Research Article

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# Anticancer and Antibacterial Evaluation of Pure Poly(*o*-Toluidine) for Tissue Engineering and Cancer Treatment

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## ABSTRACT

Chemical oxidative polymerization was employed to synthesize pure poly (*ortho*-toluidine) (POT). The synthesized POT was characterized using XRD, FT-IR, and SEM analyses. Additionally, the samples were subjected to biological evaluation. The antibacterial activity of POT was tested against both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria. Notably, *E. coli* displayed significant susceptibility to POT's antibacterial effects, especially at higher concentrations. Furthermore, *in vitro* anticancer experiments were conducted on MG-63 bone cancer cells to assess the cytotoxicity of POT. Pristine POT exhibited the highest level of cytotoxicity, as evidenced by an $IC_{50}$ value of 83.15 g/ml. In summary, this investigation highlights the robust antibacterial and anticancer activities of POT. These findings suggest potential applications of POT in areas such as tissue engineering scaffolds, anticancer therapies, and various biomedical uses.

**Keywords:** Poly(*o*-toluidine); Cytotoxicity; Human bone cancer cells; Antibacterial activity.

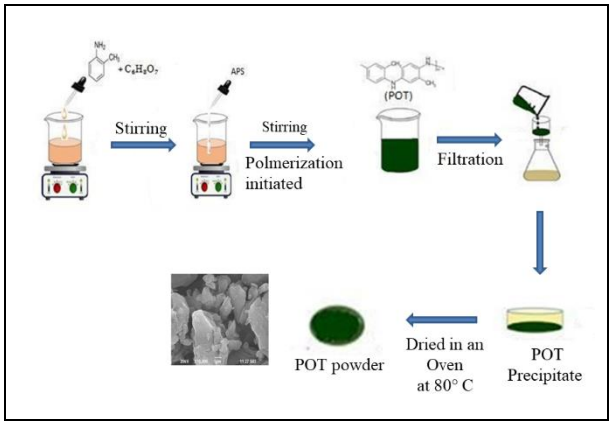
## 1.INTRODUCTION

Cancer is one of the major causes of mortality throughout the world. Charity organizations, governmental bodies and businesses provide substantial funding for cancer research aiming at developing effective treatment protocols. Cancer stands as the deadliest disease globally, causing millions of fatalities annually. Higher dosage of drugs cause cytotoxicity in healthy cells, which is one of the most critical difficulties with cancer chemotherapy. Furthermore, conventional drugs generally evoke considerable hematological reactions due to their ambiguous distribution in the liver, bone marrow and other internal organs. Also, most cancer drugs can induce mouth sores, loss of hair, poor appetite, nausea, an increased risk of infection and fatigue, among other side effects (Bagheri *et al.* 2020; Hathout *et al*. 2018; Madhu *et al*. 2012). Therefore, researchers have concentrated on developing novel drug delivery systems with improved targeting capabilities in order to prevent metastasis, minimize undesirable side effects, and alleviate the pain associated with tumor treatment. In this regard, conductive polymers could lead to substantial breakthroughs in biomedical and controlled release of drugs, especially in the treatment of cancer, because of their excellent cytotoxic properties (Boomi *et al.* 2019; Ahmed *et al.* 2017).

The potential to link electrical stimulation and cell growth is one of the most appealing features of using conducting polymers as biomaterials, which might lead to a new tissue engineering approach that uses electrical stimulation to govern tissue regeneration. This necessitates the use of a biocompatible and electrically bioconductive material. There have been few studies that detail the biological properties of polyaniline in powder form (Humpolicek *et al.* 2012). Compounds such as polypyrrole have the ability to promote and regulate the uncontrolled growth of a variety of cells that include endothelium (Wong *et al*. 1994; Jakubiec *et al*. 1998; Garner *et al.* 1999), neuron (Kotwal and Schmidt, 2001; Schmidt *et al*. 1997) and bone cells (De *et al*. 1999). Furthermore, in recent years, polyaniline (PANI) has been studied in cardiac (Fernandes *et al.* 2010), neural (McKeon *et al.* 2010) and tissue engineering (Wang *et al*. 2010). These findings emphasize the indispensable role of conducting polymers in biological applications, notably tissue engineering and cancer chemotherapy (Wang *et al*. 2003). Besides, conducting polymers are also frequently employed as antimicrobial and antifungal agents in the fields of food processing, medicine, and agriculture. Polyaniline and other conducting polymers offer antibacterial properties against pathogens such as *Staphylococcus aureus* and *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and *Campylobacter jejuni* (Namsheer and Chandra, 2021; Parthiban *et al*. 2020).

