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REVIEW

Overview of Medical and Biological Applications of Indium(III) Complexes

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Abstract

Indium(III) complexes are versatile species that emit Auger electrons which made them a choice for a wide range of biological and medical applications. The properties of these complexes depend on the primary ligand that was used for their syntheses. Herein, methods of synthesizing xanthates, dithiocarbamate, phthalocyanine, thiosemicarbazone and naphthalocyanine complexes of indium(III) are discussed. Also, the methods for synthesizing indium(III) complexes having other ligands are highlighted. Furthermore, antibacterial, antifungal and antiviral potential of the indium(III) complexes are comprehensively discussed. Other biological applications of the complexes such as anticancer, bioimaging, radiopharmaceutical, photodynamic chemotherapy, antioxidants, and optical limiting applications of these indium(III) complexes are comprehensively reviewed. In addition, toxicity of indium(III) complexes towards biological samples are examined because these must be considered in evaluating the safety and efficacy of indium(III) complexes for these numerous applications. Overall, indium(III) complexes are reported to have displayed a good performance in all these biological and medical applications. The future perspectives on the applications of indium(III) complexes are therefore suggested.

Keywords Inorganic complexes · Bioactivity · Synthesis · Medicine · Indium · Cytotoxicity

1 Introduction

Indium is a metal with low melting point, and it loses its valence electrons without attaining inert gas electronic structure. At cryogenic temperature, indium retains its properties. Asides, it is malleable, ductile, and softer than lead [1]. Although the stable state of oxidation of indium is + 3, it can exist in the oxidation state that is lower than + 3. Indium belongs to group 13 on the periodic table and its electronic configuration is [Kr] $4d^{10}5s^{2}5p^{1}$. It has 47 isomers with indium-115 having the highest abundance and highest half-life of 95.7% and 4.41×10^{14} years respectively [2]. Indium is a metal in the main Group IIIa of the periodic table along with gallium, aluminium and thallium [3]. Most of Group IIIa metals are often employed as parts of inorganic diagnostic and therapeutic agents in medicine especially gallium and indium [4]. This has drawn increasing attention and interest in these metals' medical applications as alternative therapeutic agents to established medical practices. The properties and Chemistry of indium in the oxidation state of + 1 and + 2 has been reviewed by Pardoe et al. [5].

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Indium salts react with several ligands to form organometallic complexes of indium. Indium(III) complexes (especially those with indium-111 isotope) have been investigated for various medicinal and biological application due to their ability to capture electrons when exposed to 171 and 245 keV, $t_{1/2}$ = 67.4 h gamma radiation [6]. This property has particularly made the application in medical diagnostic radio pharmacy feasible. The imaging of inflammation sites and infections were achieved using the indium complexes. Apart from this property, indium complexes emit Auger electrons which made them to be useful for the destruction of cancerous cells [7, 8]. Based on radioactive potential, indium(III) compounds can be grouped into radioactive and non-radioactive compounds. There is extensive research on the potential of the radioactive indium(III) compounds in the detection and diagnosis of infections and inflammations compared to their non-radioactive counterparts which have been rarely explored [2]. Clinical investigations are ongoing about In(III) compounds that have a better bioavailability with their potential anticancer and antioxidant characteristics when compared with their inorganic salts [4]. Due to the numerous investigations carried out on the medicinal and biological applications of indium(III) complexes, there is the need to have a detailed report on this aspect of research. Hence, the aim of the present study is to comprehensively review these biological and medical applications.

2 Methods of Preparing Selected Indium(III) Complexes

2.1 Preparation of Xanthate Ligands and Their Indium(III) Complexes

Metal xanthate complexes are dithiolates just like dithiocarbamates but the breakdown temperature of metal dithiocarbamates is higher than that of metal xanthates [9]. Their synthesis is usually in two stages and the first stage is the synthesis of the ligands while the second stage is the synthesis of the complexes. Commonly, the ligands of xanthates are prepared by reacting carbon disulphides with alcohols in the presence of potassium or sodium hydroxide inside the ice [10]. The choice of the alcohol depends on the type of xanthates to be synthesized. For instance, *S*-(+)-*sec*-butanol is required to synthesize potassium or sodium salt of *S*-(+)-*sec*-butyl xanthate ligand [9]. Indium salt and the ligands are then dissolved in tetrahydrofuran in the mole ratio of 1:3 to form precipitates. The precipitate formed are usually filtered and recrystallized in chloroform. This procedure has been used to prepare several indium xanthates and some of these are shown in Table 1. Apart from this known procedure of preparing metal xanthate, the preparation has been achieved by using electrochemical technique. The method involve oxidation of indium metal in a single

Table 1 Examples of indium xanthate complexes used for different applications

Xanthate complex	Reagents for synthesis	Characterization	Application	References
$[InCl_{3-n}(S_2COR)_n]$ (R = Me, Et, Pri, and Bus; n = 1, 2, or 3)	Chloroform, diethyl ether, carbon disulfide, sodium hydride, potassium hydroxide, 2-butanol, methanol, 1-propanol, potassium ethyl xanthogenate and Indium(III) chloride	NMR, TGA, Elemental Analyser	Synthesis of indium sulphide nanoparticles	[12]
Indium *O*-2,2-dimethylpentan-3-yl dithiocarbonate	Ethanol, potassium ethyl xanthogenate, chloroform, anhydrous magnesium sulfate	NMR, Elemental Analyser	Synthesis of indium sulphide and ternary copper indium sulphide nanoparticles	[13]
Indium-*O*-2,2-dimethylpentan-3-yl-dithiocarbonate	–	NMR and TGA	Synthesis of $CuInS_2$	[14]
Indium (III) isopropyl xanthate	Carbon disulfide, sodium hydroxide, methanol and indium(III) chloride	NMR and elemental analysis	Synthesis of indium oxide and sulphide	[15]
Indium(III) diethyl dithiocarbonate and indium(III) isopropyl xanthate	–	Crystallography-XRD	Thin film deposition of indium sulphide	[16]
tris(*O*-ethylxanthato)-indium(III)	–	Crystallography-XRD	Crystal structure investigation	[17]
Methylindium(III) dithiolate complexes	$In(S^{\cap}S)_3$ and $Me_3In{\cdot}OEt_2$	Indium analysis, IR, NMR (^1H, $^{13}C$and ^{31}P) and mass spectra	Synthesis of indium sulphide nanoparticles	[18]

step in the presence of tetramethylthiuram or ethyl dixanthogen disulphide dissolved in acetone [11].

2.2 Preparation of Dithiocarbamate Ligands and Their Indium(III) Complexes

Dithiocarbamates are formed through the reaction of carbon disulphide with either primary or secondary amine. The reactions are often carried out in the environment of alkyl halides, epoxides, transition metals and imines which are electrophiles [19]. Markovnikov's addition has also been employed to synthesize dithiocarbamates. This was achieved by mixing 6 mmol of ethyl vinyl ether, 6 mmol of carbon disulphide and 5 mmol of amine together in the presence of water. The reaction was carried out without the use of any catalyst. However, there was an improved yield when organic solvent was used in place of water for the reaction [20]. The reaction scheme for the synthesis using Markovnikov's addition is shown in Fig. 1.

Apart from synthesis of dithiocarbamate via three component system, it has also been done via a four-component system. Azizi et al. [21], carried out this reaction through a one-pot route and the reactants used are carbon disulphide, aliphatic amines, ketones and aldehydes in the presence of ethanol or alkaline. Different forms of dithiocarbamates were obtained by changing the amine used for the reaction. One of the numerous reactions where dithiocarbamates are obtained from four components is shown in Fig. 2. The formation of the indium complexes is achieved by reacting indium salt with the dithiocarbamate ligands [22].

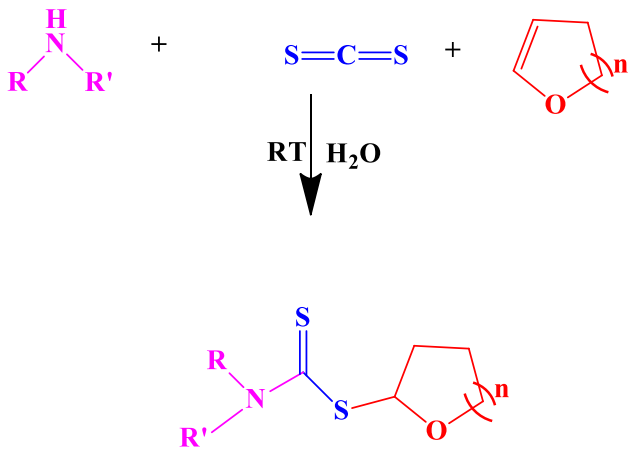


Fig. 1 Synthesis of dithiocarbamate through Markovnikov's addition reaction. *Adapted from* [20]

2.3 Preparation of Thiosemicarbazones Ligands and Their Indium(III) Complexes

The known methods for synthesizing thiosemicarbazones involves the reaction of different electrophiles with hydrazine on a step-by-step basis [23, 24]. As shown in Fig. 3, one of the synthetic routes requires four steps while two of the known synthetic routes require two steps. Hydrazine

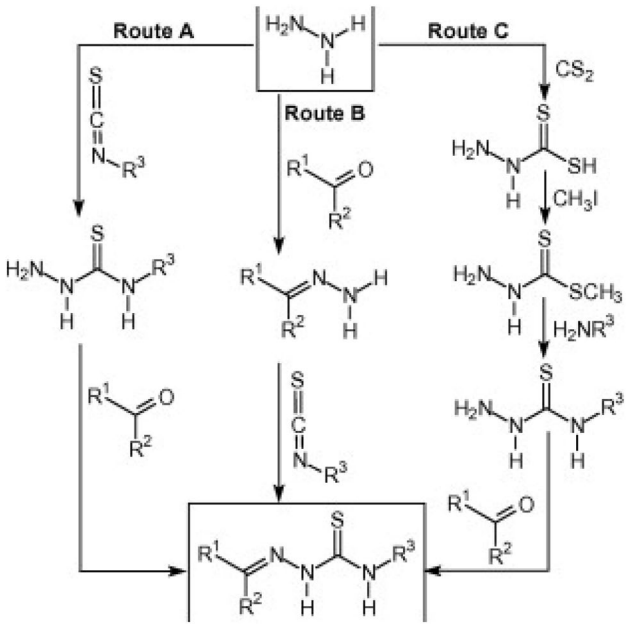


Fig. 3 Three common routes for synthesizing thiosemicarbazone [23]

