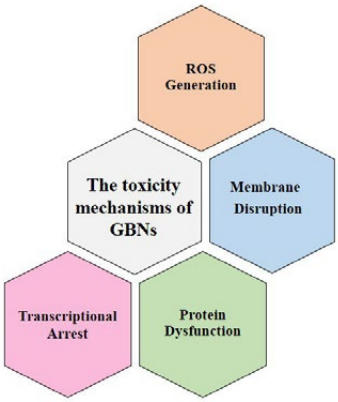

Fig. 3. Different possible mechanisms of antibacterial activity of GBNs

G and GO and other GBNs have been investigated widely. The most common proposed mechanisms are oxidative stress induction, protein dysfunction, membrane damage, and transcriptional arrest (Fig. 3) [62-66]. Generating reactive oxygen species (ROS) is the main reason for nanomaterial toxicity [45, 67-69]. Some antioxidant enzymes, such as glutathione peroxidase or superoxide dismutase, are able to diminish and eliminate ROS generation. By disrupting these enzymes balance, proteins, deoxyribonucleic acid (DNA), and lipids can be damaged. In addition, GO and rGO nanosheets have shown Fenton-like catalytic activity [70, 71]. Hence, there is a structural connection between GBNs and their redox activity that supports the ROS generation ability of GBNs as an antimicrobial mechanisms. Microorganism membrane damage is another possible outcome of hydrophobic interaction between GBNs and the membrane phospholipids that correlate with size of GBNs [72-74]. Although the protein dysfunction and transcriptional arrest were not typically proposed to be the primary antibacterial mechanism of GBNs, sometimes they contribute to the antibacterial activities. Investigations showed that G-Fe_3O_4 leads to *E. coli* protein aggregation, while, the Fe_3O_4 causes less protein degradation by itself, the same as tungsten oxide (WO_3) nanoparticles by itself [63, 64]. These results show that protein dysfunction can be augmented by G structure in comparison to when they are alone. Due to π-π stacking interactions, GBNs can interact with DNA in several groups. For instance, the presence of GO alongside Cu^{2+} can affect DNA cleavage by the chelation of Cu^{2+} ions to oxygen functional groups on the GO nanosheets [75]. Larger GO nanosheets show significant reduction in *E. coli* viability assay (40 μg/mL, 2 h) in comparison to smaller nanosheets [76].

The antifungal activity of GBNs

Fungi are able to easily colonize the surfaces of most materials and devices, and they can quickly spread fungal spores. Human health can be threatened by the formation of fungal contamination that might lead to vast economic losses. Consequently, suitable material against fungi are extremely desired. GBNs antifungal activity was studied by synthesizing different types of GBNs, especially G, GO, and rGO.

The antifungal activity of RGO nanosheets

Antifungal activity of rGO against pathogenic fungi can be used to develop GBNs as a broad spectrum antifungal agents. As a breakthrough, the antifungal activity of rGO (0-500 μg/mL) Sawangphruk et al. [77], studied against three fungal species of *A. niger, A. oryzae,* and *F. oxysporum*, and showed the efficacy of rGO against fungi. The half maximal inhibitory concentration (IC_{50}) values of the rGO against *F. oxysporum, A. niger* and *A. oryzae* were 50, 100, and 100 μg/mL, respectively. The probable antifungal mechanism, is the interaction of rGO nanosheets with the cell walls of fungi. After that the ROS generation of rGO nanosheets was able to chemically react with the organic functional groups of chitin and other polysaccharides on the cell walls of fungi and induce antifungal activity.

The antifungal activity of GO nanosheets

The main antifungal activity of GO is related to its sharp edges that can cause plasma membrane

stress on pathogenic cells. To understand the interaction mechanism of GO, an investigation was performed by Chen et al., [72] on bacterial and fungal pathogens, such as *P. syringae* and *X. campestris pv. Undulosa, F. graminearum,* and *F. oxysporum*. The results showed that GO inhibits nearly 90% of the bacteria and repress 80% macroconidia germination along with partial cell swelling and lysing. The proposed mechanism for the toxicity of GO against both the bacterial and the fungal pathogens was a wide range of GO nanosheets aggregation, which resulted in local perturbation of cell membrane, reduced cell membrane potential, and electrolytes leakage. Moreover, due to the high efficiency of GO for photothermal treatment in the near-infrared (NIR (region, it can be an effective photothermal material. The photothermal treatment of GO was investigated by Khan et al., [78], for antifungal activity to avoid wound healing infection. As a non-invasive and cheap alternative method, this therapy showed remarkable healing property for infected wounds on the dorsal surface of mice (Fig. 4). The antifungal activity of GO on *S. cerevisiae* and *C. utilis* was investigated. Results showed that the laser mediated surface activation of GO causes great antifungal efficiency (Fig. 5)