In a number of research works, polyaniline and polypyrrole have been utilized to fabricate composites,

co-polymers, and blended with some other polymeric materials for biomedical applications (Humpolicek *et al*. 2018). Yet, there is no comprehensive study about the biological properties of pure poly (*ortho*-toluidine) (POT) in terms of anticancer activity using MG-63 bone cancer cells. This work aims at synthesizing POT and developing it as a chemotherapeutic substance that may target cancer cells either indirectly or directly, diminishing adverse side effects and enhancing therapeutic effectiveness.




**Scheme 1: Preparation flowchart for pure poly (ortho-toluidine)**

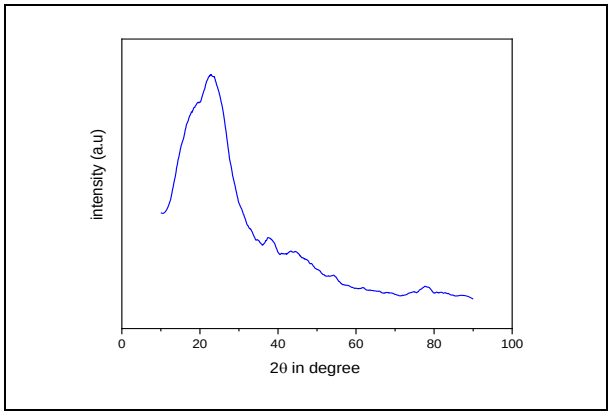



**Fig. 1: XRD pattern of pure POT**

## 2. EXPERIMENTAL DETAILS

### 2.1 Materials

*o*-Toluidine monomer (O-T) (99% purity, obtained from Lobal Chemie laboratory reagents and fine chemicals), citric acid monohydrate (CAM) (99% purity, Merck), ammonium peroxodisulfate (APS) (purity >98%, Merck), and Millipore-Q water were used in the synthesis of Poly ortho-Toluidine (POT).

### 2.2 Synthesis of Pure Poly (ortho-Toluidine)

The pure poly ortho toluidine were synthesized via chemical oxidative polymerization as seen in scheme 1. In the typical route, a solution of 3 M of O-T was added into distilled water and stirred continuously for 60 minutes. The mixture was then thoroughly mixed with 2 M of CAM for 1 hour while being continuously stirred. The aforementioned solution was again mixed with 3.5 M of APS solution to initiate the polymerization process. Continuous stirring of the combined solution at ambient temperature led to a color change of the solution from black to greenish black. In order to remove any excess acid, the resultant precipitate was separated and washed using acetone and distilled water. The washing process was continued till the polymerization process was completed and the solution became colorless. The sample was dried at 80°C in an oven. The resulting sample was powdered and characterized by various characterization methods.

