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Review Article

BIOMEDICINAL ASPECTS OF GROUP-15 ELEMENTS (As,Sb,Bi)

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Abstract-The present review article deals the advancement in bioorganometallic and Metalopharmaceuticals applications and perspectives of group-15 elements in recent past. It is well known that organometallics of group-15 elements shows vast potentiality in biomedical research in past few years and used in the treatment of various chronic and acute diseases. The authors tried to compile literature regarding this area of research in the manuscript up to date along with brief out lines of medicinal importance of metals.

Keywords- Biomedicinal Perspective, Organometallic, Antimicrobial, Entomological, Toxicological, Antitumor, and Gastroprotective activity.

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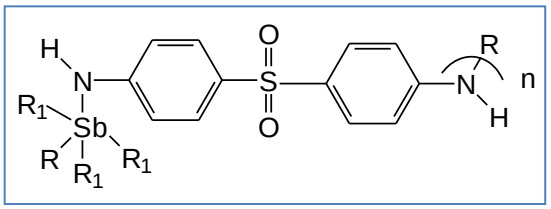
Introduction

It is now well known that metals have played an important role in medicine from so many years but people have only recently realized their significance in medical science in the treatment of various diseases. Metals have an enormous potential in medicines and their selection may offer the possibility for the discovery of new metal based drugs with novel mechanism of action. The importance of metal based drugs lies in the fact that they are essential components for various physico-chemical processes occurring in living system. The spectrum of the metal based drugs has been expanded as they have found their place among a class of potential biologically active compounds exhibiting antimicrobial, anti-inflammatory, cardiovascular, trypanosomal, anti-herpes and anti-tubercular along with the treatment of cancer and gastric disorders. It is surprising to observe recently that metals are able to do the best and the worst; i.e. metal are able to induce the diseases and also to treat them, some are able to perform both. It is known that almost all metals are able to generate reactive oxygen species, which explains the great part of treatment of cancer and other acute diseases. Basically both, transition and non-transition metals plays important role in the treatment of various infectious and acute diseases.

Organometallics of Group-15 elements as Antimicrobial

The discovery of synthetic arsenicals, *"Salvarsan"* in 1910 found as an effective medicine against *syphilis*, led to an extensive investigation on the synthesis and biological studies of organoarsenic compounds [1]. Later on, in some reviews and books it was published that organometallic compounds of group 15 elements shows higher activity against bacterial, fungal and viral strains of microorganisms [2]. The organoantimony compounds played an important role against the microorganisms. They proved highly effective against infections by *Trypanosomes* and *Leishmanian* organisms [3-6]. Some reports on the microbiological activity of organoantimony compounds have stated that most of them are toxic [7], but do not have a repetition as potential hazardous to those preparing them. It was found that the organoantimony (III) derivatives show important bactericidal and fungicidal activity [8]. The antifungal activity of organoantimony compounds has been studied by some workers [9, 10]. A number of organoantimony (V) polyamines have been synthesized and biologically characterized as antibacterial and fungicidal agent recently [11].



Organoantimony (V) polyamines

Despite the action of organoantimony compounds as potent antimicrobial, the exact mechanisms of their action were unknown but in recent few years it was reported that organometallics of group-15 generally damage the peptidoglycan peptidoglycan layer of bacterial cell wall and damage it by penetrating in such a manner that the organic group gets entered inside the cell by puncturing it followed by death of bacterial cell. Sometimes these compounds in low concentration may cause bacteriostatic condition by slow down the growth of bacterial cells [12, 13].

