Toxicity

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REVIEW ARTICLE

Toxicity and anti-tumour activity of organotin (IV) compounds

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ABSTRACT

Organotins are widely described as anti-tumor, anti-inflammatory, anti-fungal, and antimicrobial agents. In addition to their uses in biomedical fields, organotins are also used in agricultural and industrial applications. These materials are more toxic than inorganic cans, which are poorly absorbed and are excreted on the surface of the can, and cause toxicity to a variety of organisms and damage the environment. This review focuses on organotin's toxicity and uses in biomedical fields.

Keywords anti-tumor, biomedical, environment, organotin, toxicity

INTRODUCTION

In the last few decades, organotin complexes have played a vital role due to its structural and therapeutic activity **(check and proofread carefully, please)**. Organotin compounds have attracted great attention in the treatment of cancer. They are known to utilized as therapeutic on numerous tumour cells, but little is known regarding their mode of action **(check and proofread carefully, please)**. Structures, and biological actions of organotin(IV) compounds have lately been plotted.[1] Organotin carboxylates are often used because they have cytotoxic and biocidal potential, in addition to their agriculture and industrial applications. Generally, the coordination number and molecular structures of the tin atom are the main important aspect to specify the biocidal activity of organotin(IV) complexes. Although these parameters are not well understood yet, they may become more essential in the future because of their relation to the nature of tin element bonds and its coordination sphere of tin atom **(check and proofread carefully, please)**.[2] Chemical and biological factors effect characterizing tin compounds' toxicity. Even though little information revealed the consequences of tin compounds on microorganism development, progressions of several kinds of bacteria can be repressed via organotin derivatives that are associated with membrane functions and their influence on solute transport, energy conservation

and transport and substrates oxidation **(check and proofread carefully, please)**. There is limited information regarding the toxic effects of organotin compounds on microorganisms such as fungi and algae. Their impact recognized on mitochondria stems and chloroplasts mainly from higher plants as well as animal systems. The tri-organotin compounds cause action opposed to mitochondria and chloroplasts via leading to tumors **(check and proofread carefully, please)**. Another key point, that di-organotin compounds seems to work through binding to dithiol functional group on cofactors and enzymes, while ionophores work against ATPase. Furthermore, DNA does not show negative effects due to concentration. In practice, tin compounds have no effect on microbial enzymes, yet resistance is easily obtained and allows understanding of the several types of biological reaction with tin compounds.[3] **(check and proofread carefully, please; sentence structure needs careful editing)**

A plethora of organotin(IV) complexes were synthesized and characterized in recent years, and they exhibit important biological activities. The complexes compounds have been evaluated for their activities *in vitro* on a variety of tumor cells. Likewise, it is utilized for lubricants, Additive coatings to prevent microorganism attack, catalysts, polymers and organic synthesis.[4] **(check and proofread carefully, please)**

Previously, several studies have been conducted about the interaction between benzohydroxamic acid and its derivatives and di-organotin (IV) acceptors. Despite their synergistic effects, several of this type of compounds have demonstrated remarkable activity *in vitro* against a various human tumor cell.[5]

A number of cancers are reported to have viruses associated with them and a small number of supposed to be essentially caused by viruses.[6] **(check and proofread carefully, please)** Thus, an anticancer drug might be an antiviral agent although the converse is not necessarily true. The protein and nucleic acid moieties of viruses are operator chelating agents and the goal of the metallotherapeutic designer to alter the virus by metal chelation, which will therefore lessened by the viral activity.[7]

QSAR OF ORGANOTINS *(YOU SHOULD DEFINE THE QSAR)!*

The toxicity of tri-substituted (R3Sn's) and alkyl are more than that of di-substituted substituent of organotins (R2Sn's). On the other hand, mono-substituted organotins (RSn's) have lower toxicity when compared to others. When tetra-substituted organotins (R4Sn's) metabolized to tri-substituted organotins they converted to toxic **(check and proofread carefully, please)**. Tri-substituted alkyl compounds of chains contain 3, 4, 5 carbon atoms or phenyl-, and cyclohexyl organotin compounds are usually the very poisonous to microorganisms. The total molecular surface area of the tin compound and the ratio between n-octanol and water (Kow) also are responsible for identifying the toxicity of tri-substituted tin compounds that refer to the relation between hydrophilicity (water soluble) and lipophilicity (fat soluble) substances, if Kow is less than one indicates substance more soluble in water and less toxic and if it is greater than one that means more hydrophobic and predicts high toxicity.

ORGANOTIN AS ANTI-TUMOR AGENT

Over time, studies have been conducted that show that low amounts of organic tin can inhibit the growth of tumors **(check and proofread carefully, please)**. This prompted the researchers to work across the genetic pathway in cancer cells, opening up a new research sub-area around organotin compound **(check and proofread carefully, please)**.