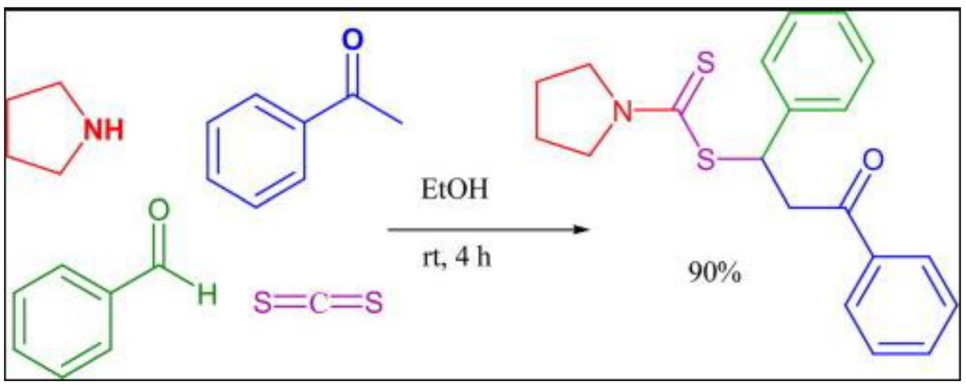


Fig. 2 Synthesis of dithiocarbamate from four components [21]

may react with isothiocyanates before reacting with either carbonyl compounds (route A). In another two-steps route (route B), the reaction with carbonyl compounds occurs before the reaction with isothiocyanates and it also led to the formation of thiosemicarbazones. In the four-step reaction (route C), there is reaction between carbon disulphide and hydrazine in the first step while the product of this reaction further reacts with methyl iodide to give methyl hydrazinecarbodithioate. Then, this product reacts with the oxo-compounds to give thiosemicarbazone. Apart from these known routes, the coupling of oxo compounds, hydrazine and aryl isothiocyanates to form thiosemicarbazone in a single reaction step in the absence of catalyst has been achieved [23]. In another research, thiosemicarbazide was reacted with aldehyde under microwave irradiation to produce thiosemicarbazone [25]. Just like the role that microwave irradiation played in the synthesis, ultrasound has also been used to achieve the synthesis of thiosemicarbazone [24]. From the reaction of ethanolic thiosemicarbazone with indium salt, the thiosemicarbazone complex of indium (III) are made [26].

These synthetic procedures have also been used to synthesize different derivatives of indium thiosemicarbazone. In a particular investigation, indium(III) benzoylpyridine *N*(4)-cyclohexyl thiosemicarbazone was synthesized from the reaction of thiosemicarbazone with hydrated indium nitrate in the presence of methanol and sodium acetate [26]. Even chelated indium(III) thiosemicarbazones with partial fluorination has been made in solution via the same synthetic procedure [6]. In a similar investigation, many indium chloride complexes of bis-thiosemicarbazones that are structurally related were synthesized from bis-thiosemicarbazones in the presence of methanol and sodium methoxide. Fluorine was introduced into the complexes via a simple exchange of halide method using $K^{18}F$ [27].The same method has been adopted for the synthesis of indium complexes of thiosemicarbazone containing pyridine. Indium nitrates and indium halides were used as the source of indium for the synthesis of 2-acetylpyridine-thiosemicarbazone and 2, 6-diacetylpyridine-bis (thiosemicarbazone) indium complexes respectively [28]. Other examples of indium complexes that were synthesized from indium salts and other reagents are shown in Table 2.

2.4 Preparation of Phthalocyanine, Naphthalocyanine Ligands and Their Indium(III) Complexes

In preparing chloro-(octa-(n-pentyl)phthalocyanito) indium (III) complex, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), dry quinoline, 4,5-bis(n-pentyl) phthalonitrile and indium(III) chloride were stirred together at 180 °C for 5 h. Where chloroform was used as the solvent, it was removed by distillation[38]. Phthalocyanine complexes of indium has also been synthesized from a reaction involving quinoline, 3-pyridyloxyphthalonitrile and anhydrous indium(III) chloride. In brief, 6.8 mmol (1.50 g) of 3-pyridyloxyphthalonitrile, 5 ml quinoline and 3.4 mmol (0.75 g) of anhydrous indium(III) chloride were stirred together for 7 h while keeping the temperature constant for 7 h. The green precipitate formed was cooled, precipitated out, filtered and purified via thin layer chromatography [39].

The synthesis of naphthalocyanine has been carried out by using different precursors. One of the precursors that has been used is aromatic nitrile and it was effectively used to synthesize quaternized 2,3-octakis-(3-pyridyloxyphthalocyaninato) indium(III) and 2,3-octakis-(3-pyridyloxyphthalocyaninato) indium(III) [40]. The aromatic nitrile precursors are often prepared via condensation reaction. In an investigation, 4-[(3,5-di-*tert*-butyl)-phenoxy]-phthalonitrile precursor was prepared in basic medium by condensing 3,5-di-*tert*-butyl-phenol with 4-nitro-phthalonitrile [41]. Another common precursor is diiminoisoindolines and is preferred to naphthalenedicarbonitriles precursor because it is more reactive [42]. The synthesis of the indium complex from the ligand is usually carried out by reacting the ligand with indium(III) salt in the presence of ring-forming non-nucleophilic base catalyst. Naphthalocyanines generally have poor solubility in organic solvents and to increase its solubility, peripheral substituents such as alkoxy, alkylthiol, halogens and alkyl are often introduced into their complexes. These are usually achieved by using Grignard reagents or halogenated compounds [43]. Several chloro(naphthalocyaninato) indium (III) complexes have been synthesized by using this procedure [42].

2.5 Preparation of Other Indium (III) complexes

Apart from the discussed indium complexes, there are other complexes of indium that have been synthesized and characterized by using different analytical techniques. Homoleptic and heteroleptic tris(dipyrrinato)indium(III) complexes were synthesized by using both plain and pie-extended dipyrrin ligands [44]. Also, novel μ-hydroxy bridged eclipsed dimer based on indium(III) tetrapyrazinoporphyrazine was made through the co-ordination of porphyrazine compound and indium ions [45]. Curcumin which is a naturally occurring extract obtained from turmeric has been used as a ligand source for indium complexes. Typically, indium complexes are obtained by reacting curcumin or its derivatives with the nitrate or chloride salts of indium in alcohol. This is usually followed by refluxing, cooling, filtration and drying to obtain solid products [46]. Examples of curcumin complexes of indium are bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione (curcumin) indium (III) complexes, indium diacetylcurcumin complex [2, 46]. Apart from indium

Table 2 Examples of indium thiosemicarbazones complexes for different applications

Indium complexes	Reagents used	Characterization	Application	References
Indium(III) complexes of 2-acetylpyridine ^{4}N-alkyl thiosemicarbazones derivatives	*N*-alkyl-3-thiosemicarbazides, 2-acetylpyridine, acetic acid, $InCl_3$	X-ray crystallographic analysis, fluorescence, UV–Vis, IR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry	–	[29]
Indium complexes of *N*(4)-*para*-iodophenyl-2-acetylpyridine thiosemicarbazone, *N*(4)-*para*-chlorophenyl-2-acetylpyridine thiosemicarbazone, *N*(4)-*para*-fluorophenyl-2-acetylpyridine thiosemicarbazone and *N*(4)-*ortho*-chlorophenyl-2-acetylpyridine thiosemicarbazone	*p*-iodophenyl-,*p*-fluorophenyl-, *p*-chlorophenyl-, *o*-chlorophenyl-isothiocyanate, hydrazine dihydrate, indium(III) chloride and 2-Acetylpyridine	Elemental analyses, FT-IR Spectrum, Electronic spectra,melting point determination and molar conductances determination	Antimicrobial cytotoxic	[30]
Indium complex of benzoylpyridine *N*(4)-cyclohexylthiosemicarbazone	Ethanol, indium chloride salt and thiosemicarbazone	X-ray crystallography, elemental analysis, IR, UV–vis, NMR and mass spectrometry,	Cytotoxicity investigations	[26]
$N_2O_2S_2$-donor bis (thiosemicarbazone) complex of indium	Methanol, *N*,*N*′-[bis-(2-hydroxy-3-formyl-5-methylbenzyl)(dimethyl)]-ethylenediamine, indium (III) acetylacetonate and methyl nitrile	Single crystal X-ray diffraction, NMR (^{1}H, ^{13}C, COSY, HSQC), FTIR and ESI(+)-MS and analysis	Radiopharmaceutical application	[31]
Indium(III)-bis(thiosemicarbazonato) complex	Indium trichloride, sodium methoxide, methanol and thiosemicarbazone ligands	UV/Vis, fluorescence, ^{1}H and ^{13}C NMR	Imaging	[32]
Indium(III) complex of α-diketone bisphenylthiosemicarbazones	Indium trichloride, dimethylforrnamide, methylglyoxal, lyoxal and biacetyl	–	spectrophotometric determination	[33]
Indium complex of 2-acetylpyridine *N*(4)-phenylthiosemicarbazone	–	X-ray crystallography, spectral analysis (IR, UV–vis, NMR) and elemental analysis	Antibacterial and cytotoxic evaluation	[34]
Indium(III) thiosemicarbazone	Isatin, indium isopropoxide, semicarbazide,sodium acetate, thiosemicarbazide and absolute alcohol	Microanalytical analysis, melting points, molar conductance measurements, molecular weight determinations and electronic, IR, proton/ ^{13}C NMR spectral studies	Antibacterial application	[35]
Indium(III) quinoline-2-formaldehyde thiosemicarbazone	Thiosemicarbazone, indium(III) chloride and quinoline	Ionization time-of-flight mass spectrometry spectrum,	Imaging and therapy	[36]
Indium(III) complexes with 2-acetylpyridine-*N*(4)-*ortho*-fluorophenylthiosemicarbazone	2-Acetylpyridine-*N*(4)-*ortho*-fluorophenyl thiosemicarbazone, methanol solution, indium trichloride	IR, NMR and melting point determination	Cytotoxicity	[37]

curcumin, other complexes of indium made from different ligands are shown in Table 3.

