Graphene Oxide Composites as Environmentally-Friendly Enzyme Inhibitors

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Abstract: This work presents a concise approach to synthesizing water-soluble and homogeneous nanocomposites of "graphene oxide/phosphoramide ligands" (GO/L) without the need for additional reducing agents. These nanocomposites have the potential to exhibit enhanced biological applications, such as antifungal, enzyme immobilization and antibacterial activities, compared to bare graphene oxide (GO) and phosphoramides. This research delves into the detailed investigation of three GO-based membranes, where GO serves as substrate for phosphoramide ligands. It has been demonstrated that these membranes possess wider interlayer D-spacing compared to GO. The compounds were characterized using various analytical techniques, including IR and NMR spectroscopy, AFM, XRD analysis, and UV-visible spectroscopy. Furthermore, this study delved into the mechanisms underlying the immobilization of Acetylcholinesterase enzyme (AChE) by GO and its newly synthesized derivatives. The results obtained from this study demonstrated that the GO/L films possessed enhanced biological activity compared to both phosphoramide ligands and bare GO alone. The objective of this research was to develop simple and efficient methods for synthesizing potent compounds that can find applications in various biological fields. Notably, these compounds offer advantages in terms of their environmental friendliness, cost-effectiveness, and time efficiency. The findings of this investigation contribute to a deeper understanding of GO-based membranes and open possibilities for rational design in diverse areas such as drug development and food industry.

Keywords: Acetylcholinesterase enzyme, Biological applications, Graphene Oxide, Phosphoramide, Fluorescence.

INTRODUCTION

Graphene, a two-dimensional material composed of a single layer of carbon atoms arranged in a honeycomb lattice, has attracted considerable interest due to its remarkable thermal, mechanical, and electronic properties (Holm and Baron, 2002). Additionally, graphene shows great promise for various biological applications. However, a major challenge with graphene is its poor dispersion in organic solvents and aqueous solutions (Soltani *et al*. 2010). Achieving stable dispersion is crucial for enabling its effective utilization in a wide range of applications, such as electronics, energy storage, and biomedical devices (Akamatsu *et al*. 2011). To overcome this challenge, graphene oxide sheets (GO) are commonly used in experiments due to their wide range of oxygen-containing groups (*e.g*., hydroxyl, epoxide, and carboxylic) on their surfaces. GO and its nanocomposites hold great potential for applications spanning biomedical science (Gholivand *et al*.2017) energy, and safety concerns. In the biomedical field, they have shown promise in therapeutics, such as drug screening, targeted delivery, diagnostics, vaccine production, surgical intervention, gene delivery, the agnostics, biomarker-assisted mapping, and studying the toxicity of pathogenic organisms. Additionally, they find practical utility in polymer material fabrication, particularly for enhancing flame retardancy and in energy-related applications, such as molecular-level electronics, sensors, solar cells, photovoltaic, heavy metal detoxification, devices,, interfacial electron transfer, molecular diagnostics and catalysis. The abundance of surface functional groups on GO provides numerous reaction sites for linking external compounds, including small molecules, polymers, bio macromolecules and, inorganic nanoparticles, , without requiring additional surface modification or cross-linking reagents. GO's oxygen-containing groups play a crucial role in its biological and biomedical applications (Sparks *et al*. 2015). The laboratory-scale fabrication of GO is feasible and cost-effective. GO sheets serve as an ideal solid substrate for enzyme immobilization, antibacterial and antifungal purposes (Chen *et al*. 2018; Moghtaderi *et al*. 2017). One prominent enzyme that has been extensively studied for its inhibition by various substances is acetylcholinesterase (AChE). AChE is the main source of metabolism of the neurotransmitter acetylcholine, and its inhibition would result in therapeutic applications (*e.g*., drugs for Alzheimer's disease) or neurotoxic consequences (*e.g*., pesticides). Pesticides based on phosphor amides, which are commonly used on a large scale, exhibit numerous side effects and are environmentally unfriendly. Furthermore, these compounds often have

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low solubility in water and aqueous solutions, posing challenges in the synthesis process (He *et al*. 2021). This study aims to address these issues, particularly the side effects associated with harmful materials. New nanocomposites have been synthesized to improve solubility in water and other solvents, crucial for biological studies, while also exhibiting significantly enhanced efficacy in targeting bacteria, fungi, and proteins compared to previous compounds. The main advantages of this study compared to previous works include the simplicity of synthesis and its potential for economic feasibility in industry. The synthesis process is straightforward, requiring simple tools, and even small quantities of these nanocomposites can have a substantial impact over a large area, providing opportunities for further investment in this valuable field.