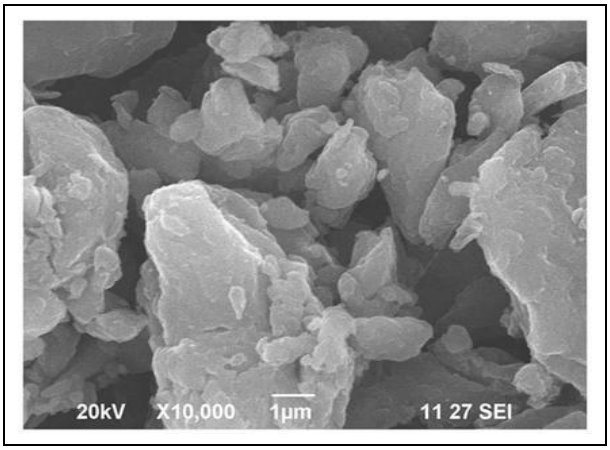



**Fig. 2: SEM images of pure POT**

### 2.3 Material Characterization

The X-ray diffraction study of POT was performed on an XPERT diffractometer. The morphology of POT was studied by SEM micrographs. The FT-IR spectrum of POT was recorded on an ATR-FTIR, Germany.

## 3 BIOLOGICAL EVALUATION

### 3.1 Antibacterial Study

The antibacterial efficacy of pristine POT was examined using the well diffusion method. *Staphylococcus aureus* and *Escherichia coli* were used as model pathogenic organisms. The spread plate method was used to inoculate the sterile plates containing nutrient agar medium with 0.01 ml of the culture solution. The filter sheets (5 mm in diameter) were carefully placed on the seeded plates after they had solidified. The antibacterial test was performed using the standard antibiotic chloramphenicol (10 µg), after which the sample plates were kept for one day at 37°C and the zone of inhibition (in mm) was measured.

### 3.2 Anticancer Study

#### 3.2.1 Cell Growth and Treatment

Human bone cancer cells (MG-63) were cultured in Eagle's medium and reinforced with 10% Fetal Bovine Serum and the cells were maintained at 5% of $CO_2$ humidified atmosphere at 37 ℃. Trypsin-EDTA acid was used to exfoliate monolayer cells. The live cells were counted by a hemocytometer. The cultured cells were grown at a density of $1\times10^5$cells/ml, and 100 µl cell suspensions were dispensed into samples of varying concentrations. The Petri dishes were kept at 37℃ for 48 hours, and the Muller-Hinton agar solution was changed twice a week. As a control, a sample-free medium was employed.

#### 3.2.2 MTT Assay

The anti-cancer activity of POT was investigated using MTT assay. Human bone cancer cell lines MG-63 were seeded on 96 culture plates and kept for 24 hours at 37 ℃ with 5% $CO_2$ atmosphere. Thereafter, cells were exposed with samples of 5 different concentrations (6.5 µg - 100 µg) in an organic solvent, DMSO and incubated for 2 days. Then, each well was filled with 15 µl MTT and kept for 4 hours at 37℃. Thereafter, the MTT were aspirated and about 100 µl of DMSO were poured to solubilize the formazan crystals. The absorbance of each well was determined at 570 nm using a microplate reader.

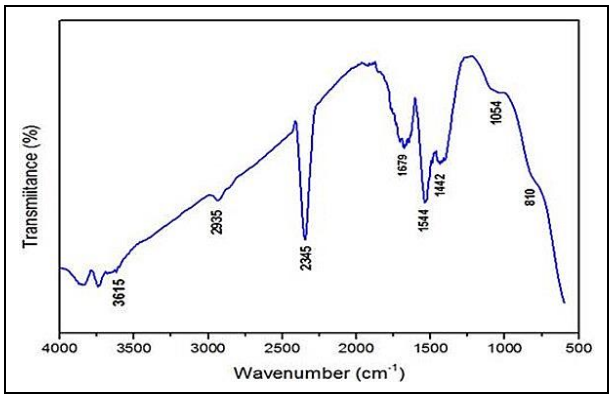



**Fig. 3: FT-IR spectra of pure POT**

## 4. RESULTS AND DISCUSSIONS

### 4.1 Structural Analysis

The X-ray diffraction studies indicate that the POT protonated by citric acid is semicrystalline in nature as seen in Fig.1. An intense peak was found at 23° along with peaks at 37°, 43°, and 77°, indicating that the increased crystallinity of POT might be due to protonic acid doping, which produces a conformational change in the structural order. As per the earlier literature, the XRD pattern of polymer depends on the doping of protonic acid medium (Ebrahim and Gad, 2010; Seshadri and Bhat, 2007; Lakshmi *et al*. 2007; Pande *et al*. 2020).