3 Pharmacological Applications of Indium(III) Complexes

See Scheme 1.

3.1 Antimicrobial Applications of Indium (III) complexes

The escalating prevalence of antimicrobial resistance among pathogenic microorganisms has prompted the exploration of new and effective antimicrobial agents. In this pursuit, metal complexes have emerged as a promising avenue for developing novel antimicrobial agents due to their distinctive chemical and biological properties. Among the metal complexes, indium(III) complexes have garnered attention for their potent antimicrobial activities. While the pharmacokinetics and pharmacodynamics of indium(III) complexes influence their properties, their applications in antifungal, antibacterial, antiviral, therapies have been well-documented and warrant further exploration. Indium(III) complexes have been extensively studied for their antimicrobial activities against various microorganisms, including bacteria, fungi, viruses, and parasites. The specific mechanism of action of indium(III) complexes in antimicrobial therapy can vary depending on the type of microorganism being targeted.

Bacterial infections are a major cause of morbidity and mortality worldwide. Indium(III) complexes have shown antibacterial activity against both Gram-negative and Gram-positive bacteria. For instance, indium(III) complexes with ligands containing, oxygen, nitrogen and sulfur donor atoms have shown potent antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA), a common multidrug-resistant bacterial pathogen [55]. Rodgers and his colleagues also showed that indium(III) complexes with the iron chelator enterochelin exhibited antibacterial activity against *Klebsiella pneumoniae* [56]. Specifically, from this study, indium(III) complex increased *K. pneumonia* generation time, suggesting a growth inhibitory effect on the bacteria. Another study also showed that indium iii complex inhibited growth of *Mycobacterium tuberculosis* [57]. They observed that free indium(III) and indium(III) complexes with the macrocyclic chelator displayed significant radiometric inhibition, with inhibition levels above 80% [57]. In addition, indium(III) complexes with Schiff base ligands have also exhibited antibacterial activity by disrupting the bacterial cell membrane, altering central dogma, and inhibiting the DNA replication process [58]. The attachments to the indium complexes may influence their antibacterial activities. For instance, indium diacetylcurcumin displayed better antibacterial performance than indium curcumin. When both were tested against *P. aeruginosa*, *S. epidermidis*, *S. aureus* and *E. coli*, it was observed that indium diacetylcurcumin was active against all the tested microbes while indium curcumin was active against *S. epidermidis* and *P. aeruginosa* only. Even the MIC obtained against these two bacteria strains were lower than what was obtained against indium diacetylcurcumin [59].

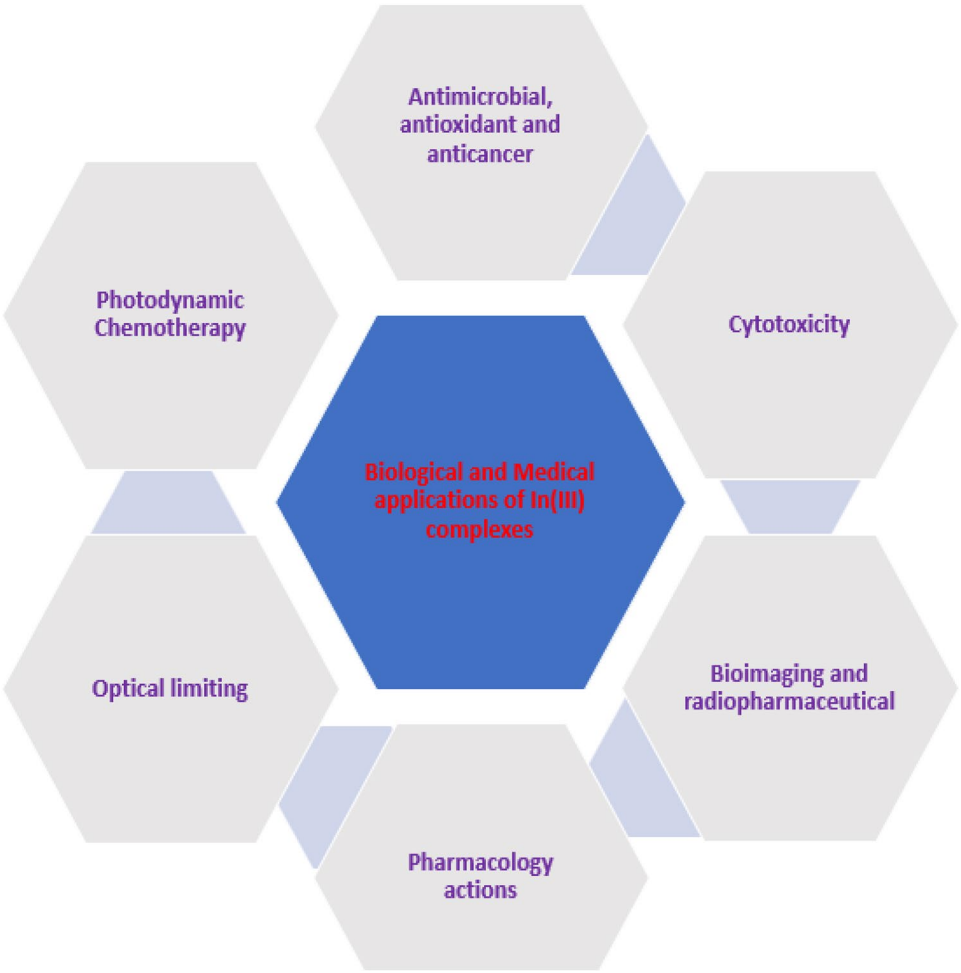
In one of our investigations, several Gram-positive and Gram-negative bacteria strain were tested against selected dithiocarbamate complexes. We observed that indium(III)-*N*-methyl-*N*-phenyl dithiocarbamate displayed better antimicrobial performance than copper(II)-*N*-methyl-*N*-phenyl dithiocarbamate and antimony(III)-*N*-methyl-*N*-phenyl dithiocarbamate complexes. In addition, it is active against all the tested bacteria except *L. monocytogenes* [60]. In a different investigation, trans-[In(III)Cl_2(4-Me-pzH)$_4$]Cl·(4-Me-pzH)$_2$·(H_2O) and mer-[In(III)Cl_3(4-Me-pzH)$_3$] were found to possess good antibacterial activities. The complexes were also found to be a potential antituberculosis and antipseudomonal drugs [61].

Viral infections are a significant public health concern, especially in the absence of effective antiviral therapies. Indium(III) complexes have shown antiviral activity against a variety of viruses, including herpes simplex virus (HSV), human immunodeficiency virus (HIV), and influenza virus, [62, 63]. For instance, indium(III) complexes containing pyridine ligands have shown potent anti-HIV activity by inhibiting the reverse transcriptase enzyme [62]. In addition, indium(III) complexes with Schiff base ligands have also exhibited antiviral activity by inhibiting the entry and replication of the virus within the host cell [64].

Fungal infections pose a significant public health concern, particularly for individuals with compromised immune systems. In antifungal therapy, indium(III) complexes play a crucial role by targeting the biosynthesis of ergosterol, an essential component of the fungal cell membrane [65]. They achieve this by binding to the active site of the lanosterol 14α-demethylase enzyme, which is involved in ergosterol biosynthesis, thereby inhibiting its function [65]. In addition to azole ligands, indium(III) complexes with Schiff base ligands have also shown promising antifungal activity [66]. These complexes disrupt the integrity of the fungal cell membrane, contributing to their efficacy against fungal pathogens. Notably, indium(III) complexes exhibit broad-spectrum antifungal activity against various fungi, including *Aspergillus niger,* and *Cryptococcus neoformans* [67, 68]. Moreover, they have been investigated for their effectiveness against drug-resistant fungal strains, such as *Candida krusei* and *Candida albicans* [69]. These strains are known for biofilm formation and are challenging to treat with conventional antifungal agents. indium(III) complexes have demonstrated potent antifungal activity against these drug-resistant strains,

Table 3 Other indium complexes, reagents needed for their synthesis and characterization techniques

Indium complexes	Reagents	Characterizations	Application	References
Tetraphenyl porphyrin Indium (III) complexes having substituted salicylates	Pyrrole, benzaldehyde, Indium Chloride, glacial acetic acid and sodium acetate	Mass spectroscopy, UV–Vis, IR, ^{13}C NMR and ^{1}H NMR	Antimicrobial application	[47]
indium (III) complexes of 2,6-diacetylpyridine bis(benzoylhydrazones)	2,6-diacetylpyridine-derived *bis*(benzoylhydrazones), triethylamine lead, DMSO and ethanol	Elemental analysis, TGA, melting point determination	–	[48]
Polymeric indium(III) pyrazolido complexes	Indium chloride, pyrazole dichloromethane and methanol	^{1}H NMR and single crystal X-ray diffraction	Luminiscence properties determination	[49]
Chloroindium(III) porphyrin	Sodium acetate, acetic acid, hexane and CH_2Cl_2	UV–visible, IR, mass spectrometry, ^{1}H-NMR,	Anticancer	[50]
Carbohydrate-bearing 3-hydroxy-4-pyridinone indium(III) complex	Benzyl chloride, glycine, acetone, methanol and DMF	^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis	Radiopharmaceuticals application	[51]
Indium(III) diaryldithiophosphates complex	Indium(III) chloride, toluene and triethylammonium salts of *O*,*O*′-bis(dimethylphenyl) phosphorodithioate	Hirshfeld surface analysis, NMR and FT-IR	Molecular interractions	[52]
Indium(III) derivatives based on 4,6-di-*tert*-butyl-*N*-(2,6-di-*iso*-propylphenyl)-*o*-iminobenzoquinone	–	X-ray chrystallography	–	[53]
Thiosemicarbazone and semicarbazone indium(III) complexes	Acetophenone, sodium acetate, ethanol isatin, hydrazinecarbothioamide, hydrazinecarboxamide and indium isopropoxide	'H NMR spectral studies, UV and IR	–	[54]



Scheme 1 Medical and biological applications of indium(III) complexes

positioning them as potential candidates for the development of novel antifungal agents. Indium(III) complexes have also been discovered to be active against *Leishmania major* promastigotes better than their ligands [2, 70]. Overall, indium(III) complexes show promise as potential antimicrobial agents. Their diverse mechanisms of action and effectiveness against multidrug-resistant strains make them attractive candidates for the development of novel therapies against bacterial, viral, and fungal infections.