METHODS

Graphene Oxide (GO) Preparation

GO was synthesized by utilizing natural graphite powder and through a modified Hummers method (Gholivand *et al*.2021b)

Synthesis of Phosphoramide Derivatives

To prepare phosphoramides ligands (L) numbered 1 to 3, a solution was prepared by combining 2 mmol of the corresponding amines in acetonitrile with 1 mmol of the relevant phosphoric dichloride derivatives. The resulting mixture was cooled to -8 °C and stirred for 6 hours. Afterward, the solvent was evaporated, and the resulting product was purified by washing it with chloroform (Tung *et al*.2009). For the synthesis of L3, L4, and L5, a mixture was prepared by adding 1 mmol of the corresponding amines to dichloromethane containing 1 mmol of Na2SO or Et3N salt (Stankovich *et al*. 2007). The mixture was stirred for 10 minutes at -5 °C with the use of ice to maintain the temperature (Biazar and Ferdowsi 2020c). Then, 1 mmol of the phosphoric dichloride derivatives was added to the mixture. To produce L2 and L6, a solution was prepared by mixing 1 mmol of the amine with 1.5 mmol of Et3N salt in THF (tetrahydrofuran) solvent (Zhang *et al*. 2010). The mixture was stirred at a temperature of -5 to -8 °C for about 24 hours. Afterward, the solvent was evaporated, and the resulting product was washed with water to remove any remaining salt. The product was further purified by washing with dichloromethane. While stirring the mixture at a temperature of -5 to -8 °C, 1 mmol of the phosphoric dichloride derivatives was added and the mixture was stirred for approximately 24 hours. After the solvent was evaporated, the resulting product was washed with water to remove any remaining salt. Subsequently, the product was washed with dichloromethane to purify it. The ligands obtained from this synthesis were characterized using various spectroscopic techniques, including H NMR (proton nuclear magnetic resonance), NMR (nuclear magnetic resonance), P NMR (phosphorus nuclear magnetic resonance), and IR (infrared) spectroscopy (Dinpashoh *et al*. 2022). These characterization methods provide valuable information about the structure and properties of the synthesized ligands. Additional details and spectral data for the synthesized ligands can be found in the Supplementary Information file (S file), which accompanies this article. The synthesis of the remaining ligands not specifically mentioned in this paper followed the procedure outlined in reference (Mohan and Panicker. 2012).

THREE PARTIAL GO/L/SN NANO-COMPOSITES ARRANGEMENT

GO/L3/Sn

In this investigation, a new procedure was developed to synthesize stable water-dispersible nanocomposites of "GO/L" (graphene oxide with ligands). The synthesis process involved the combination of FeCl3 • 2H2O (0.0005 g) and L3 (0.01 g), which were heated to 210 °C for 30 minutes to form the FeCl3.L3 complex (Goncalves *et al*. 2009). Next, a dispersion of GO (0.02 g) in ethanol was added to the FeCl3.L3 complex, and the solution was refluxed for 4 hours. Then, SnCl2 • 2H2O (0.005 g) was introduced to the solution, and the refluxing process continued for another 4 hours. The resulting mixture was transferred into an autoclave and subjected to hydrothermal treatment at 120 °C for 8 hours (Gholivand *et al*.2021b).Afterward, the nanocomposite was washed with water and ethanol using centrifugation. To ensure complete drying, it was left at 150 °C for 2 hours. X-ray spectroscopy studies confirmed the successful synthesis of the three-part composite, GO/L3/Sn (graphene oxide with ligand L3 and Sn). These nanocomposites exhibited stability and dispersion in water in the form of a colloidal solution. The synthesis process and characterization studies, including X-ray spectroscopy, were conducted to confirm the successful formation of the desired nanocomposite (Wu *et al*. 2012).