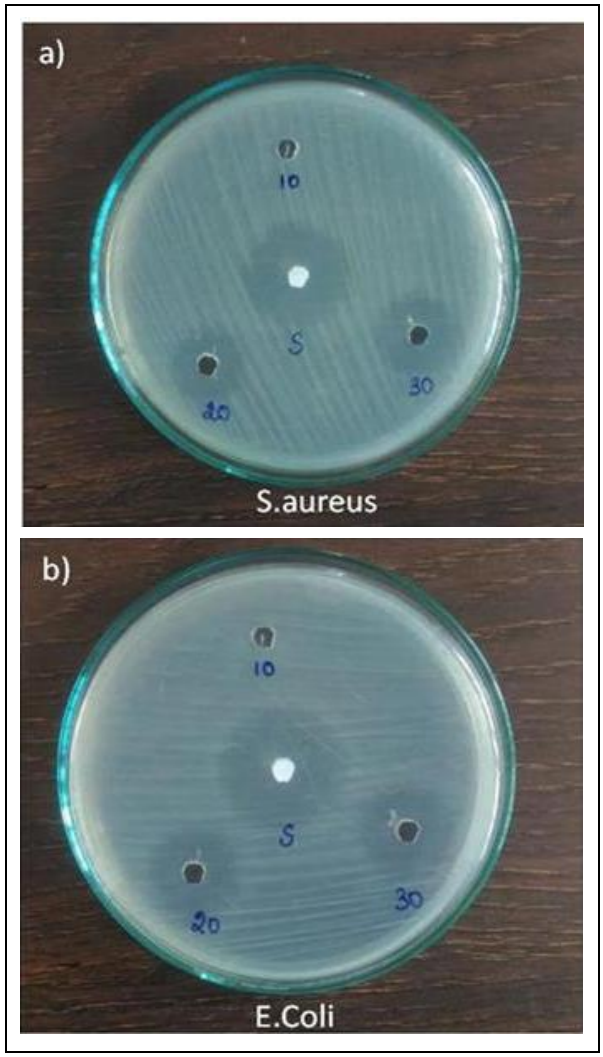



**Fig. 4: Antibaterial activity of pristine Poly ortho toluidine against *Staphylococus aureus* (Gram +ve) and *Escherichia Coli* (Gram −ve)**

### 4.2 Morphological Analysis

The surface morphology of pristine POT was investigated using SEM analysis. The SEM image of POT in Fig.2 shows that it possesses flaky morphology. Amorphous areas with undefined shapes were identified. They were combined with crystalline areas having sharp edged particles and lamellar sides. This morphological finding is clearly reflected in SEM data of extremely crystalline and soluble dodecylbenzene sulfonic acid doped POT (Ebrahim *et al.* 2010).

### 4.3 FT-IR Spectroscopy

Fig. 3 shows the FT-IR spectrum of POT. A peak at 3615 $cm^{-1}$ is ascribed to aromatic amine N-H stretching (Borriello *et al.* 2011). Formation of the POT

polymer was confirmed by the peak appearing at 2935 $cm^{-1}$, related to methyl group C-H stretching.[26] The N-H stretching mode of unsaturated amine was observed at 2345 $cm^{-1}$ (Kulkarni *et al.* 2005). Furthermore, the $CH_3$ bending mode is represented by a peak at 1679 $cm^{-1}$. The quinoid and benzenoid rings of the POT polymeric chain generated peaks at 1544 and 1442 $cm^{-1}$ due to C=C stretching vibrations.[26] Peaks of C-H in-plane bending vibration of quinoid rings and C-H out-of-plane vibration were found at 1054 $cm^{-1}$ and 810 $cm^{-1}$, respectively (Ghosh and Siddhanta, 1999; Reddy *et al*. 2008).