3.2 Pharmacology Actions of Indium III (^{111}In) Complexes

Research work on the pharmacological values of indium complexes have been growing over the years. Apart from the therapeutic effects of indium, it has been extensively used as a diagnostic tool in nuclear medicine in the labelling of various cellular components and detection of pathological sites [71, 72]. Indium(III) emits Auger electrons, therefore, it complexes have both imaging and pharmacological actions [36, 73, 74].

Various synthesized non-radioactive indium compounds have been extensively researched on to unravel their specific therapeutic advantage. Asides the anti-tumourigenic effects of indium compounds, they have also been observed to have significant antimicrobicidal [59] and antiproliferative [75] actions. The probable toxic or synergistic effects of indium maltolate (InMal) with mitoxantrone (MTX) was reported in a study, which focuses on breast cancer (MDA-MB-231) and fibroblast (NIH-T3) cell lines [76]. It was asserted that the indium compound decreased the viability of both cell lines in a dose and time-dependent measure. The combined administration of InMal and MTX was noted to be more effective than the sole administration of MTX. Interestingly, the toxicity of the indium compound was reversed by the inclusion of iron citrate on the fibroblast and not the cancer cell lines. These findings most likely suggest that the mechanism of action of indium may be inclusive of iron metabolism [76]. Pathogenic enterobacteria produce enterochelin, which is an iron chelator that has been shown to be an essential metabolite for the replication of bacteria within the host cell [56]. Enterochelin chelates iron from complexes in association with transferrin and lactoferrin that binds with

iron within the host. The resulting ferric compound from the above interaction is then endocytosed by bacteria. This could be related to the observed antibacterial effects of enterochelin complex with indium against *K. pneumoniae* [56].

In an in-vitro study, indium-1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid complex was indicated to exhibit antimicrobial action against *M. tuberculosis* [57]. The antioxidant and antibacterial effects of indium(III) complex against *E. coli*, *B. cereus, B. subtili*, and *P. aeruginosa* have also been reported [77]. The antibacterial effects of indium curcumin, diacetylcurcumin and indium diacetylcurcumin relative to curcumin was extensively demonstrated against different bacteria species of clinical relevance, viz; *P. aeruginosa, S. aureus, E. coli*, and *S. epidermidis* [59]. Indium curcumin showed antibacterial action against all the bacterial strain. Surprisingly, it was observed that the minimum inhibitory concentration of indium curcumin was lower for *S. epidermidis* and *S.aureus*, compared to that recorded after curcumin treatment. Hence, the authors satisfactorily concluded that the antibacterial effect of indium curcumin exceed that of curcumin [59].

Indium-phthalocyanines complex have been used as photosensitisers and antimicrobial agent in photodynamic and chemotherapy of neuroblastoma cells [78, 79] and *E. coli* [80] respectively. The anti-carcinogenic effects of another indium compound – indium tin oxide is of interest. The compound alters DNA integrity in adenocarcinoma cells in the pulmonary tissue [81]. In like manner, indium thiosemicarbazones complex expresses cytotoxicity against white blood cell cancer and solid tumor cells [82]. Thiosemicarbazone, in particular, is known to have cytotoxic property, apart from mediating the intracellular transport of indium ions. Therefore, complexation of thiosemicarbazones to indium might cause an improvement of the cytotoxicity of the former. Indium(III) complexes of thiosemicarbazones also have anti-tumorigenic property [34]. The cell toxicity of indium-porphyrin complex has been demonstrated against breast, prostate, and lung tumor cell lines [50].

3.3 Anticancer Application of Indium(III) Complexes

Cancer is the general name used for a large group of diseases characterised by rapid and uncontrolled growth of abnormal cells beyond their usual limit and leading to invasion of adjoining cells and organs [83, 84]. According to World Health Organisation, cancer is the leading cause of death in the world [84]. Studies have shown that Gallium and Indium (including Aluminium salts in some cases) have anticancer properties [3]. They can prevent the growth of various experimental solid tumours. There are many investigations that have shown the cytotoxic nature of many indium(III) complexes against leukaemia cells and solid tumours [2]. Anticancer activities have also been observed with indium curcumin complex, diacetyl curcumin, and indium diacetyl curcumin [85]. Li et al. [86] reported anticancer properties of four novel indium(III) complexes of 2,6-diacetylpyridine thiosemicarbazide, The performance of these indium(III) complexes were found to depend on their structures. One of the novel indium(III) complexes (C4) displayed a better performance against T24 cells. Apart from inhibiting the T24 cells, it also prevented the metastasis and invasion of the cell via a multi-targeted mechanism. As revealed by the Western Plot analysis, telomerase activity and densitometry analysis (Fig. 4), the performance of the novel indium(III) complex depends on the concentration introduced into the cell.

Here are some other ways indium(III) complexes have been used as an anticancer agent;

3.3.1 The Use of Indium-III Labelled Monoclonal Antibodies (MoAb) in the Imaging of Cancers

Goldenberg et al. [87] made a novel attempt at using radiolabelled antibodies in tumour imaging and it gained widespread acceptance from medical experts. Radiolabelled antibodies such as monoclonal antibodies have been shown to be effective in the treatment of cancers, especially lymphoma [88]. They have been used in cancer diagnosis for more than four decades and as early as 1985, Fawwaz et al. [89], already reported that about 412 patients have been investigated for a variety of gastrointestinal malignancies since 1984 through the IV administration of a variety of monoclonal antibodies [89]. Monoclonal antibodies are a

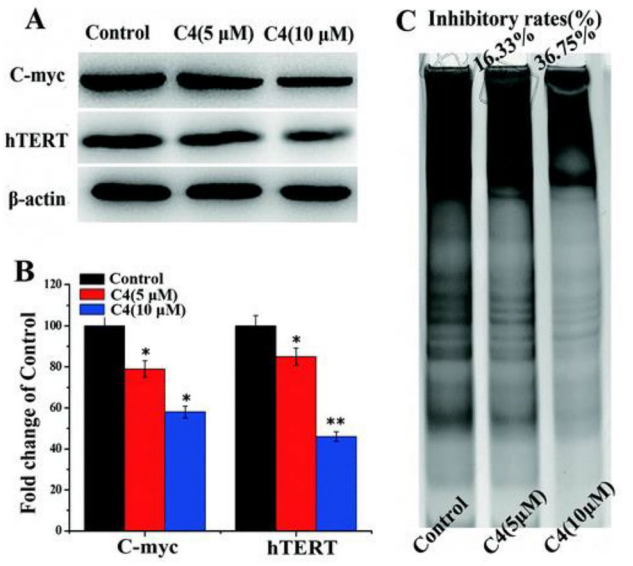


Fig. 4 **a** Western blot analysis of 24 h treatment of hTERT and c-myc in T24 cells with novel indium(III) complexes (C4); **b** hTERT and c-myc proteins' densitometric analysis after the treatment with In(III) complex (**c**) telomerase activity in the T24 cells after the treatment with the novel indium(III) complex [86]

group of antibodies produced from a cell lineage or a single clone of cells by cloning a unique white blood cell against a particular antigen [90]. For a while, there has been advocacy for the use of Iodine-131 (^{131}1) labelled monoclonal antibodies against tumour-associated antigens in tumour detection and therapy [89]. However, shortcomings in the use of the Iodine-131 labelled monoclonal antibodies have reduced the prospect and potential of these agents in tumour detection and therapy. This led to the quest for alternative strategies in the use of radio-labelling antibodies. One of such is the use of Indium III labelled monoclonal antibodies. The tumour imaging of several tumour-associated antigens has been conducted successfully using Indium III labelled monoclonal antibodies. The first clinical use of Indium III labelled monoclonal antibody was reported in 1987 in which Indium III labelled murine MoAb ZCE 025 was used to investigate colorectal carcinoma in patients [91]. After the IV administration of the In-labelled ZCE 025 antibody in addition to the unlabelled antibody doses, 18 tumour sites were successfully discovered out of the 20 documented sites [91].

Also, Pandit-Taskar et al. [92], did a lesion-detectability study in which the imaging capacity of Indium III J591 was compared with conventional imaging in patients with different types of solid tumours. J591 is a type of monoclonal antibody that is used against prostate-specific membrane antigen (PSMA) but it can also be used to target non-prostate metastases. Of the 170 lesions detected in 20 patients, 108 were attributed to the Indium III J591 antibody scan and these lesions cut across skeletal lesions, lesions of nodes and of soft tissues and organs. It was concluded based on the result that radiolabeled J591 antibody may be used as a targeting agent for a wide array of solid tumors and also lesion detection. This potential for lesion is perhaps in part due to the presence of indium(III).