GO/L2/Sn

To synthesize the L2 composite, 0.01 g of L2 was dissolved in ethanol. Then, 0.02 g of dispersed GO in

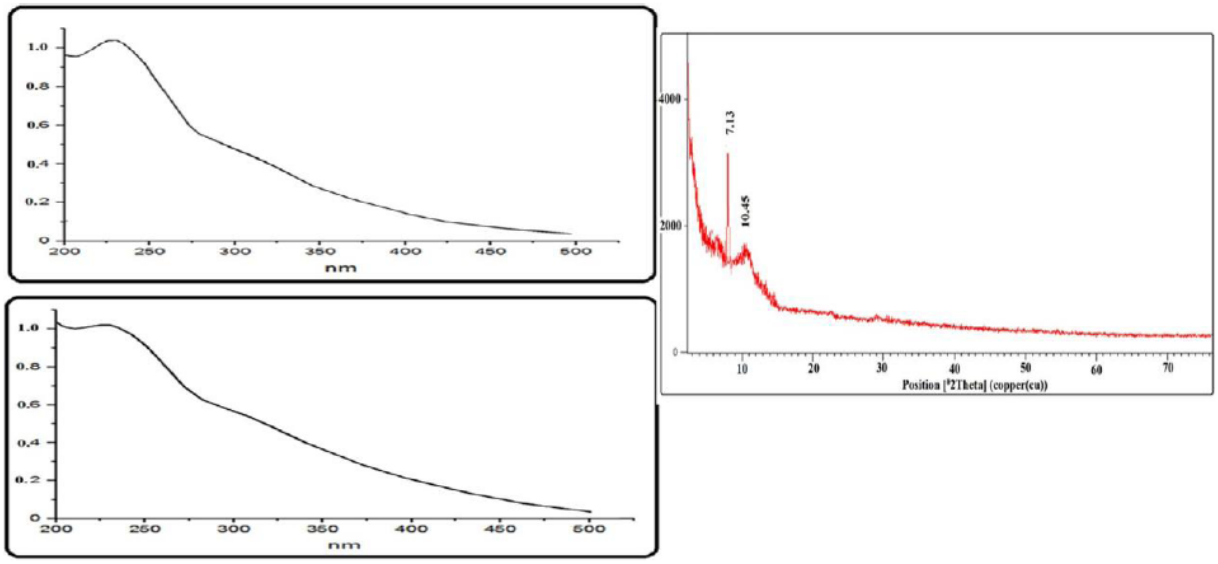

Figure 1: (**A**). UV-visible spectrum of GO in ethanol solvent. (**B**) UV-visible spectrum of GO/L1 (**C**) XRD scatter of GO/L1.

ethanol was added to the solution. The same procedure as the L3 composite was followed for this solution (Lomeda *et al*. 2008).

GO/L1 Nano-Composite Arrangement

To synthesize the L1 composite, 0.01 g of GO was dispersed in 5 mL of ethanol. Then, 0.004 g of L1 was added to the solution. The mixture was stirred for approximately 12 hours at room temperature. After evaporating the solvent, the resulting product was washed several times with water (Isazadeh *et al*. 2017; Biazar *et al* 2020a; Biazar *et al*. 2020b.

Study of Anti-Acetylcholinesterase

For many years, Themephos has been extensively used as a pesticide by farmers (Gholivand *et al*.2017). However, this compound has several adverse effects, prompting efforts to find alternative compounds (Gholivand *et al*.2017). Since Themephos targets the AChE enzyme, we focused our study on this particular enzyme. In this experiment, we used AChE from drosophila, which has been shown through various spectra to have a high similarity to human AChE. In a previous paper (Gholivand *et al*.2021a). we introduced a novel approach to assess the inhibitory potency of phosphoramide compounds using fluorescence spectroscopy and emission spectra. This method has proven to be reliable, sensitive, and time-saving, as well as relatively simple. In this article, we applied this sensitive technique to evaluate the inhibitory capabilities of the newly synthesized GO nanocomposites (Dubin *et al*. 2010). The fluorescence spectra exhibited a linear correlation with both the concentration of the fluorophore and pH levels, further validating the effectiveness of this method. Our focus for spectroscopy was on the tryptophan region of the enzyme. This region emits light at 340 nm, and upon inhibition, the intensity of this emission decreases. By measuring the reduction in intensity, we can determine the inhibitory potency of the compounds. The IC50 value, which represents the concentration of the inhibitor required to reduce the enzyme's emission to 50% of its initial maximum, is used to quantify the inhibitory potency (Li *et al*. 2008; Lagunin *et al*. 2000). To prepare the solutions, we first determined the optimal concentration for each compound as a standard. From the standard solutions, different concentrations were prepared to obtain a range of concentrations for testing. In order to achieve solubility and stability of the phosphoramide ligands in the buffer solution, we determined the optimal ratio of ethanol/water. The ligands were dissolved in 100 µl of ethanol, and then water was added to reach the desired concentration. This specific ratio of ethanol was found to prevent sedimentation of the ligands and ensure their solubility in the solution. Because the Quartz cell had a volume of 350 µl, the small amount of ethanol used had a minimal impact on the accuracy of the data. Furthermore, any emission from ethanol was removed from the spectra during the experiment. Subsequently, 25 µmol/L of AChE was added to the cell containing a 10 mmol/L pH 7.4 buffer, and the mixture was incubated at room temperature for 2 minutes. The emission of AChE was then measured (Gholivand *et al*.2021a).