In a study by Zhu et al., [79] selected *S. cerevisiae* as a model and the potential toxicity of GO was evaluated at the concentration ranging from 0 to 600 mg/mL. The results showed a dose dependent cytotoxicity. The antifungal mechanism was attributed to the synergy of reduced mitochondrial transmembrane potential and increased ROS generation. Hence, the expressions of apoptosis-related genes, such as SOD, Yca1, Nma111 and Nuc1 were significantly changed. Xie et al., [80] exposed *P. chrysosporium*, white rot fungus to GO at the concentration of 0-4 mg/mL for 7 day. Their results showed that low concentrations of GO stimulate the cells growth and causes more acidic pH values of the culture media. In addition, the scanning electron microscopy investigations images exhibited that GO induce the disruption of fiber structure of *P. chrysosporium*, where some very long and thick fibers were formed at 4 mg/mL. In another study, single-walled carbon nanotubes (SWCNTs), multi-walled carbon nanotubes (MWCNTs), GO, rGO, fullerene (C60) and activated carbon (AC)

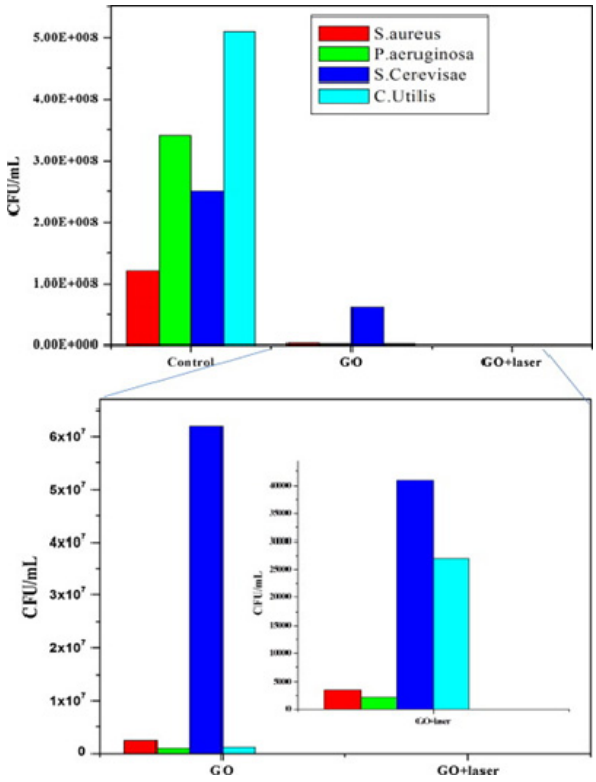

Fig. 4. Standard microdilution protocol of the antibacterial activities of GO and their photothermal treatment [78].

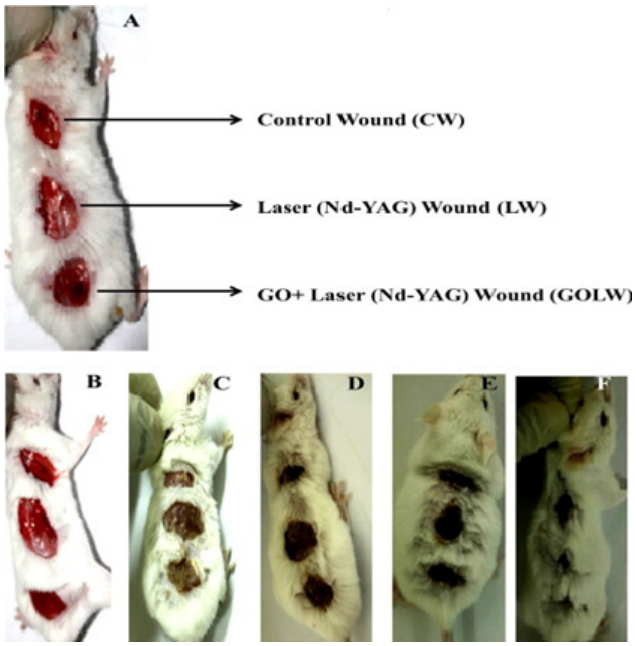

Fig. 5. (a) Location of wounds (CW, LW, and GOLW) on mice model, (b) three fresh wounds mounted on mice dorsal surface, (c) show infection started after 3 days of injected S. aureus on wounds, (d) the picture shows the condition of wound after 6 days of treatment on the wound, (e) the photographs also shows the condition of wound after 9 days of treatment on the wound, and (f) show changed in the treatment of wounds on the dorsal surface of mice model by using GO and Nd-YAG laser [78].