3.3.2 The Use of Neutron Activation of Indium(III) Complexes on Cancer Cells

Oliveira et al. [93], investigated the cytotoxicity activities of four neutron-activated indium(III) complexes on MCF-7 breast cancer cells and against non-malignant MRC-5 fibroblast cells. In the work, four samples of indium(III) complexes (1–4) were subjected to neutron activation using gamma spectrometry and their level of radioactivity was evaluated. The four indium(III) complexes contain naturally abundant amounts of ^{113}In (4.3%) and ^{115}In (95.7%). The process of neutron activation led to the formation of new indium(III) analogues (*1–*4), ^{114}mIn/^{115}mIn. Complexation of In(III) resulted in a noteworthy enhancement in cytotoxicity against MCF-7 cells in complexes (1–4), indicating that the strategy of forming complexes proved beneficial in enhancing the cytotoxic effect of indium(III). In contrast, both non-radioactive and radioactive In(III) salts exhibited no activity against MCF-7 cells, whereas the radioactive complexes (*1–*4) demonstrated significantly increased potency, ranging from 102 to 104 times more effective than their non-radioactive counterparts (1–4). The observed cytotoxic effects, evaluated after 48 h of treatment and 72 h following neutron activation, were primarily attributed to ^{114m}In, while the contribution of the shorter-lived isomer, ^{115}In (with a half-life of 4.5 h), was deemed insignificant. In comparison to the original compounds, complexes (*1–*4) demonstrated higher levels of intracellular ROS in MCF-7 cells. These findings indicate that thiosemicarbazone complexes with ^{114}In have the potential as radiopharmaceuticals for the treatment of breast cancer. This is evidence of the anticancer potential of Indium in indium(III) complexes.

3.4 Cytotoxicity Related Applications of Indium(III) Complexes

Researchers have looked into how many different indium(III) combinations kill solid tumor and leukemia cells. Orvig and colleagues tested InL_3 clusters with curcumin (CUR) and diacetylcurcumin (DAC) on mouse lymphoma cells. When indium(III) was added to [In(CUR)$_3$], the cytotoxic activity went up, while [In(DAC)$_3$] had the same cytotoxicity as the curcumin ligand. [In(CUR)$_3$] was a stronger antioxidant than curcumin, while [In(DAC)$_3$] was almost as active as DAC that had not been complexed, but had less antioxidant power than [In(CUR)$_3$]. Curcumin is thought to have these benefits because it has free aromatic OH groups [46]. Indium(III) binds to 1,4,7,10-tetraazacyclododecane-1-[4-[(3-chloro-4-fluorophenyl)amino]quinazoline-6-yl] [2]-propionamide-4,7,10-triacetic acid (InL1) and 1,4,7,10-tetraazacyclododecane-1-[4-[(3-chloro-4-fluorophenyl)amino] quinazoline-6yl] They made hexanamide- 4,7,10-triacetic acid (InL2). Also, ^{111}InL2, which is radioactive, was made. H_3L2 and InL2 did not stop the growth of A431 epidermoid carcinoma cells that had EGFR-TK, the epidermal growth factor receptor tyrosine kinase, which is linked to tolerance to chemotherapy. A431 cells did not take up much ^{111}InL2, which shows that these chelating ligands aren't good enough for making indium(III) complexes that target EGFR-TK [94]. In another research, chloro(5,10,15,20-tetraphenylporhyrinato) indium(III) and its phenolato derivatives (X = phenol or substituted phenol) were prepared. They were tested for lethal effects on MCF-7 (mammary tumor), PC-3 (prostate cancer), and A549 and NCI 4322 (lung cancer) cells. They were more effective against the lung and prostate cancer cell lines [95].

In the dark, SH-SY5Y neuroblastoma cells were put up against a chloro-indium-phthalocyanine photosensitizer. When SH-SY5Y cells were exposed to this same photosensitizer for 5 days, it did not stop cell growth much. When cells treated with the photosensitizers were exposed to

radiation, 50% of the cells went through death. The results show that In-Pc is a photosensitizer that has the features of photodynamic therapy and could be used to treat neuroblastoma [79]. Also, an indium complex with tetrasubstituted cinnamic acid phthalocyanine was made and then attached to magnetic nanoparticles with amino groups. The chemical killed MCF-7 breast cancer cells when light was shined on them [96].

The indium(III) and zinc(II) complexes of a biotinylated chlorin photosensitizer were made so that it could be used in PDT to treat cancer. Biotin (Vit B7) receptors that are overexpressed in CT26 colorectal cancer cells were used to test the phototoxicity of the biotin-chlorin (CBTN) conjugate and its complexes. Cell growth was stopped more by biotin-chlorin and its indium(III) complex than by the zinc(II) product and the chlorin precursor. It was proven that cells treated with the indium(III) complex went through apoptosis after being exposed to light [97]. In both triple-negative and triple-positive mammary tumor cells, the PDT effects of chlorin-bexarotene (CBX) and its zinc(II) and indium(III) complexes were compared to those of chlorin-biotin derivatives. CBX and CBTN were made to target the overexpressed parts of cancer cells, which are the nuclei and vitamin receptors, respectively. At nanomolar concentrations, biotinylated chlorin was photoactive against triple-negative mammary tumor cells, but at higher doses, it was toxic in the dark. CBX, on the other hand, was photoactive at nanomolar concentrations, but at the highest concentration tested, it was not toxic in the dark [98].

Also, pantothenic acid (Vitamin B_5) and lipoic acid were made to work with zinc(II) and indium(III) by adding the chlorophyll compound methyl pheophorbide to them. At nanomolar amounts, the photodynamic effects of the vitamin–chlorin derivatives were stronger than those of the methyl pheophorbide precursor on PC-3 prostate cancer cells. This led to apoptosis and the formation of cytoplasmic vacuoles in the light-sensitive tumor cells. Complexation to indium(III) made PDT work better than when the vitamin B_5–chlorine ligand or zinc(II) complexes were used [99]. Researchers have also looked at how indium(III) complexes with thiosemicarbazones kill cancer cells and healthy cells. So, it has been shown that $[In(III)(L)_2]NO_3$, HL = 2-benzoylpyridine N(4)-cyclohexylthiosemicarbazone has strong cytotoxic effects on HepG2 hepatocellular cancer cells, with IC_{50} values seven times lower than the uncoordinated thiosemicarbazone. Also, the complex was much less dangerous to healthy QSG7701 hepatocyte cells. The molecule also fluoresces, which suggests that it could be used in photochemistry [26].

It has been observed that the $[In(III)(L)_2]NO_3$ complex, HL = 2-acetylpyridine N(4)-phenyl thiosemicarbazone is more cytotoxic than the free thiosemicarbazone and mitoxantrone employed as positive controls, resulting in low-concentration antiproliferative action on HepG2 cells (IC_{50} = 3.33 0.21 mM). This fluorescence-displaying compound may find use as a fluorescent probe [34]. N(4)-Meta-chlorophenyl-, N(4)-para-chlorophenyl-, and N(4)-para-iodophenyl-$[In(III)(L)_2]NO_3$ complexes with HL = N(4)-phenyl-2-acetylpyridine thiosemicarbazone were produced. THP-1, Jurkat, and HL-60 leukemia cells, HCT-116, MCF-7, and MDA-MB-231 solid neoplasia, and mammalian non-malignant Vero cells were used to test the cytotoxic effects of the thiosemicarbazone ligands and indium(III) complexes. The indium(III) complexes, in contrast to $In(NO_3)_3$, proved to have more potent cytotoxic effects than the free thiosemicarbazones in a number of tests. Selectivity indexes, SI = IC_{50} Vero/IC_{50} neoplastic cell, for one of the complexes ranged from 3 to 144 [82]. This compound was effective against all tested cell lines at low concentrations.

An indium(III) complex of the $[In(L)_3]$ type, where HL = 5-hydroxyflavone (primuletin), has been reported to exhibit modest cytotoxic activity [100], while its aluminum(III) analogue has been shown to have cytotoxic effects on HeLa, LoVo, MCF-7, and Sk-Ov-3 human cancer cell lines. In more recent times, 2-acetylpyridine-N(4)-orthofluorophenyl thiosemicarbazone, H2Ac4oFPh, and in(III)(2Ac4oFPh)Cl_2(MeOH) and indium(III)(2Ac4oFPh)Cl_2 have been produced. The ^{114m}In isotopologues of the complexes were produced through neutronic activation. Despite the inactivity of both the radioactive and non-radioactive $InCl_3$ precursors, the cytotoxic effects of the non-radioactive complexes and their ^{114m}In counterparts were found to be equivalent and both were shown to be as powerful as the uncoordinated thiosemicarbazone against U87 glioma cells. However, if synthesized with high specific activity, ^{114m}In complexes could constitute a potential platform for the development of radiotracer medication candidates to treat glioma tumors, as they preserved the deadly effects of the thiosemicarbazone ligand [37].

3.5 Bioimaging Applications of Indium(III) Complexes

Labeling of platelets and white blood cells with the neutral [^{111}In(oxine)$_3$] (oxine = 8-hydroxyquinoline) complex has been a standard practice for many years [101]. SPECT pictures of infection sites were obtained by drawing blood, sorting the white blood cells, and then injecting them back into the patient after being labeled with [^{111}In(oxine)$_3$]. The ^{111}In is trans-chelated within the cells, most likely to biological iron chelators, resulting in irreversible entrapment of the isotope [102, 103]. There has been no research into the possible radiopharmaceutical applications of the similar ^{67}Ga oxine derivative. Using X-ray crystallography, the structure of [In(oxine)$_3$] was solved [104]. As predicted, the indium

takes on a pseudo-octahedral shape, and the 3N donors adopt a mer arrangement. No other structural isomers could be substantiated.