RESULTS AND DISCUSSION

Synthesis and Characterization of Ligands and GO

The synthesized ligands and GO were characterized using various methods. The ligands were characterized through HNMR, PNMR, and IR spectroscopy, as shown in Figure **1s** of the Supplementary Information. GO was characterized using AFM, XRD, IR, and UV-visible spectroscopy. The XRD spectrum of GO, as depicted in Figure **2s**, exhibited similarities to standard reported spectra (Zhang *et al*. 2009) Notably, the sharp graphite peak observed at 26.7° was absent, while a minor intensity peak at 11.1° corresponding to a D-spacing of 8.29 Å (0.01 reflection of GO) was evident. These findings support the assumption of fully oxidized graphite. The increased gap between carbon sheets and the larger size of GO sheets can be attributed to the penetration of inter-planar groups, displacement of sp3-hybridized carbon atoms, and the presence of covalently bound oxygen atoms (Zhang *et al*. 2009; Deb *et al*. 2021; Paredes *et al*. 2008).

THREE PARTIAL GO/L/SN NANO-COMPOSITES

GO/L3/Sn

To verify the formation of the GO/L3/Sn nanocomposite, the synthesized sheets were compared to both bare L3 and GO using various spectroscopic and characterization techniques. X-ray diffraction (XRD) analysis was utilized as the initial method. The XRD spectra of L3 (Figure **1A**) displayed a prominent peak at a D-spacing of 12.08 Å, which corresponds to the "P=O" functionality (Gholivand *et al*.2021b; Gholivand *et al*. 2014). This peak was also observed in the XRD spectra of the GO/L3/Sn nanocomposite, indicating the presence of L3 in the composite material. Furthermore, the XRD spectrum of GO showed a distinct peak at a D-spacing of 8.3 Å, confirming the characteristic structure of graphene oxide in the nanocomposite. The XRD spectra of L3 displayed a prominent peak at a D-spacing of 12.08 Å, which corresponds to the "P=O" functionality. This peak was also observed in the XRD spectra of the GO/L3/Sn nanocomposite, indicating the presence of