Organobismuth compounds as Antimicrobials

The organobismuth compounds have also attracted the attention owing to their microbiological and material utility [12-16] from more than 200 yrs. It was found that organobismuth compounds were active against the treatment of gastrointestinal disorders like dyspepsia, diarrhea and in peptic ulcers by inhibiting *E. coli* [17-26]. In recent a group of Japanese workers synthesized a series of organobismuth compounds which shows potent antimicrobial activity against fungus and bacterial culture responsible for human pathogenic disease [27]. The salts of organobismuth compounds, such as colloidal bismuth subsalicylate (CBS), bismuth subcitrate (BSC) and ranitidine bismuth citrate (RBC) are now common

for controlling bacterial and fungal infections [28]. The recent demonstrations has shown that these salts are useful for *Helicobacter pylori* eradication therapy (*Helicobacter pylori is now well known for the formation of gastro intestinal ulcer in Human beings and organobismuth compounds are the only cure against this bacteria*) [29,30] and has promoted the antibacterial and antifungal studies of various organobismuth compounds [31-40]. Some investigators have synthesized a lots number of organobismuth compounds which might have highest antimicrobial activity [41-54].

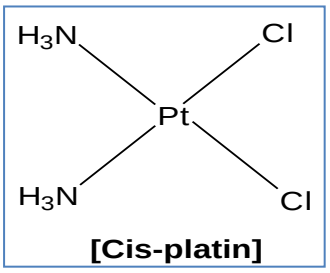
Organometallics as Antitumor Drugs

The existence of relationships between tumor (cancer) and metal is known to all oncologists. However various aspects about these relationships are ignored by many. It is surprising to observe that metal are able to induce cancer and also to treat the cancer while some are able to perform both. It is known that almost all metals are able to generate reactive oxygen species, which explains and play the greatest part of treatment of cancer. Both transition and non-transition metals plays important role in the treatment of tumors.

Transition Metal compounds as Antitumor Drugs

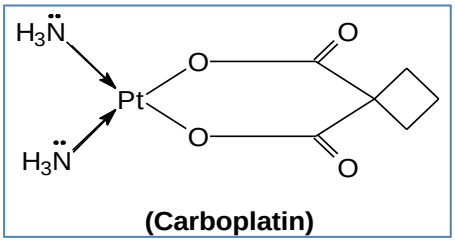
In the category of transition metal; organoplatinum compounds were the first, which were used in the treatment of cancer. The common organoplatinum compounds to be used are; cisplatin, carboplatin, oxaliplatin and nedaplatin. The last three compounds of platinum are analogs of cisplatin [55-57].

Cisplatin: [Cis-dichlorodiammine platinum (II)] Cisplatin was found active against testicular and ovary cancer and also in lungs, gall bladder, cervix, head and neck, esophageal cancer cell line [58-61].



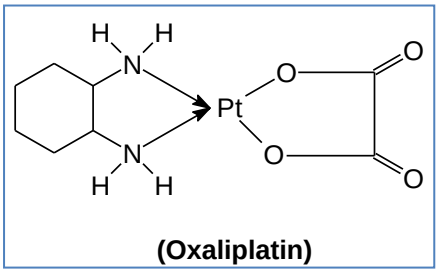
[Cis-platin]

Carboplatin: Because of its low hematological toxicity in comparison to cisplatin, it is widely tested in a large number of tumor cell lines. It is found active against ovarian, head and neck, gall bladder, and in small cell lungs cancers [58-61].



(Carboplatin)

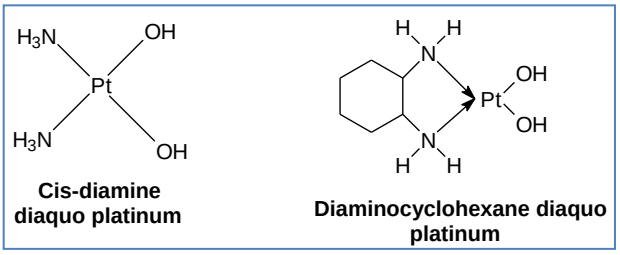
Oxaliplatin: Because of its low toxicity and high efficacy than cisplatin, it gave interesting results in ovarian, breast, head and neck and in acute blood cancer [62]. The best result to date has been obtained in the treatment of colon cancer.