In this review the testing of the yields of organotin compounds *in vivo* and *in vitro* was illustrated. Studying organotin compounds gives way to new horizons for the potential prosperity of anti-tumor drug industry. When the early studies of anti-tumor with *cis*-platin
(Figure 1) revealed to have a remarkable effect against leukemia L1210 and sarcoma 180 in mice. The compound has been approved for clinical use and it has continued to be used for medical purposes. The *trans*-isomer shown in Figure 1 mutant of this compound displays limited activity against tumors, either because it is chemically incapable of showing specific endogenous metabolites or because the biological treatment of the complex from this compound differs from that of the *cis*-isomer.[8] **(check and proofread all the paragraphs of this section carefully, please)**

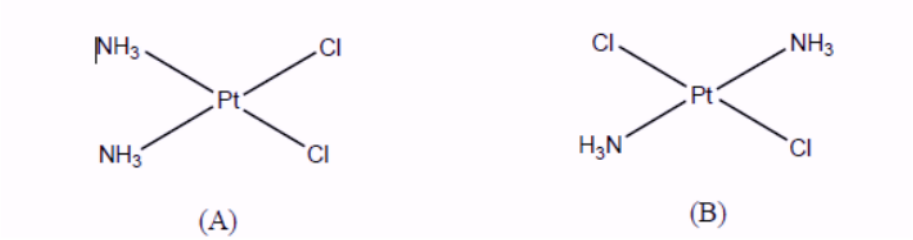

Figure 1 **The platinum complex (A) *Cis*-platin, (B) *Trans*-platin.**

Over the last five decades there has been considerable interest in the organometallic field which is a branch of chemistry that links the organic and inorganic fields. Since the discovery of organometallic compounds in the 1980s, these compounds have been proved to be useful catalysts for extensive industrial applications such as antiknock additives for gasoline and biocides.[9] Furthermore, the wide medicinal usage area of titanium dichloride provoked great interest in research into organometallic compounds as anti-tumor agents because of their structure being related to *cis*-platin and its derivatives.
Organometallic-based compounds possessing anti-tumor activities can be classified into three fundamental classes: metallocene diacido deriviatives, ferricenium salt, and diorganotin complexes as shown in Figure 2 that displays the structural formulas of the complexes classes.[10,11]

Iron(III) ion in ferrocinium salts has two cyclopentadienyl coordination bonds at a sandwich formation. These compounds are hydrophilic due to their high stability in water which can prevent the growth of various types of tumors, and they are potentially valuable for clin-

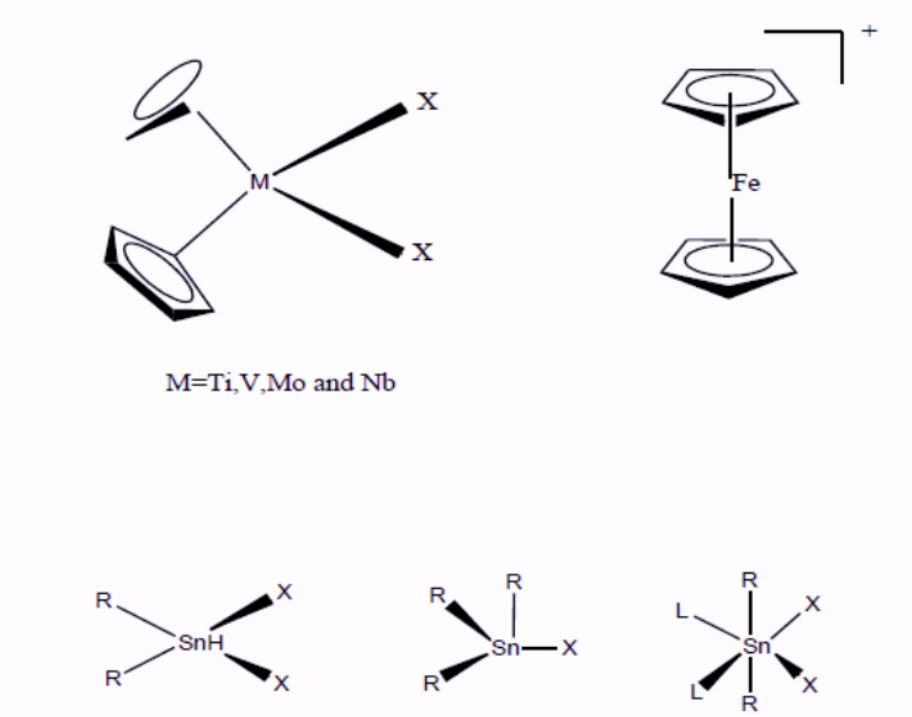

Figure 2 **Structure of some organometallic compounds which exhibit antitumouractivity.**

ical use because of their powerful oxidizing characteristics and their low toxicity and exceptional water solubility.[12] Bi-organic (IV) complexes comprise a class of potential anti-tumor agents, which have been effective against P388 lymphocytic leukemia and MCF-7 breast tumor.