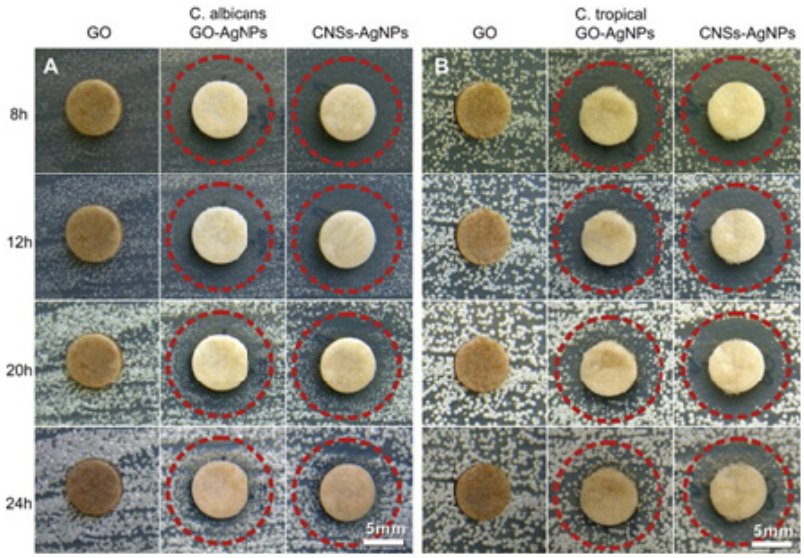

Fig. 6. Inhibition zone of GO, GO-AgNPs and CNSs-AgNPs to (a) C. albicans and (b) C. tropical by the disk diffusion assay [84].

were examined by Wang et al., [81] against two important plant pathogenic fungi, *F. graminearum* and *F. pooae*. The strongest antifungal activity was observed for SWCNTs, followed by MWCNTs, GO, and rGO, where C60 and AC exhibited no noteworthy antifungal activity. The antifungal mechanism included three steps; depositing on the surface of the spores, preventing water uptake and prompting plasmolysis.

The antifungal activity of GO nanocomposites

The synergistic effect of GO and other nanoparticles can be applied to formulate more efficient antimicrobial products [82, 83].

Hence, in recent years scientists have explored Ag nanocomposites more than ever before. To increase antifungal activity of carbon nano scrolls (CNSs), Li et al., [84] filled it with silver nanoparticles (AgNPs) and compared it with antifungal activity of GO-AgNPs nanocomposite. The CNSs-AgNPs exhibited prolonged activity against *C. albicans* and *C. tropical* in comparison with the GO-AgNPs nanocomposites. The results of antifungal activities of GO and its AgNPs nanocomposites showed that there were no inhibition zone for GO; while for GO-AgNPs samples a clear inhibition zones were observed. By increasing incubation time, the inhabitation zone become smaller, and the viable fungal colony increased (Fig. 6). Moreover, the inhibition zone of *C. albicans* was much smaller than the *C. tropical* in the same concentration of GO-AgNPs and same incubation time.

In another study by Chen et al., [85] they explored antifungal activity of GO-AgNPs nanocomposite against phytopathogen *F. graminearum in vitro* and *in vivo*. The GO-AgNPs nanocomposite showed to be three to seven-times more potent than pure AgNPs and GO, respectively. The antifungal mechanism was based on the notable synergistic effect of GO-AgNPs, making physical injury and generating chemical reactive oxygen species. In addition to silver nanocomposites, G-TiO_2 nanocomposite was investigated by Karimi et al., [86] as a new route to prepare antibacterial and antifungal cotton fabric without toxicity. The result showed that G-TiO_2 nanocomposite-coated cotton has an excellent antibacterial and antifungal activity on bacteria (*E. coli and S. aureus*) and fungi (*C. albicans*). Indeed, G was added to TiO_2 nanoparticles aiming to facilitate effective bacterial decomposition by increasing the contact between nanoparticles and microorganisms. Furthermore, fabrics treated with GO did not show any antimicrobial activity. Graphene oxide-borneol (GOB) composite, is borneol-grafting with great antifungal effect on *M. racemosus*. In comparison with GO nanosheet, GOB composite displayed no significant antifungal activity. In addition to long-term antifungal effect of GOB composite, the fallen spore does not germinate even after 5 days [87]. The studies are summarized in the Table 1.