(Oxaliplatin)

Nedaplatin: It was selected for the cancer treatment because it produced better results than cisplatin in preclinical studies. It was generally used in the treatment of head and necks, testis, ovaries, lungs, esophageal, and cervical cancer [63].

Mechanism of action: These four platinum drugs could be considered as pro-drugs and their hydrolysis is a key step in mechanisms of action. The product of double aquation forms the active metabolites.



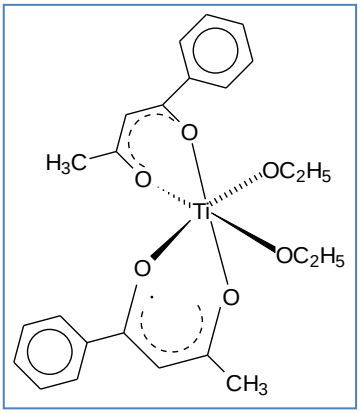
Cis-diamine diaquo platinum

Diaminocyclohexane diaquo platinum

The diaquo-platinum species reacted with amino group of proteins, RNA and DNA, forming the respective adducts, which appears to be associated with clinical activity. They generally reacted with the N-7 position of adenine and guanine and produces cross linking between bases in the same or in opposite strand [64] and mediated cytotoxcity by inhibiting DNA replication and transcription [65]. The efficacy of platinum drugs against cancer cells could be related to inhibition of new DNA synthesis [66].

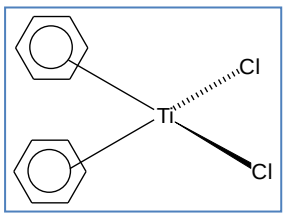
Non-platinum Organometallics as Antitumor Drugs

In past twenty years new metal complexes other than platinum have been explored for this wide spread disease. The first non platinum complex tested in clinical trials was cis-[$(CH_3CH_2O)_2$ $(bzac)_2$ Ti(IV)].



This complex of titanium was used first against a variety of ascites and solid tumors [67-70] such as Ehrlich ascites, Sarcoma-180 ascites tumor. Their marginal responses were found in leukemia p-388 and L-1210. The biomedicinal properties of transition metal organometallics compounds were not explored until 1979, when Kopf Maier and Kopf published the first metallocene with antitumor activity [71].

Titanocene dichloride: It was the most effective organometallic compounds, showing its best activity against colon, lungs and breast cancer cell line [72] *in-vitro*. In contrast to platinum complexes, titanocene dichloride showed no evidences of nephro and mylotoxicity [73-80]. Because of their low toxicity this compound is presently in clinical trials [80-86]. It was found that titanocene dichloride showed enhanced activity over cis-platin [87] and cis-platin resistant ovarian carcinoma cell line [88-90], and higher effective against ovarian cancer cell line in comparison to 5-fluorouracil and cyclophosphamide [91-95]. A series of ionic titanocene complexes containing thiomiclobases has been synthesized and investigated [96] and have been found to be more potent antiproliferative agent [97].



Mechanism of action: The nucleic acids have been proposed to be the target site in the cellular system [98-102] and the binding of titanium complexes with calf thymus DNA have been pursued by spectrophotometrically and fluorescence spectroscopy [103]. The interaction of titanocene dichloride and a mixture of 5'-AMP and 5'-TMP have shown that the complex disrupts the hydrogen bonding of the A-T base pair, which suggested the part of antitumor activity [104-106]. Titanocene dichloride may also inhibits the protein kinase-C, an enzyme responsible for cell proliferation [107], Human topoisomerase-II, an enzymes responsible for DNA replication [108] and stops the cell proliferation.