**Table 1. Average inhibition zone for pristine poly (ortho-toluidine)**

| Material | Bacteria | Inhibition zone (mm) for different concentration of POT | | | Control positive (mm) |
|---|---|---|---|---|---|
| Pristine POT | *S. aureus* | 10 µl | 20 µl | 30 µl | Chloramphenicol |
| | | 0 | 03 | 05 | 06 |
| | *E. Coli* | 0 | 04 | 05 | 06 |

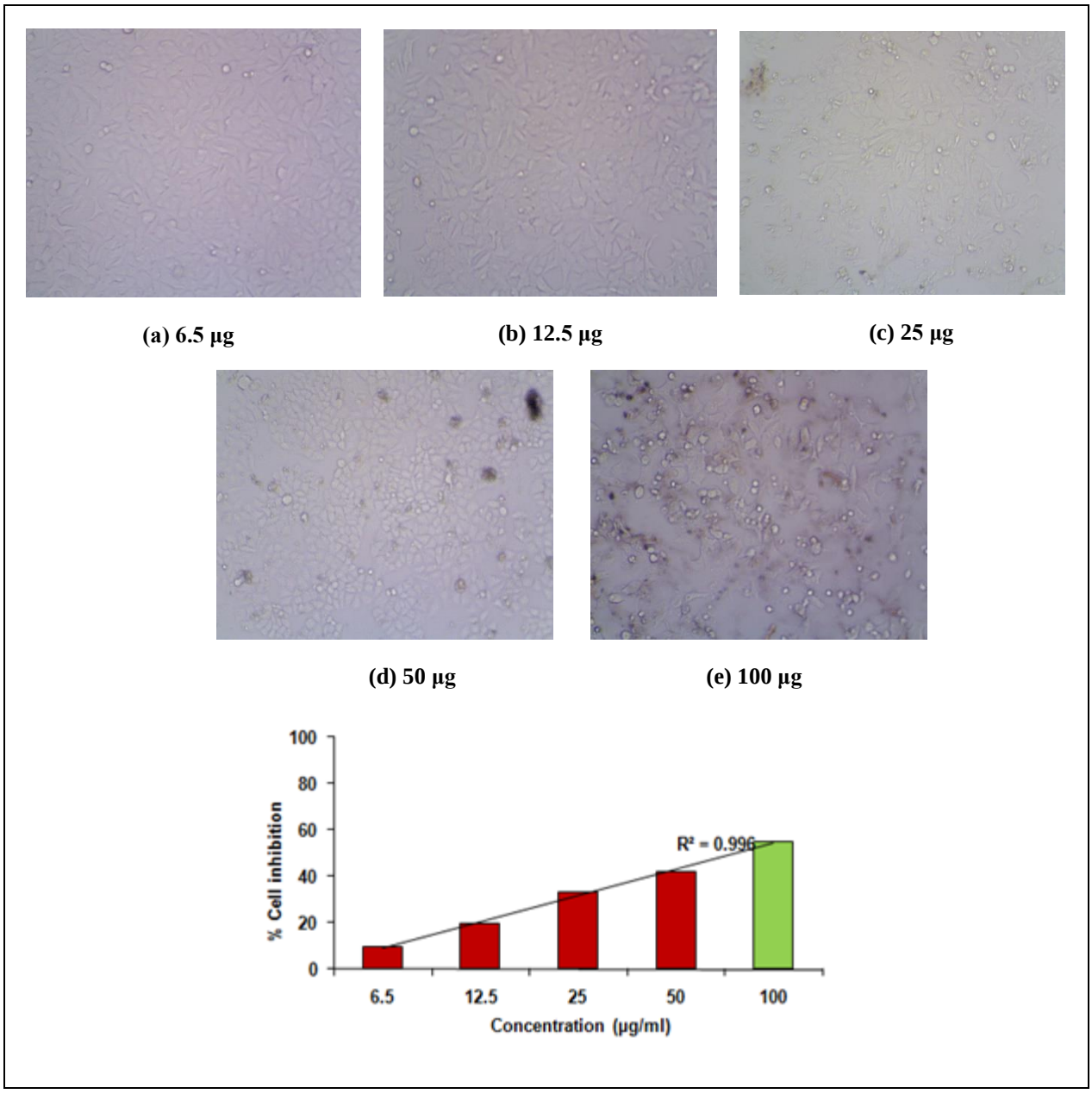



**Fig. 5: Anticancer activity of pristine poly ortho toluidine against MG-63 bone cancer cells**

### 4.4 Antibacterial Activity

The decreased concentration of residual low-molecular-weight by-products, the polymer chain length (Gizdavic *et al*. 2021), electrostatic interaction (Huang *et al.* 2016) and also PANI amino groups exhibit antimicrobial effects towards certain bacterial pathogens (Wu *et al.* 2012). The results of antibacterial studies are shown in Fig. 4. The strains *S. aureus* and *E. coli* were used to assess the activity of POT with the dosage range of 10-30 µg/ml and chloramphenicol was used as a standard drug for comparing the bacterial action (Table 1). The antibacterial action is caused by the binding of conducting polymer-based composites to the outer membranes of Gram +ve and Gram –ve bacteria, as well as biological macromolecules, which inhibit active transport and slow the enzyme activity. The conducting polymer-based composites interact with the thiol groups on the bacterial cell surface. As a result, the proteins are deactivated, the cell membrane is ruptured and finally bacterial death occurs. However, it is noteworthy that inhibition zone is typically expanded and the bacterial growth is prevented only when the concentration of POT is higher.

### 4.5 Cytotoxicity

Charge delocalization on polymeric chains, electrostatic adsorption between polymer and cell lines, and the presence of amino groups (creating probable contact between the polymer's surface and cells) contribute to the cytotoxicity of conducting polymers.