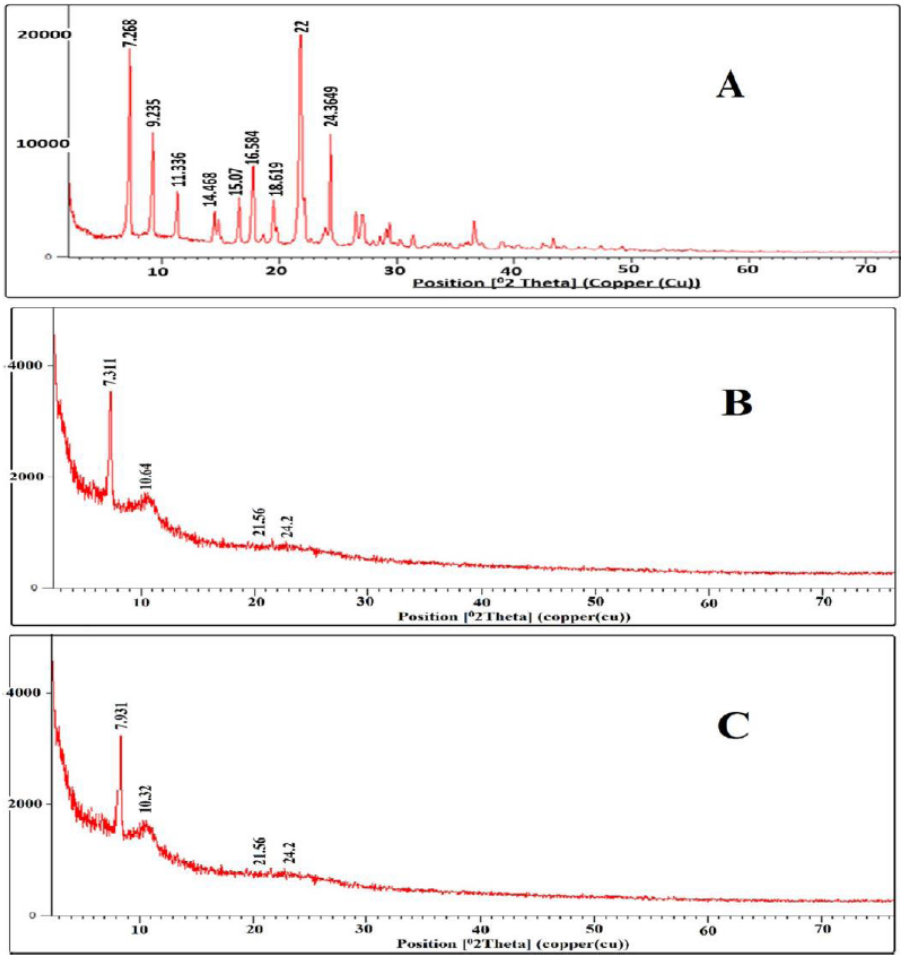

Figure 2: XRD spectrum of **A**) L3. **B**) GO/L3/Sn nanocomposite **C**) GO/L2/Sn nanocomposite.

L3 in the composite material. Furthermore, the XRD spectrum of GO showed a distinct peak at a D-spacing of 8.3 Å, confirming the characteristic structure of graphene oxide in the nanocomposite.

GO/L2/Sn

The XRD analysis of this compound revealed peaks corresponding to the Sn-GO bond and the GO-P=O bond, similar to the GO/L3/Sn composite. Additionally, the presence of 1181 nm in the IR spectra, corresponding to P=O in the composite, further confirmed the adsorption of L2 on the GO surface. The presence of <1100 nm peaks related to NH and Sn indicated an interaction between L2 and GO, suggesting the formation of this composite.

AChE inhibition

AChE inhibition can be achieved by directly immobilizing enzyme molecules on graphene oxide (GO) due to its natural functional groups, such as π-π stacking and hydrophobic interactions (Zhang *et al*.2013; Brown and Wright, 2016). This approach allows for the efficient use of phosphoramides as a bed on GO, resulting in a significant increase in GO's effectiveness against pesticides while reducing the amount of substances needed. To determine the inhibitory activity of the compounds, fluorescence spectroscopy can be used, focusing on the tryptophan emission spectra at 340 nm. The hydrophobic components of biomolecules interact strongly with GO, potentially altering their conformation and disrupting their biological activity [43,66]. In this study, it was observed that the inhibitory potency of phosphoramide ligands was greatly enhanced when combined with graphene oxide (GO) as a support material. The utilization of GO nanocomposites offers several advantages, such as the ability to solubilize water-insoluble phosphoramides and a significant reduction in pesticide usage. This innovative approach demonstrates the potential of GO as an adsorbent material for phosphorus-based pesticides, enabling their efficient removal from the environment using magnetic fields, thanks to the magnetic properties of GO [67, 42, 28, 3]. The IC50 values of the ligand, GO, and two partial GOs showed significant variation (from 84 mM for L1 to 0.013 mM for GO/L1, Figure **5**). The mechanism of interaction indicates that GO sheets act as inhibitors by covering the active site hole, preventing substrate access to the gorge and active site. The epoxy groups of GO interact with Trp-amino acids and cover the hole, rendering substrates unable to bind. The active site of Acetylcholinesterase (AChE) primarily consists of aromatic residues, particularly tryptophans (Trp), which create binding sites for cationic substrates. While acetylcholine forms a π-