Vanadium Compounds as Antitumor Drugs

The chemical composition and antitumor activity along with toxicity of the vanadium compounds play a significant role in controlling the various kinds of tumors [109]. The peroxovanadates [110,111] may play dynamic role in controlling the tumor growth. Vanadocene, containing vanadium (IV), belongs to the metallocenes class of antitumor agent [112-116] shows both *in-vitro* and *in-vivo* antitumor activity [117-120]. The reduction of vanadium (V) to vanadium (IV) seems to regulate various cellular actions such as cytotoxic, cytostatic and some morphological effects [121-123]. The vanadium complexes are best effective against breast cancer, cell line [124-128].

Mechanism of action: Fluorescence activated cell sorting assessments shows that peroxovanadates block the G_2-M transition state of the cell cycle in cancer cell line leading to significant reduction in growth of tumors [129]. Vanadium compounds may also play important role in controlling cell proliferation via interaction with DNA. Vanadocene complex interact with DNA nucleotide phosphate group forming a liable outer sphere complex via a water group [130] and inhibits the cell proliferation.

Non-transition Organometallics as Antitumor Drugs

Not only transition metals but a series of non-transition metals complexes are known to possess antiproliferative activity.

Gallium Complexes as Antitumor Drugs

The anticancer properties of gallium compounds were first time reported in 1997 [131,132]. The radioactive gallium^{67} and gallium^{68} shows some prominent activity against bone marrow cancer [133]. The new compounds of gallium maltolate, doxorubicin-gallium transferrin conjugate and tris (8-quinolinolato) gallium (III) shows interesting antiproliferative activity against tumor cell line [134-137]. Gallium nitrate was reported as potent antitumor agent for human leukemic cell line and breast cancer cell line [138,139]. Gallium chlorides are also active against breast cancer when taken orally [140,141].

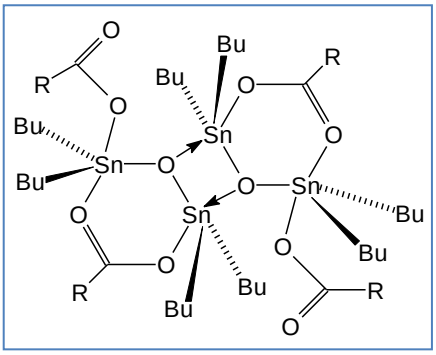
Mechanism of action: Gallium compounds generally interact in trivalent state with the DNA molecules in aqueous solution under different pH conditions [142]. Gallium compounds bound to DNA phosphate forming a stable complex and acting as a competitor with magnesium for DNA binding. It has been found that the affinity of gallium for DNA is 100 times higher than that of magnesium [143]. Gallium compound may inhibit the RNA-reductase and inhibits the replication of DNA therefore inhibiting the growth of cells [144-146].

Organotin Compounds as Antitumor Drugs

The first organotin compounds, for which the antitumor activities were examined, were formally similar to cisplatin [147-155] or to its analogous carboplatin and paraplatin [156-158]. These compounds show borderline activities against leukemia P-388 and L-1210 [159-163]. Many diorganotin compounds, R_2SnX_2, were investigated in context of their antitumor activity [164-166]. The Di-n-butyltin analogue of carboplatin was synthesized and screened against MCF-7 and WiDr tumor cell line of humans [167]. Besides this, a series of organotin derivatives of carboxylic and dicarboxylic acids were synthesized [168-170] which show better efficacy. The organotin derivatives of pyridoxine and erythromycin were synthesized and tested against tumors cell line [171,172]. Some triorganotin compounds were also found active against various tumors cell line [173]. The steroid based carboxylate series is one of the major early development in this area [174-177]. They appear to contain pronounced *in-vitro* antitumor activity [178,179] but their solubility still remains drawbacks [180] which affect the tumor activity. In order to make this kind of compounds more soluble in water a less complicated structure was designed which contains polar moieties [181].