The antibacterial activity of GBNs

World Health Organization (WHO) reports showed that in recent years, death of millions of people has been due to the diseases created by bacterial infections [88]. Thus, the treatment of bacterial diseases using antimicrobial drugs are vital. Also, there is an urgent need for novel and effective antimicrobial agents to fight against the bacterial infections [89, 90]. G has been found to be a capable candidate as an antibacterial material due to its bacterial toxicity. Therefore, the toxicity investigation of GBNs in microorganisms as a

Table 1. The antifungal activity of GBNs

GBNs	Treatment concentration	Fungal	Summary results	Reference
rGO	0 and 500 µg/mL	*A. niger, A. oryzae*, *F. oxysporum*	rGO was effective against on the nonpathogenic *A. oryzae* and on the pathogenic *A. niger* and *F. oxysporum*	[77]
GO	500 µg/mL	*F.* graminearum, *F. oxysporum*	nearly 90% of the bacteria and repressed 80% macroconidia germination along with partial cell swelling and lysis	[72]
SWCNTs, MWCNT, GO, rGO, C60, AC	0 and 500 µg/mL	*F. graminearum*, *F. poae*	No noteworthy antifungal activity was detected for C60 and AC	[81]
GO	0 to 600 µg/mL	*S. cerevisiae*	Dose dependent cytotoxicity	[79]
GO	0–4 mg/mL	*P. chrysosporium*	Induced the disruption of the fiber structure	[80]
GO-Ag	0-8 µg/mL	*C. albicans*, *C. tropical*	CNSs-AgNPs exhibited ideal lengthened activities against Candida albicans and Candida tropical compared with the GO–AgNPs nanocomposites based on silver nanoparticles directly deposited on the surface of grapheme oxides, which is caused by CNS-AgNPs' controlled durative slow-releasing of silver ion	[84]
GO-AgNPs	-	*F. graminearum*	Exhibited nearly a three and seven-fold increase of inhibition efficiency over pure AgNPs and GO making physical injury and chemical reactive oxygen species generation	[85]
GOB	-	*M. racemosus*	It is also worth noting that on the GOB sample the fallen spore does not germinate even after 5 days	[87]
G-TiO_2	-	*C. albicans*	They had negligible toxicity and possessed excellent antimicrobial activity	[86]

new class of antibacterial material, is vital for their production in environmental and clinical applications [37].

The antibacterial activity of RGO and GO nanosheets

For the first time Hu et al., [37] investigated antibacterial properties of GBNs by studying the interaction of Gram-negative bacteria, *E. coli* DH_{5a} with GO. The results showed that GO at a concentration of 85 µg/mL could significantly suppress the growth of *E. coli,* while having low cytotoxicity for mammalian cells. Transmission electron microscope (TEM) analysis showed that antibacterial properties were attributed to damage cell membrane, which results in leakage of the cytoplasm (Fig. 7). They further found that macroscopic GO papers prepared by vacuum filtration of the GO suspension could effectively restrain the growth of *E. coli*.

Also, dental caries and periodontal diseases are related to microbes, such as S. mutans, P. gingivalis and F. nucleatum. The antibacterial influence of GO was examined by He et al., [91]. TEM analysis showed GO can disrupt the cell walls, membrane integrity and leakage of the intracellular contents. The antibacterial activity were also observed for a UV irradiated GO by Veerapandian et al., [92] that showed higher antibacterial activity for UV irradiated GO due to more cell disruption action than typical GO nanosheets. The antibacterial activity of GO and rGO was evaluated by Gurunathan et al., [93] using cell viability, ROS generation and DNA fragmentation assays. The results suggest that GO and rGO possessed a time and concentration dependent antimicrobial activity against *E. coli.* In comparison with rGO, GO formed more superoxide anions than rGO. Therefore, the bacterial cell death might be due to oxidative stress that consequently leads to DNA fragmentation. The antibacterial activity of pG, GO, and rGO against food-borne bacterial pathogens, such as *L. monocytogenes* and *S. enterica* were evaluated by Kurantowicz et al., [94]. This study reported GO to have the highest antibacterial activity due to bacteria adherence at the surface of GO, while with pG and rGO, they adhered to their edges. Also, Wu et al.,[95] observed a concentration dependent antibacterial activity for GO against K. pneumonae.