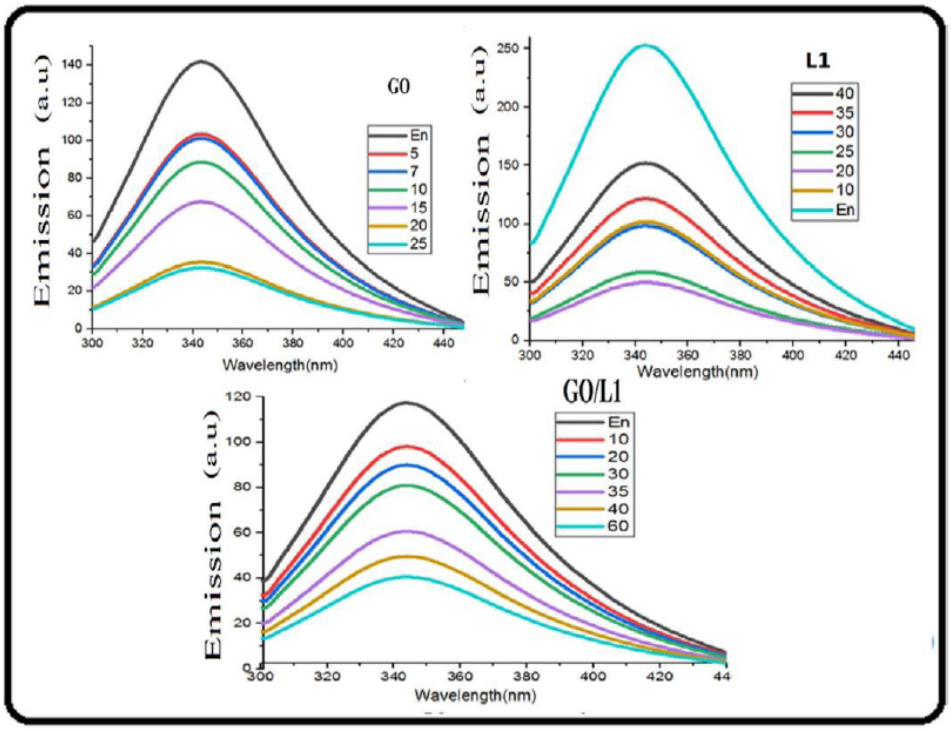

Figure 3: Fluorescence spectra of AChE in the presence of Different substances.

Table1: Physical Constants of the Reaction between the Ligands and AChE

Sample	L1	L7	L8	L9	L10
Ksv	5.454×10^{4}	6.42×10^{3}	4.2×10^{3}	17.3×10^{3}	0.336×10^{3}
Kq	5.454×10^{12}	6.42×10^{11}	4.2×10^{11}	17.3×10^{11}	0.336×10^{11}
Kb	59.36	45.83	44.13	315.9	92.41
R square	0.9673	0.9953	0.8873	0.9771	0.8585
Bmax	56.79	124.0	78.89	314.3	101.3

cation interaction with AChE, phosphorus compounds exhibit higher inhibitory potency (Gholivand *et al*.2021a). These compounds rapidly react with Trp in the active site, forming an oxygen-phosphorus bond that irreversibly modifies the catalytic tryptophan, resulting in the inactivation of the enzyme. Among the aromatic/aliphatic derivatives of Temephos, the ones exhibiting the best interaction with AChE are achieved through non-covalent bonds Gholivand *et al*.2017; Sharifi *et al*. 2017).Ligand L10 exhibits the highest inhibitory activity among the bare ligands. Molecular Docking (MD) analysis of L10 reveals its rigid structure, particularly in the P-C bond, which enables it to effectively interact with the amino acids in the active site of AChE. Figure **7** illustrates the D3 structure of L10 obtained from MD simulations. The physical constants related to the ligand-AChE reaction, including Ksv and Kq associated with the IC50 concentration, are provided in Table **1**.

CONCLUTION

In summary, graphene-based materials have made significant progress in the past decade and are now widely used in various scientific fields, particularly in biology. These materials have diverse applications ranging from targeted drug delivery to heavy metal, detoxification solar cells, and sensors,. The interaction between graphene oxide (GO) and biomacromolecules, like enzymes and DNA, has been demonstrated, indicating their potential impact on biochemical properties. The synthesized graphene oxide-phosphoamide nanocomposites in this study have shown high efficiency in antibacterial and antifungal activities, as well as enzyme immobilization. These nanocomposites can be utilized for enzyme immobilization, drug screening. DNA detection, theragnostics ,vaccine production , diagnostics, gene delivery, surgical interventions, toxicity, , and biomarker-assisted mapping, assessment of pathogens.The advantages of this study include the introduction of facile methods for synthesizing these unique compounds that are not only also environmentally friendly but also active in various biological areas compared to harmful compounds like Temephose. These materials are also cost-effective and time-saving. Further research on GO-based membranes and their applications in the agricultural industry can potentially revolutionize the field. The hope is that these investigations will enhance our understanding of GO-based membranes and enable future rational designs for applications in drug design and food industry.

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