The use of ^{111}In-labeled DTPA complexes for Auger electron therapy is described, as is its application in imaging epidermal growth factor receptor (EGFR) for breast cancer [105]. For the purpose of visualizing brain tumors, ^{111}In-labeled DTPA has also been used to radiolabel peptidic nucleic acids that are antisense to messenger RNA (m-RNA) [106]. For many years, ^{111}In-DTPA conjugated to octreotide (trademarked as OctreoscanTM) was routinely used in clinical practice for imaging somastatin-expressing tumors [107]. Although this compound was once widely used, it has now been replaced by various radiolabelled analogues of octreotide (for examples of DOTA ligands, see below). A glycoprotein that is overexpressed in ovarian and colorectal cancers is the target of the Fab satumomab known as OncoscintTM, it was one of the first antibody-based imaging agents to receive FDA approval in the mid-1990s, thanks to its conjugation to ^{111}In-DTPA. However, because similar PET agents were available, this was taken off the market in 2002 [108].

The cyclohexyl backbone of the DTPA 10 analogue (CHX-A″-DTPA) was chosen for its stereochemical rigidity to increase the ligand's binding properties and to offer an isothiocyanato group for conjugation to biomolecules. Although this ligand system, like DTPA, may be best suited for tetravalent metal ions, it has been used to label trastumuzab (Herceptin) with ^{111}In, and the resulting conjugate binds to tumor cells at a similar affinity to natural Herceptin [109]. Additionally, In-DTPA conjugated to a tiny phenylarsonous acid that binds to heat shock protein Hsp90, one of the most ubiquitous in the cytoplasm of cells, has proven to be an intriguing method to ^{111}In SPECT imaging of apoptosis. This combination allowed for high-quality imaging of apoptosis in vivo, which may be relevant for tracking the efficacy of different chemotherapy protocols [110]. In recent years, PET-emitting ^{68}Ga has essentially supplanted ^{111}In; studies have shown that ^{68}GaDOTA TOC [111, 112] and ^{68}Ga DOTA NOC [113–115] are both highly successful for imaging neuroendocrine tumors. Although ^{68}Ga DOTA TOC has had the most application among all three PET imaging agents, there are notable distinctions between them in terms of receptor binding and selectivity. cases of sst imaging with octreatide receptors employing DOTA derivatives and other peptidic targeting drugs are discussed in a recent review [116] including some recent cases that demonstrated improved melanoma uptake and reduced renal uptake [117].

Good clinical results have been documented with the use of DOTA conjugates with octreotide analogues for the treatment of neuroendocrine tumors [116]. The proto-oncogene C-kit is a target molecule for cancer diagnostics and therapies due to its overexpression in gastrointestinal stromal tumors (GIST) and small cell lung cancer (SCLC). Recently, in vitro binding and cellular internalization studies were performed on a ^{111}In-labeled C-kit (including the ligands DTPA and DOTA for radiometal chelation). In vivo PET evaluation of a similar ^{64}Cu system showed that tumors could be well visualized in a mouse model, suggesting that it may be used as a decision-making aid before targeted therapy [118]. DOTA mono-N-hydroxysuccinimide ester (DOTA-NHS ester) and the bifunctional cross-linker sulfosuccinimidyl 4-[*N*-maleimidomethyl]cyclohexane-1-carboxylate (Sulfo-SMCC) have recently been used to modify human serum albumin (HSA). Subsequently, the cross-linked compound was covalently coupled with the HER2 affibody analogue Ac-Cys-Z(HER2:342) with HSA, the resultant bioconjugate DOTA-HSA-Z(HER2:342) was radiolabeled with ^{111}In, and assessed it in vitro and in vivo using SPECT. In this case, the data were matched to ^{64}Cu PET scans. SKOV3 cell cultures showed strong and selective absorption of radiolabeled DOTA-HSA-Z (HER2:342) conjugates. In vivo imaging using SPECT and PET in mouse models revealed strong absorption in both tumors and livers [119].

3.6 Radiopharmaceutical Applications of Indium(III) Complexes

Indium-111 is a single-photon emission computerized tomography (SPECT) isotope having low gamma-emission energy of 171 keV, 245 keV [120]. Indium (as well as gallium) radionuclides are usually used to radiolabel blood cells and platelets and investigations involving the use of complexes of indium has been reported [121, 122]. For instance, 8-hydroxyquinoline of radio-labelled indium(III) complex has been used as radiopharmaceutical agents. The use of this complex involved mixing of the suspension of the cells with that of the radio-labelled complex using plasma or acid citrate dextrose solution to form 8-hydroxyquinolate. The 8-hydroxyquinolate is lipophilic in nature and it can diffuse into the cells. However, the use of acid citrate dextrose solution is preferred to the use of plasma because some of the radiolabelled indium in the complex exchanges with label transferrin instead of the cells. This can then reduce the overall radiolabelling efficiency of the complex [123]. Pentetreotide is a bifunctional compound that has been used to form chelate with indium-111 and used for radiopharmaceutical applications. The peptide part of the chelate is important because it helps in directing the indium complex in-vivo to the receptors. Due to this, one of the indium-111 complex called OctroScan has been approved by FDA for diagnostic imaging [51]. The success attained in the use of the indium(III) complexes as radiopharmaceutical agents has led to the synthesis of other complexes of indium(III). Examples of those complexes are lipophilic tris(tropolonato) indium(III) complexes [124], lipophilic indium complexes

of 1-aryl-3-hydroxy-2-methyl-4-pyridinones[125] and several indium (III) 3-hydroxy-2-methyl-4-pyridinones [126]. Pruller et al. [127], obtained the image of the lung, liver and heart of a male mice in vivo by using 5T33 cells labelled with [^{111}In]In-DTPA-CTP (a cytotopic peptide) which bound to the extracellular membrane of the cells. This was compared with the image obtained when the same cell was labelled with [^{111}In]In-(oxine)$_3$ and the cell-free [^{111}In]In-DTPA-CTP. The image obtained at varied time are shown in Fig. 5.

3.7 Antioxidant Applications of Indium(III) Complexes

Antioxidants are a group of man-made or naturally occurring substances that can prevent or delay cell damage [128]. Antioxidants are found in many food items such as fruits and vegetables and they help in preventing oxidative stress of the physiological system [129]. For effective function of the body system, there is a need for constant supply and use of oxygen. Consequently, free radicals are produced as by-products of the oxidation process in the body. Free radicals cause harm to the cells and are contributors to health problems such as cancer, coronary heart disease, macular degeneration and diabetes [128, 129]. Antioxidants are therefore produced to eliminate or reduce the impact of these free radicals on the body system. A good example that shows the antioxidant activity of Indium III complex/compound is the work of Kostova et al. [85]. They demonstrated how the antioxidant potentials of Indium (III) complexes or compounds are expressed with their inorganic salts. Since the clinical investigation of the antioxidant potential of Indium (III) compounds that have better bioavailability with their inorganic salts have been demonstrated. This group of researchers explored the antioxidant activities of Indium (III) compound using orotic acid (HOA) salt.

To uncover the potential antioxidant activity of oronic acids in a model of non-enzyme-induced lipid peroxidation on isolated rat microsomes, three compounds of oronic acids, HOA, NaOA and InOA were investigated. Since metabolism of most pharmaceutical drugs occurs in the liver targeting hepatocytes and subcellular fractions such as cytosols and microsomes, the use isolated liver microsomes seems to be one of the most reliable in vitro models for studying drug metabolism [130]. Liver microsomes collected from Wistar rats were incubated with

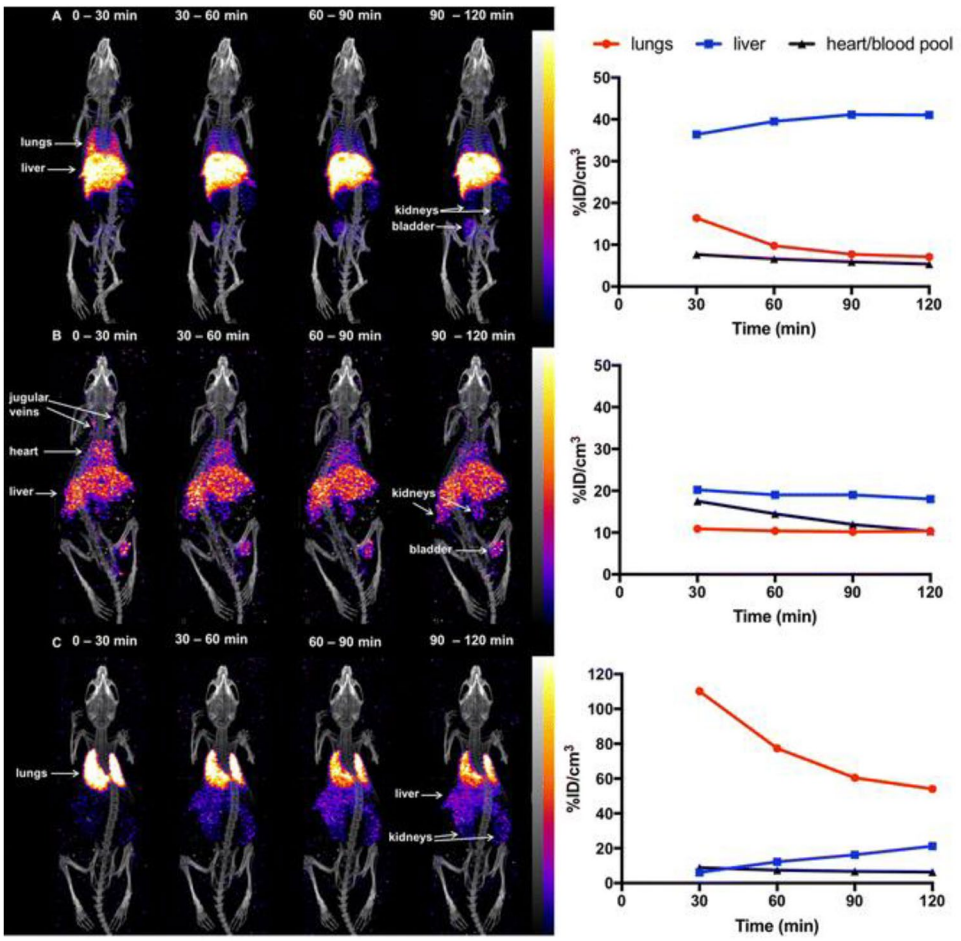


Fig. 5 SPECT/CT images obtained from mice by using indium-111 labelled cells.Image obtained by using: **A** [^{111}In] In-DTPA-CTP-labelled 5T33 cells. **B** [^{111}In]In-DTPA-CTP (cell-free) and (C) [^{111}In]In-(oxine)$_3$-labelled 5T33 cells at varied post-ejection time [127]

standard concentrations of the compounds that were being investigated. The level of lipid peroxidation in the liver microsomes was determined using the Malondialdehyde (MDA) levels. MDA is a common bioindicator used to determine the oxidative stress and antioxidant status especially in cancerous patients [131].The results revealed that when the oronic compounds, HOA, NaOA and InOA, were administered alone, there was no statistically significant pro-oxidant effects seen on isolated rat microsomes. In other words, there was no statistically significant increase in the level of the biomarker for lipid peroxidation, malondialdehyde (MDA) from the three compounds when compared to the control, the non-treated microsome (Fig. 6).