Some reports showed that GO exhibited no significant antimicrobial effect against *E. coli* or *P. aeruginosa* bacteria alone; however, Ag nanoparticle-modified GO could effectively inhibit bacterial growth. Interestingly, another research showed that GO presented neither intrinsic

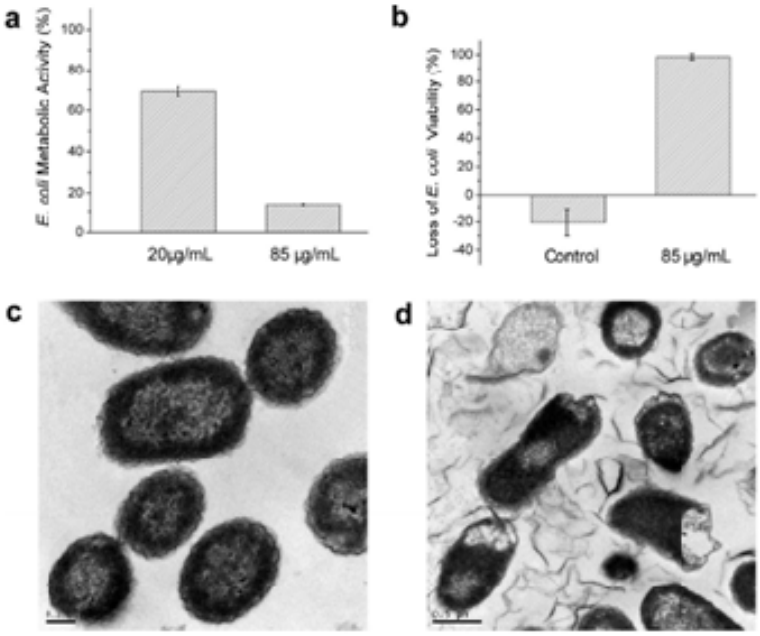

Fig. 7. Antibacterial activity of GO. (a) Metabolic activity of E. coli incubation with 20 and 85 mg/mL of GO at 37 °C for 2 h. (b) Antibacterial activity of 85 mg/mL GO against E. coli DH5 cells. (c,d) TEM images of untreated E. coli (c) and E. coli exposed to GO nanosheets (d) at 37 ˚C for 2 h [37].

Table 2. The antibacterial activity of GBNs

GBNs	Treatment concentration	Fungal	Summary results	Reference
rGO	0 and 500 µg/mL	*A. niger, A. oryzae*, *F. oxysporum*	rGO was effective against on the nonpathogenic *A. oryzae* and on the pathogenic *A. niger* and *F. oxysporum*	[77]
GO	500 µg/mL	*F.* graminearum, *F. oxysporum*	nearly 90% of the bacteria and repressed 80% macroconidia germination along with partial cell swelling and lysis	[72]
SWCNTs, MWCNT, GO, rGO, C60, AC	0 and 500 µg/mL	*F. graminearum*, *F. poae*	No noteworthy antifungal activity was detected for C60 and AC	[81]
GO	0 to 600 µg/mL	*S. cerevisiae*	Dose dependent cytotoxicity	[79]
GO	0–4 mg/mL	*P. chrysosporium*	Induced the disruption of the fiber structure	[80]
GO-Ag	0-8 µg/mL	*C. albicans*, *C. tropical*	CNSs-AgNPs exhibited ideal lengthened activities against Candida albicans and Candida tropical compared with the GO–AgNPs nanocomposites based on silver nanoparticles directly deposited on the surface of grapheme oxides, which is caused by CNS-AgNPs' controlled durative slow-releasing of silver ion	[84]
GO-AgNPs	-	*F. graminearum*	Exhibited nearly a three and seven-fold increase of inhibition efficiency over pure AgNPs and GO making physical injury and chemical reactive oxygen species generation	[85]
GOB	-	*M. racemosus*	It is also worth noting that on the GOB sample the fallen spore does not germinate even after 5 days	[87]
G-TiO_2	-	*C. albicans*	They had negligible toxicity and possessed excellent antimicrobial activity	[86]