Water Soluble Organotin Compounds as Antitumor Drugs

The introduction of polar groups in the organotin molecules leads to some improvement in the solubility and *in-vitro* antitumor activity. Fluorine containing organotin compounds were synthesized to check the effect of compounds on tumor cell line [182-183]. Fluorine containing compounds are more soluble in water and still soluble in non-polar solvents and have found useful application in tumor activity [184-187]. We can also increase the solubility by preparing salts of organotin compounds [188-191]. The most recent development in the field of antitumor active organotin compounds has been achieved by the synthesis and screening of compounds containing polyoxaalkyl moiety [192] which exhibit high antitumor activity.



Organotin polyoxa-substituted carboxylates

Mechanism of action: The study of the interaction of organotin compounds with DNA was recently undertaken using NMR study [193]. At round pH-7, a very weak hardly detectable interaction is observed in contrast with the results found in the case of platinum [194]. The interaction of DNA and DNA fragment with dimethyltin dichloride was also studied very recently [195-201]. It was found that by affecting the DNA replication by interacting with it, they stop the growth of cell line.

Main Group Organometallics as Antitumor Drugs

It is well found and established that main group 15 organometallics *viz*., organoarsenic organoantimony and organobismuth compounds also play an important role in controlling the tumor growth.

Organoarsenic Compounds as Antitumor Drugs

It was reported that arsenic can induce the cancer and also used to treat the cancer that is it shows paradox behavior [202]. Arsenic is well known to its acute toxicity and it can induce the cancer. Although it does not seem to be a mutagen *in-vivo*, it interacts with DNA molecules. Arsenic exposure in certain animal modules and in humans contributes to skin neoplasia by stimulation of several growth factors. Arsenic acts at the levels of tumor promotion by modulating the signaling pathways which are responsible for cell growth. Arsenic induces chromosomal abnormalities and disruption of DNA methylation and of repair systems. Arsenic induced oxidative stress with subsequent DNA damage could explain the toxicity of arsenic. By inducing the apoptosis, arsenic can eliminate transformed cells, which could protect organisms from cancer and possibly could

be its mechanisms of action against tumors cells [202].

Organoantimony Compounds as Antitumor Drugs

It was found recently that the organoantimony compounds in both of their +3 and +5 oxidation show pronounced antitumor activity against different types of tumor cell line and ascites tumor [203].

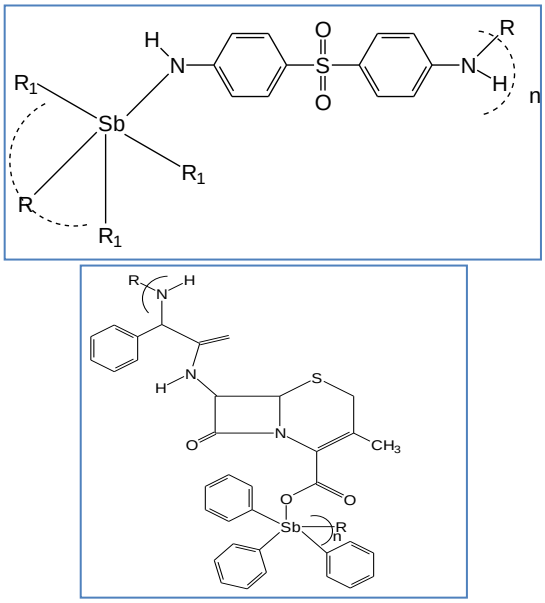
Organoantimony (III) Compounds as Antitumor Drugs