On the other hand, statistically significant antioxidant activity was only observed in InOA complex in conditions of non-enzyme-induced lipid peroxidation in comparison to toxic agent – $Fe^{2+/}$AA (iron/ascorbate). There was about 64% significant reduction in the level of lipid damage compared to toxic agent, $Fe^{2+/}$AA. The two other compounds, HOA and NaOA, revealed no antioxidant activity (Fig. 7).

From the results of the investigation, it is safe to attribute the antioxidant activity of the complex InOA, to the presence of Indium (III) in the structure of InOA which confirms the antioxidant potential of Indium (III) as seen in many similar investigations.

3.8 Optical Limiting Applications of Indium(III) Complexes

The interaction of matter with light causes nonlinearity and this property is desirable for shielding sensitive part of the body such as eyes. To achieve this, several materials have been investigated. These materials usually work by either reverse saturable absorption or saturable absorption. Though, the materials working via reverse saturable absorption are preferred for shielding sensitive part of the body [132]. Indium complexes are among numerous materials that have been investigated for this application. For instance, indium 5,10,15,20-tetrakis(4-aminophenyl) porphyrin (InTAPP) showed better nonlinear optical behaviour than the metal free derivative. This was shown by the investigation

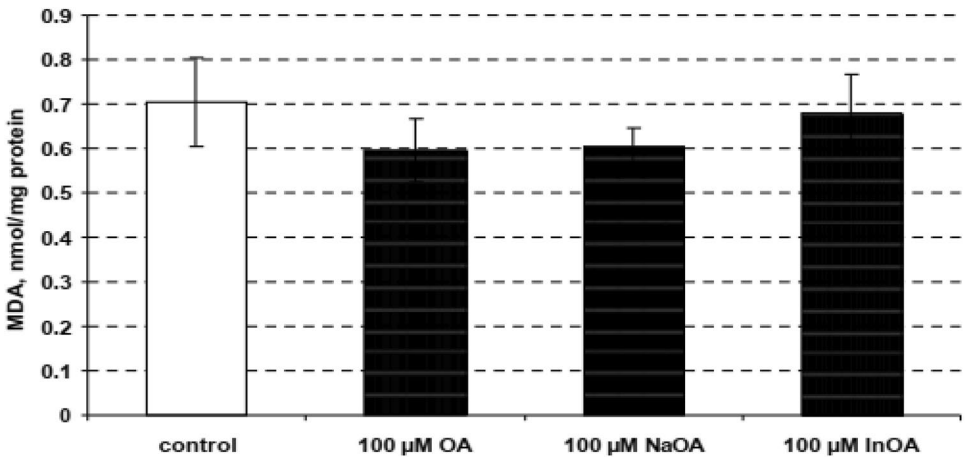


Fig. 6 MDA levels in response to 100 µM each of HOA, NaOA and InOA administered alone on isolated liver microsomes of rates [85]

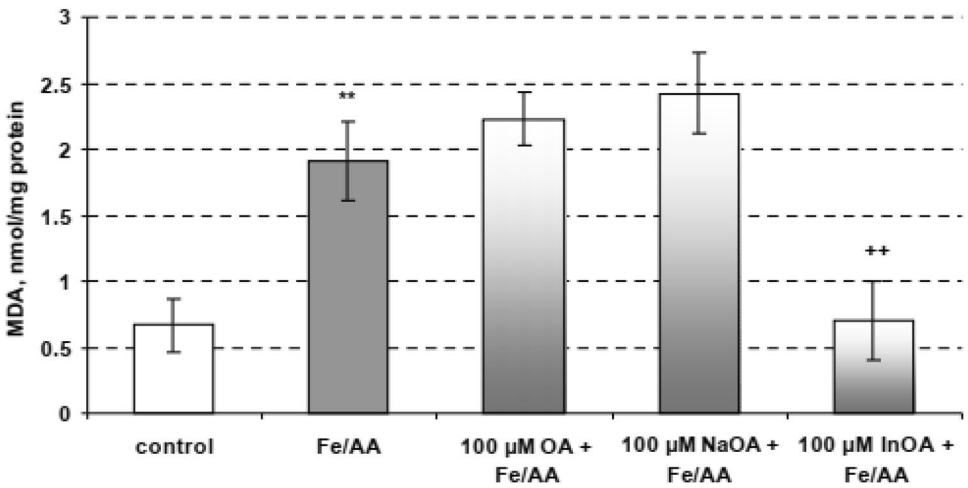


Fig. 7 MDA levels in response to 100 µM each of HOA, NaOA and InOA administered in non-enzyme-induced lipid peroxidation on isolated liver microsomes of rates (**P < 0.01 vs control (non-treated microsomes);$^{+}$P < 0.01 vs toxic agent (Fe^{2+}/AA)) [85]

carried out via the Z-scan technique at 532 nm and 10 ns pulse in dimethyl sulfoxide [133]. Phthalocyanine complexes containing paramagnetic groups or atoms have been observed to possess good limiting properties because they boost triplet state absorption [134]. Several indium phthalocyanines have been investigated for optical limiting properties. Some of these are chloro-indium phthalocyanines, *p*-(trifluoromethyl)phenyl-indium(III) tetra-*tert*-butyl-phthalocyanine and axially substituted alkyl- and arylphthalocyaninato indium compounds [42, 134–136]. Layers of anionic lithium tetracarboxyl indium phthalocyanine chloride has also proven to be a good optical limiter. It showed reverse saturable absorption properties of $\beta \sim 5.19 \times 10^{-10}$ m/W and excellent self-focusing effect of $n_2 \sim 8.86 \times 10^{-17}$ m^2/W [137]. Sanusi and Nyokong [138] observed that embedding the indium complexes inside transparent polymer support led to enhanced performance in the optical limiting. Their investigation was carried out by embedding different derivatives of indium phthalocyanine inside poly(methyl methacrylate) and poly(acrylic acid) polymers. There was high dynamic range and high damage threshold compared to the values obtained without polymers. Indium phthalocyanines are good optimal limiters in the frequency range of 480–580 nm. Also, the scotopic and photopic transmission of indium phthalocyanines are high [135]. Just like phthalocyanine complexes, naphthalocyaninato-indium complexes have also been employed for optical limiting applications. Examples of naphthalocyaninato-indium complexes that have been used include chloroindium(III) phthalocyanine [139], 2, 3-octa-[(2-hexyl)-ethyloxy]-phthalocyaninato indium trifluoroacetate, 2,(3)-tetra-[(3, 5-di-tert-butyl)-phenyloxy]- phthalocyaninato indium iodide, 2,(3)-tetra-[(3, 5-di-tert-butyl)-phenyloxy]-phthalocyaninato indium bromide and 2,(3)-tetra-tert-butyl-phthalocyaninato indium chloride [41]. Apart from these, other indium complexes that have been investigated for optical delimiting applications are (octaaryltetraazaporphyrinato)indium(III) complexes [140], ferrocene-functionalized indium-based metal–organic frameworks[141] and indium nickel oxo-cluster ($In_{10}Ni_8$-oxo cluster)[142], All these have shown good optical limiting properties.

3.9 Photodynamic Antimicrobial Chemotherapy Applications of Indium(III) Complexes

As shown in Fig. 8, the mechanism of antimicrobial chemotherapy involves seven stages (1–7). It starts with the absorption of photon leading to the excitation of one of the electrons to higher energy orbital. Therefore, it is activated to short-lived excited singlet state ($^1PS^•$). This singlet state dissipates heat energy by releasing fluorescence. On the other hand, the singlet state is converted to the triplet state ($3\ PS^•$) via intersystem crossing. The reconversion of the triplet state to the singlet state leads to the emission of phosphorescence. Instead of the conversion, it can also react with the substrates such as unsaturated fatty acids in the cell membrane and form organic radicals. Reaction of these radicals to the cellular oxygen leads to the formation of reactive oxygen species [143, 144].