[4] In order to evaluate the cytotoxic effect of the synthesized POT, MG-63 bone cancer cell lines were used. Fig. 5 shows that cell viability decreased in the MG-63 bone cancer cell lines from the concentrations of 6.5 µg/ml to 100 µg/ml. In addition, POT-treated MG-63 cells showed morphological changes in condensed chromatin, cytoplasmic apoptosis and detachment from the surface. This might be attributed to increased positive charge as well as higher peptide concentrations (Futaki *et al*. 2013). Furthermore, increasing the concentration of the POT resulted in a considerable drop in cell viability. This suggests that POT, at a maximum concentration of $IC_{50}$ = 83.15 µg/ml, has an effective action in inhibiting the propagation of human MG-63 bone cancer cells. Poly(*o*-Toluidine) could potentially be introduced into the lipid membrane with the assistance of DMSO, as it facilitates the penetration of both hydrophobic and hydrophilic substances into the cell membrane (Williams *et al*. 2016). Dimethyl sulfoxide molecules non-specifically integrate beneath the hydrophilic head group, enhancing the average head group area and rendering the membrane more flexible for bending. This mechanism encourages the entry of water molecules and results in the formation of non-specific water channels (Notman *et al*. 2006). Previous research found that DMSO induced ocular damage in animals, including lens abnormalities (David *et al*. 1972). When used as a solvent for hydrophobic anticancer drugs, DMSO may induce harm to the central nervous system. In the present investigation, POT shows moderate toxicity against human MG-63 bone cancer cells.

## 5. CONCLUSION

In this study, chemical oxidative polymerisation method was employed to synthesize poly (*ortho*-toluidine). The results of XRD and FT-IR studies of the sample confirmed the successful formation of POT. The SEM studies show flaky morphology of the particles. The polymer has significant antimicrobial effect against *Staphylococcus aureus* and *Escherichia coli*. It also exhibits moderate cytotoxicity against MG-63 bone cancer cells. These data imply that POT with an $IC_{50}$ value of 83.15 µg/ml has high selectivity for cancer cells and might be useful in cancer treatment.

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## CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.



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