It was found that the cyclophosphamide; an alkylating agent, possess significant antitumor activity in selected malignant neoplastic cells [204]. However, its 1:1 adduct formed with $SbCl_3$ does not show significant activity against L-1210 leukemia and Ehrlich ascites tumor [205]. The other metal coordination compounds containing cyclophosphamide were also found inactive. A series of organoantimony (III) compounds with polydentate carboxylate has also been investigated for their antitumor potentiality [206,207]. Although, the full details are not yet to be published, but the preliminary results have indicated that coordination of antimony (III) by these ligands results in compounds having greater potency than that displayed by the uncoordinated ligands, indicating the importance of the presence of antimony (III) for the activity. Out of the metal ions investigated with ligands of this type, only organoantimony (III) species displayed the better activity [208]. By use of colorimetric methods, the cytotoxcity of organoantimony (III) compounds was examined in human promylocytic leukemia HL-60 cell line. After 24 hours exposure at conc. of 100, 10, and 1 mg/ml, inhibition of cell growth was 100, 70, and 18% respectively. The antitumor activity against mice inoculated with S-180 solid tumors show a reduction in tumor weight to 74% of the control values after 9 days has lapsed [208]. It was noticed that the fore mentioned antimony (III) compounds have Sb-O and/or Sb-N bonds, but the next class of compound described have Sb-S bonds. The most studied antimony (III) compounds in the context of antitumor activity are organometallic compounds having Sb-C bonds [209].

Early work on organoantimony (III) both *in- vitro* and *in- vivo* showed that these compounds were more active than their organotin congeners and the compound $Ph_2Sb(S_2P(O'Pr)_2$ was more active than the $Ph_2Sb(S_2Ph_2)$ against Ehrlich ascites tumor. Three of the four antimony (III) compounds were found to have marginal activity. The compound $Ph_2Sb(S_2(O'Pr)_2)$ was found most active but increased doses were associated with increased toxicity [210]. A subsequent study showed that both the above compounds had mutagenic potential with $Ph_2Sb(O^1Pr)_2S_2P)$ having the higher effect [211]. Not only molecular compounds the minerals derivatives of tungustic heteropolyanion when incorporated with antimony are known to posses some antitumor activity in addition to their known antiviral activity [212-214]. The reported toxicity of Sb_2O_3 not withstanding and reported to offer therapeutic benefits to patients with acute promylocytic leukemia [215]. The study of potential of the Sb_2O_3 in this regards is motivated by the known activity of As_2O_3 [216] which is normally regarded as poison; as Sb_2O_3 is less toxic to As_2O_3. The cross resistance of this compound and cisplatin in a human ovarian carcinoma [216-218] and other human cell line [219] has been demonstrated and the results suggesting that these complexes share a common mechanisms of resistance due to an accumulation defect [220]. The recent studies also indicated that organoantimony compound is implicated in the over expression of the multi-drug resistance associated protein (MRP), which is a drug export pump [221,222] also they binds with nitrogen 7 position of purine bases in DNA molecule and form complexes with DNA strands affecting replication and transcription of DNA molecule and stop the cell division along with protein synthesis.. This is a possible mechanism by which human cells can avoid the cytotoxic effect of heavy metals administered as drugs.

Organoantimony (V) Compounds as antitumor Drugs

There are about two reports available on the cytotoxicity of organoantimony (V) compounds. A number of organoantimony (V) compound of polyamines were described as effective against various kinds of tumor cell line [223].



Organoantimony (V) polyamines

It was also found that the product from triphenylantimony dichloride and cephalexin shows good antiproliferative activity against tumor cell line [224,225]. All these compounds show some inhibition and the assays showed that increased inhibition is associated with increased doses.

The organoantimony (V) compounds studied for cytotoxicity are monomeric species of the general formula $R_3Sb(O_2CC_6H_3$-2-OH-5-Y)$_2$ where R = Me or Ph, and Y = H, Me or OMe [226]. Screening against a variety of human tumor cell lines showed that these species had no significant activity and their study was not further pursued.