antibacterial functions nor cytotoxicity properties to mammalian cells [96, 97]. Several studies evaluate the antibacterial activity of Gram-negative and Gram-positive bacteria and showed that GO inhibited Gram-positive bacteria more effectively than Gram-negative bacteria, while some Gram-negative bacteria, such as *E. coli*, were resistant to GO [98]. *E. coli*, gram-negative and *S. aureus*, gram-positive were selected by Akhavan et al., [38] as model bacteria to investigate the bacterial toxicity of GO and rGO nanowalls. Results showed bacteria interaction between the very sharp edges of the nanowalls causes cell membrane damage. In addition, the cell membrane of Gram-positive *S. aureus* was strictly damaged in comparison to the Gram-negative *E. coli,* which was due to sharp edges and better charge-transfer ability of rGO nanowalls and bacteria. Moreover, rGO nanowalls exhibited stronger antibacterial activity than GO nanowalls. The antibacterial mechanism of G was also studied by exploring the interactions between different types of GBNs with the Gram-negative *E. coli*. Again, GO showed the strongest antibacterial activity under similar concentrations and incubation time among all materials, followed by rGO, graphite, and graphite oxide. Their antibacterial mechanisms were attributed to the synergy of the membrane stress and oxidative stress induced by the interactions between bacteria and materials. However, by increasing the concentration of GBNs, the inhibition activity against the growth of Gram-negative *E. coli* and Gram-positive *B. subtilis* was increased [99]. A similar study by Chen et al., [100] studied the antibacterial activity of rGO and GO. And, GO showed higher bactericidal effects due to its sharp edges and production of ROS.

Furthermore, disrupting the membrane integrity, ROS generation can be potentially made by antibacterial activity. Krishnamoorthy et al., [101] examined antibacterial activity of G nanosheets that can be applied in the development of biomedical devices. They observed that G nanosheets have antibacterial activities against *E. coli, S. typhimurium, E. faecalis*, and *B. subtilis*. These results support the idea of G, as a hopeful antibacterial material with low mammalian cell cytotoxicity. Conversely, recent studies have shown that GO might miss any antibacterial properties [96]. These studies are summarized in Table 2.

The antibacterial activity of GBNs nanocomposites

The advancement of nanotechnology provides opportunities to prepare antibacterial G nanocomposits. Antibacterial properties of GBNs include ZnO/GO [102], TiO_2/GO [103], Ti-GO-Ag [104], and CuO/rGO nanocomposites [105] have been explored recently. To date, Ag nanoparticle-modified GO films, not bare GO, have exhibited stronger antibacterial activity. The oxygen-containing functional group of GO adhere to lipopolysaccharides of bacteria through hydrogen

bonds formation between the lipopolysaccharides of the bacteria and the oxygen-containing functional groups of GO [106-108]. Hence, GO decreases the intake of nutrition from the media and increases the interaction between Ag nanoparticles and bacteria [109]. Ag can also disrupt the bacterial membrane that prevents the respiration and replication of bacteria, which leads to cell death [110]. The Ag-modified GO nanostructure exerts its antibacterial effect through a "capturing-killing process" that increases the deposition of bacteria, as well as the contact between cells and Ag-modified GO nanoparticles [96]. Due to these controversial findings, further studies should be carried out to determine the detailed mechanisms and controlling factors with respect to the interaction between GBNs and microbes. There are some studies that have shown recent progress in antimicrobial activity of G nanocomposits [111, 112].

CONCLUSION

Today antibiotic resistance has emerged as a strong health concern worldwide. To eradicate this problem, synthesis and application of new antimicrobial materials are necessary and required. Emerging nanotechnology has provided a suitable platform to resolve the problem of resistance, by the use of antimicrobial nanomaterials, identified as nanomaterials with antibacterial properties to contest infections by antibiotic-resistant bacteria. Several investigations have focused on the antimicrobial mechanism of GBNS, but a deeper and more consistent understanding of the underlying molecular mechanisms is required. Recent studies revealed that GBNs have high efficiency in antifungal and antibacterial activity via damage of cell membranes and other mechanisms. To increase GBNs antimicrobial effect, nanocomposite preparation by the incorporation of inorganic nanostructures has increased their antimicrobial properties. GBNs preferably as a new group of nanomaterials can be used in nanomedicine in the near future.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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