Hydroxy acids such as arylhydroxamic acid are biologically active due to their high ability to donate oxygen. Previously, scientists studied the interactions between benzohydroxamic acid and di-organotin(IV) acceptors and its derivatives, with the synergistic effect of those compounds, they found that most of the di-organotin (IV) derivatives showed remarkable activity against a sequence of diverse cancer cells in humans. The study also demonstrated that the complexes of benzohydroxamic acid, diethyltin (IV) and dibutyltin (IV) are predicted to be leading materials.

The studies about organotin(IV) compounds anti-tumor activities date as far back as 1929 (U S Patent 1930) and a key development in the field of bio organotin chemistry in the last two decades to find that organotin compounds have the potential to be used as anti-carcinogenic,[13–15] and also as fungicides, biocides and pesticides.[16] Tetrahedral, trigonal bi-pyramidal and octahedral are most common geometries of tin(IV) complexes. Addition of neutral organic donor ligands may raise the coordination number of tin atom from four to five or six.[17]

The organotin derivatives containing ligands with O, N or S donor atoms may coordinate to the tin to make the Sn-N, Sn-O or Sn-S bonds which have a potential to play an essential factor in their activity against the tumor cells, the mechanism of action has not yet been known. One of the most important organic ligands containing two oxygen atoms are hydroxamic acids and have the potential to interact with organotin(IV) compounds may generate complexes with different geometric structures and features to make them biologically active.[18] Recently, studies about the biological mechanisms of these complexes have failed to add data on this issue.[19,20] However, only scanty and scattered information are available on the specific anti-carcenogenic activities of organotin(IV) unsubstituted mono-and dihydroxamates[21,22] but N-substituted hydroxamic acids have not been studied yet properly.

Organotin hydroxamates derivatives were discovered in 1984,[23] but their application as a anti-tumor agent was not recognized until 1991. They have been used against normal and preneoplastic rat hepatocytes. The preneoplastic hepatocytes were found to be obviously sensitive to organotin hydroxamtes, whereas the normal hepatocytes were less sensitive. In addition to this a series of dibutyltin(IV) complexes of unsubstituted arylhydroxamic acids have been used on human A-549 tumour cells and P388 leukaemia[22] and the results illustrate that nearly all compounds exhibit significant activity against human A-549 tumor cells and showing a significant difference in the activity of the same compounds against A-549 and P388.

Several naturally occurring acids and the synthesis of a number of medicinally active hydroxylamine derivatives has been reported in recent years while some of the hydroxamic acids have already found applications in drug-delivery system[24,25] in iron-solubilisation and transport[26] and in DNA cleavage.[27–29]

Studies regarding antitumour applications of the organotin are still not enough to have complete understanding of the mechanism. It is established that the drug molecules goes through a series of procedures such as crossing of cell-membrane,chemical hydrolysis, transfer in the physiological intermediate, and subsequently arrive at the close of goal DNA molecule and figure active intermediates R2Sn2+ which may have direct interaction with the phosphate group of DNA structures, invoking cancer cells via damaging the DNA, which leads to cell-death. The molecular structure of organotin complexes which are consistent with the two-pole complementary standard,[30] usually present two types of alkyl groups one leaving (R') and the other is the remaining (R) group which is stable in an aqueous solution. The organic ligand R can go through the lipid bilayers and reach closer to the target molecules and the binding modes flanked by the ligand R' and tin undergo the mechanism of hydrolysis in the physiological medium. Therefore, a successful application may require the drug molecules to possess a good oil/water partition coefficient and the hydrophobic groups must not be too bulky.[22] **(check and proofread carefully, please)**

CONCLUSIONS

The main aim of this review was to demonstrate the toxicity of organotin **(the title is defined to organotinIV)** derivatives and its application in biomedical field as anti-tumor agent. Dif-

ferent studies have been done on organotin(IV) compound but still much efforts need to be done on this aspect to evaluate and found the specific uses in biochemical area.
It can be concluded from this study that organotin(IV) compounds have a significant uses in medical fields as T-cells inhibitor by chelate with specific complexes that have the ability to form *cis*-platin moieties.

ABBREVIATIONS

Should be added.

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Should be added.

DECLARATIONS

Authors' contributions

Should be explained.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval and consent to participate

Not applicable.

Data availability

Not applicable.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9