Organobismuth Compounds as Antitumor Drugs

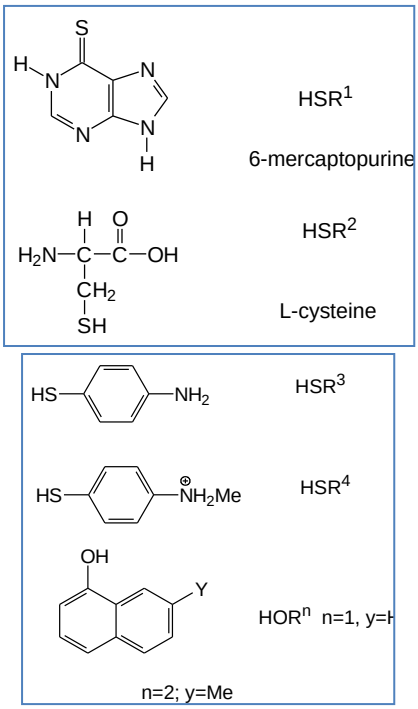
The synergic administration of cis-platin and bismuth compounds are known to reduce the toxic side effects of cis-platin; an effect that may be traced to the increased production of metallothionein induced by bismuth compounds [227-230]. The α-particle emitting bismuth compounds shows potential as radio therapeutic agents [231-233]. These compounds often incorporate ligands related to those found in the reported antitumor active compound $Na[Sb(Hdtpa)]4.5H_2O$. The organobismuth compounds are extremely potent cytotoxic agent when attached to a monoclonal antibody as these can target leukemia, lymphoma and other tumors [234]. Against this Background, it is perhaps a little surprising that three have been relatively less studies on the antitumor activity of bismuth compounds. With the exception of a very early report [235] no bismuth (V) compound has been evaluated for antitumor activity.

Organobismuth (III) Compounds as Antitumor Drugs

The first antitumor trials for organobismuth compounds were those containing the anion derived from 6-mercaptopurine (HSR^1). These were motivated by the known anti-leukemic activity of thiol [236]. The results for $Bi(SR^1)_3$ in mice and rats inoculated with L-1210 leukemia and ascites leukemia respectively. In case to HSR^1, at higher doses i.e. 400 mg/kg had lower toxicity [237]. Further, $Bi(SR^1)_3$ was more active than the platinum (II) analogue $[Pt(SR^1)_2]$, and at higher doses, than the palladium (II) species. In the rat model, similar results were found but at higher doses (i.e. 100mg/kg) toxicity was apparent in all but the platinum (II) compounds subsequently. The $Bi(SR^2)_3.H_2O$ compound was found to have no antitumor activity against lymphocytic leukemia P-388 in mice and at doses of 25 mg/kg was lethal [238]. Three organobismuth(III) compounds, $MeBi(SMe)_2$, $MeBi(SR^3)_2$ and $MeBi(SR^4)_2$ were investigated for antitumor activity in mice inoculated with Ehrlich ascites tumor [239]. The 100% cure rates were reported for doses 15-20, 40 and 60-80 mg/kg for all the three above mentioned compounds respectively.

The other remaining study reported the cytotoxicity and antitumor activity of a

range of bismuth compounds including organobismuth compounds [240]. The results of cytotoxicity were good and demonstrated that the presence of bismuth was essential for the activity of the compounds.



The several compounds without these ligands, with the notable exception of Ph_3Bi, were also active in this cell line. It was postulated that activity might be related to partially hydrolysed species and therefore the inactive Ph_3Bi could be traced to its insolubility in aqueous solution [241, 242].

Organobismuth Compounds as Gastroprotective Agents

Bismuth therapy has shown efficacy against two major gastrointestinal disorders that is peptic ulcer disease and diarrhea [243-245]. In peptic ulcer disease it is as effective as the H2-receptor antagonists and offers a lower rate of relapse. In recent studies, bismuth compounds have been used with conventional antibiotics, producing elimination of the organism, histological improvement, and amelioration of symptoms for periods longer than one year [246-248]. Bismuth subsalicylate has shown modest efficacy in treating traveler's diarrhea and acute and chronic diarrhea in children and it is effective prophylactically for traveler's diarrhea. Recently some novel compounds of bismuth also reported with biomedicinal and pharmacological efficacy against different pathogenic microbes, tumor cell lines along with gastro disorders in humans [249,250].

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Author Contributions: All author equally contributed

Author statement: All authors read, agree and approved the final manuscript

Conflict of Interest: None declared

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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