Indium, being a heavy atom, has been used as a central metal for the complexes utilized for the photodynamic antimicrobial chemotherapy because it allows intersystem crossing to the triplet state [145]. The performance of the indium complexes for this application is related to the presence of bridging atoms and the overall charge of the complexes

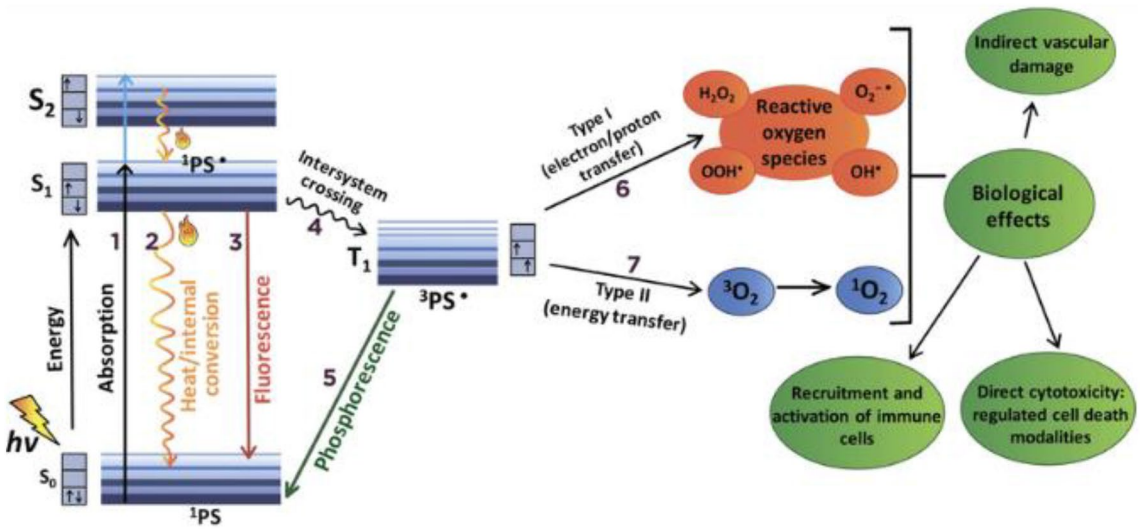


Fig. 8 Mechanisms of photodynamic therapy [143]

[146]. As demonstrated by the investigation carried out using octa-pyridylsulfanyl substituted indium (III) phthalocyanines having different overall charges, the highly positive complex showed better log reductions against *C. albicans*, *S. aureus* and *E. coli.* Among the positively charged complexes, the reduction values were found to be influenced by the bridging atoms linking the ligands [146].The quantum yield of the indium complexes has also been reported to be influenced by the solvent used for the photodynamic investigations. Osifeko et al., reported that the mono- and tetra-pyridyloxy substituted indium(III) phthalocyanines exhibited high singlet oxygen quantum yields (Φ_{Δ}) from 0.44 to 0.69 in DMSO while in DMF, it exhibited between 0.44 and 0.66 [147]. It clearly showed that indium complexes are active for photodynamic application even in different solvents. Apart from using indium complexes alone, incorporation of indium complexes into nanoparticles has also proven to be effective for photodynamic antimicrobial chemotherapy [148]. For instance, indium porphyrin complex was linked to silver-core shell magnetic nanoparticles. There was reduction of *E.coli* with a value ranging from 7.19 to 9.58 [149]. Indium tetramorpholine has also displayed good photodynamic performance against *Candida albican, Escherichia coli* and *Staphylococcus aureus* [150].

4 Toxicity of Indium(III) Complexes

In the early 1960, Leach and colleagues in their study administered a dose range of 24–97 mg/m^3 of indium oxide to rats for a period of 4 h/day for a total duration of 12 weeks. Although they observed varying symptoms, edema of the alveolar and the manifestation of alveolar protein throughout the 3 months of the study were notable findings. Based on this report, the American Conference of Governmental Industrial Hygienists decided on the acceptable level of exposure to indium in 1969 [151, 152]. It should however be noted that over the years the interest of various regulating bodies grew regarding the need to control the level of exposure and associated toxicity of indium and its complexes following reports of indium-related severe pulmonary injury among Japanese workers. Regulatory guidelines on the handling of indium and its complexes become necessary after the recorded death following occupational exposure among these workers. Consequently, the Ministry of Health, Labour and Welfare in Japan realised the need for a safety data sheet for the compound, therefore, they mandated the monitoring of work environment every 6 months and approved a permeable level of 0.1 mg/m^3 for indium complexes [153].

The toxicity of indium complexes is not well reported because the few studies done on the compounds focused on their therapeutic and industrial values. Present findings seem to indicate that indium has a more toxic action than gallium, however, the toxicity and carcinogenic effects of indium compound in humans seems to happen at extreme doses of exposure [76]. There is dearth of information on the pharmacokinetics of indium compounds, which plays a role in the levels of toxicity observed following exposure to these chemicals. It has been observed that indium complexes mostly get into the systemic circulation after inhalation through the lungs. Absorption of these compounds through the gastrointestinal tract appears not to be significant, hence, removal from the body following exposure is basically through faeces. Nevertheless, the kidney plays a little role in clearing the compounds from the circulation through urine [154].

The lethal effects and distribution of indium compounds in the body is secondary to their polarity, chemical nature, dose and route of exposure to the body. Occupational exposure to indium compounds occurs primarily through breathing, hence, the lungs and pulmonary function is directly compromised. Clearance of indium compounds from the body is slow following long-term exposure. Early studies showed the toxicology profile of indium compounds following tracheal exposure in animal experiments [155, 156]. Nevertheless, observations on the pulmonary toxicity of these compounds were not reported among workers until year 2003.

Extreme interstitial pneumonia was found out among workers following 3 years of occupational exposure to indium tin oxide [157]. The main clinical presentations of indium toxicity following exposure include granulomas, emphysema, pneumonia, pulmonary fibrosis and elevation in serum bioindicators of interstitial pneumonia e.g. SP-D, SP-6 and KL-6 [158]. Cross-sectional studies among those who work with indium revealed that the level of the compound in the systemic circulation is closely associated with the duration of exposure and the degree of pathological changes in the lung tissue. Surprisingly, the observed emphysematous lesions among heavily exposed personnel continue to increase post-exposure. Hence, irreversible changes to the lungs tissues could only be prevented by early detection [158]. Now, there is no specific treatment for lung toxicity due to indium exposure. The disease has a poor prognosis and patients' mortality has been basically ascribed to respiratory collapse or pneumothorax.

Large number of studies focused on the effects of indium complexes on the respiratory system. This could not be far from the fact that the major route of occupational exposure to indium complexes is via the pulmonary tract. However, there are reports on the effects of indium compound on the integumentary system. The activation of the immune system and subsequent hypersensitivity reaction, secondary to dose-dependent elevation in lymphocytes count have been observed following exposure of indium tin oxide to the skin [159].

Yang et al. [160] reported significant correlation between the serum level of inflammatory indices like GM-CSF, TNF-α, IL-4 and 5, and β levels and the amount of indium compound. The increase in the levels of inflammatory markers in the serum explain the inflammation of the lungs tissue that has been reported in several studies. The inflammatory reaction could be due to the attempt of the tissues to get rid of the insult. However, chronic pulmonary disease may ensue owing to prolonged presence of the foreign agent and the incoordination of the reparative process. Alongside inflammatory events, Liu et al., reported on the oxidative stress manifested, secondary to excessive production of free radicals and hence imbalance between pro-oxidative and anti-oxidative species. Significant elevations in the total antioxidant capacity, catalase and alkaline phosphatase were realised after indium exposure. This explains part of the mechanisms by which indium compounds instigate tissue destruction and consequently overall poor health status [161].

Intravenous and oral administration of indium chloride to gravid rats and mice has been noted to cause embryo toxicity and malformation of fetus. This suggests that indium could possibly cross the placenta barrier. However, the carcinogenic effects of the compound have not been documented in mice [162]. Indium compounds accumulate in the renal tissue, especially in the cytoplasm and the mitochondria of the kidney cells. The complexes attenuate the enzymes of heme biosynthesis in the kidney, causing the excretion of the compound alongside urine [163].

In a cross-sectional study conducted by Chonan and colleagues [158], it was observed that those workers with high level of exposure to indium concentrations experience considerably longer duration of exposure, more alterations in high-resolution computed tomography, reduced diffusing ability of the pulmonary tissue for carbon monoxide and elevated serum level of KL-6 levels, relative to those with lower exposure to the chemical. Hamaguchi and associates [164] presented a data on more than five hundred subjects who were presently or previously exposed to indium compounds. They documented a dose-related elevation in the serum level of KL-6 and surfactant proteins, which was significantly associated with an elevation in the endogenous level of indium. No doubt their observations further confirmed and established the association between exposure to indium compound and pathology of the pulmonary tissue. It is noteworthy to state that Nakano et al. had speculated a cut-off value of 3 ng/ml with respect to indium exposure in order to curb the manifestation of early pulmonary defects [165].

Exposure of pregnant animal to indium complexes is known to cause varied manifestations at different doses, especially at higher doses in different species of animals. Notable findings include inhibition of fetal growth, teratogenicity, death of embryos, caudal hypoplasia, malformations especially at the digit and tail regions, among others [162]. Toxicokinetic findings have affirmed that the concentration of exposure of embryo to indium complexes is a more important index than the duration of exposure. In humans the manifestation of developmental toxicity is low following indium exposure during pregnancy unless there is accidental exposure to extreme doses [162].

Previous studies have explained the possible pathogenesis and mechanism of developmental toxicity mediated by indium complexes. At various concentrations, the compound enhances apoptotic process in rats thymocytes and attenuates intercellular communication among liver cells via the gap junction [166, 167]. Caudal hypoplasia, as a result of tail malformation during developmental processes is secondary massive cellular apoptosis in the tail region of the embryo [162]. The skeletal system also presents pathological manifestation because of indium exposure. The chondrocytes in rat embryo showed inhibited activity of chondrocytes [168], which evolve to skeletal deformities.

5 Conclusion and Future Perspectives

Indium(III) complexes have proven to be the solution to several medical and biological challenges based on the investigation carried out till date. The performance of the indium complexes generally depends on the ligands that was used for the preparation of the complexes among other factors. Despite the success recorded so far, there are still a lot of research vacuums that still need to be filled for full utilization of these complexes. For instance, the use of indium(III) complexes for the treatment of various viral infections has not been fully studied. Therefore, further research should be conducted on the potential of the indium(III) complexes in the treatment of viral diseases such as human immunodeficiency virus (HIV) and coronavirus disease. Interaction of these inorganic complexes with biomolecules such as human serum albumin should be further investigated by using density functional theory (DFT) calculations and Hirshfeld surface analysis (HSA). Furthermore, the discovery of new ligands that will be the basis for the synthesis of novel indium(III) complexes should be pursued.

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Declarations

Conflict of Interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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