

AN OVERVIEW OF BIOMEDICINAL PERSPECTIVES OF ORGANOBISMUTH COMPOUNDS

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ABSTRACT

There is the enormous potential of metal-based drugs as they have more efficacy against different chronic and acute diseases. The transition and non-transition metal played significant roles in the synthesis of active potential scaffolds as a catalyst and also played a significant role in enhancing the biomedical importance of organic and organometallic drugs. Members of group-15 put up an important signature in this area as they are used in the treatment of microbial infections and also as antitumor, antiulcer, antiasthmatic, antitubercular and gastric disorders. The present review article highlights the potential applications of organobismuth compounds on the human body both clinically and industrially.

Keywords: Organobismuth Compounds, Metal-based Drugs, Antimicrobials, Antitumor, Gastroprotective.

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INTRODUCTION

It is now well known that metals have played an important role in medicine for so many years but people have only recently realized their significance in medical science in the treatment of various diseases.^{1,2} Metals have enormous potential in medicines and their selection may offer the possibility for the discovery of new metal-based drugs with a novel mechanism of action.^{3,4} The importance of metal-based drugs lies in the fact that they are essential components for various physicochemical processes occurring in a living system.^{5,6}

The metal-organic or organometallic compounds are included in a series of versatile, reactive materials in which a metal is bonded directly through at least one primary valence to the carbon atom of a hydrocarbon radical.⁷⁻⁹ On the other hand, there is a number of metal-organic compounds are also reported in which the organic moiety is bonded to the metal through oxygen or another non-metal such as nitrogen, phosphorous, sulphur.^{10,11} The tremendous growth could be attributed due to the fact that organometallic chemistry lies on the border area of organic and inorganic chemistry and it has supported and contributed to the advancement of bioorganic, bioinorganic and biophysical.¹²⁻¹⁴ Recently the medicinal importance of organometallics led to the newer term "Bioorganometallic chemistry". In the last few decades organometallic chemistry became a coherent self-aware discipline. The organometallic chemistry of group 15 elements (As, Sb and Bi in particular) has been a unique and fruitful area of study and research for chemists for the last several decades.¹⁵⁻²⁰ The effective use of organoarsenic compounds in the treatment of syphilis, led to the synthesis and screening for other biomedical and chemotherapeutic activity of a large number of analogous organoantimony and organobismuth compounds.²¹⁻²⁸ Partial success was achieved in the treatment of *Bilharzia* and *Leishmaniasis* with organoantimony compounds although the development of antibiotics has slowed down the pack of biomedical and pharmacological interest probably due to the inherent toxicity of these elements.^{29,30} Apart from this, they have had considerable importance in the past few years from an industrial point of view as biocides and chemotherapeutic agents.^{31,32} Admittedly, they are progressively being superseded by other less toxic materials.³³⁻³⁹

Despite the reported toxicity of compounds of group 15 elements, when injected in patients they do not have a reputation as potentially hazardous for those who prepare them and tested in the pharmaceutical

industry as potential drugs.⁴⁰ The extensive chemical, biochemical, biomedical and pharmacological studies of bismuth compounds have enabled the medical applications of clinically used bismuth compounds to be extended.⁴¹

Bismuth in the oxidation state of +3 behaves like a Lewis acid when bonded to an electronegative atom, because of this Lewis acid property it is used as an important catalyst for various industrial applications. Due to the Lewis acidic nature of the bismuth(III) center, additional intra- and inter-molecular bonds can develop and thereby result in extended coordination structures (coordination number is 3 to 10). Example bismuth nitrate pentahydrate, $[\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}]$ exhibits a ten coordinate geometry around the bismuth(III) center compounds of bismuth (IV)⁴² may also exist. The compounds of bismuth (V)-alkali metal bismuthates are known only in the solid-state. The ions of bismuth (V) do not exist in the solution.⁴³ There is also a single report of Bi (I) complex in the solution obtained by dissolving metallic Bi in concentrated hydrochloric acid however; this solution is reported to be unstable.⁴⁴ In three coordinate triaryl and alkyl bismuth (III) compounds, the Bi (III) center obeys the octet rule resulting in trigonal pyramidal coordination geometry, which is in agreement with the valence shell electron pair repulsion theory.

Bismuth compounds offer potential in gastroprotection and cancer therapy not only directly but also by indirectly reducing the side-effect of the clinically used antiulcer and anticancer drugs. The high effectiveness and low toxicity of bismuth drugs to treat gastrointestinal diseases are due to their antimicrobial activities. It is to observe recently that bismuthines can do better due to the generation of reactive oxygen species, which help in the treatment of cancer and other acute diseases.⁴⁵⁻⁵⁰

Organobismuth as Antimicrobials

The organobismuth compounds have attracted attention owing to their microbiological and material utility for more than 200 yrs.⁵¹⁻⁵⁴ It was found that organobismuth compounds were active against the treatment of gastrointestinal disorders like dyspepsia, diarrhea and peptic ulcers by inhibiting *E. coli*.⁵⁵⁻⁶¹ A group recently synthesized a series of organobismuth compounds which show potent antimicrobial activity against fungus and bacterial culture responsible for human pathogenic disease.⁶² 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.⁶³ The recent demonstrations have shown that these salts are useful for *Helicobacter pylori* eradication therapy (*Helicobacter pylori are now well known for the formation of a gastrointestinal ulcer in Human beings and organobismuth compounds are the only cure against this bacteria*)⁶⁴⁻⁶⁶ and has promoted the antibacterial and antifungal studies of various organobismuth compounds.⁶⁷⁻⁶⁹ Some investigators have synthesized a lot of organobismuth compounds which might have the highest antimicrobial activity.⁷⁰⁻⁷³

Organobismuth as Antitumor

The synergic administration of cis-platin and bismuth compounds is 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.⁷⁴⁻⁷⁶ The α -particle emitting bismuth compounds show potential as radio therapeutic agents.⁷⁷⁻⁸⁰ The organobismuth compounds are extremely potent cytotoxic agents when attached to a monoclonal antibody as these can target leukemia, lymphoma and other tumors.⁸¹ Against this background, it is perhaps a little surprising that there have been relatively fewer studies on the antitumor activity of bismuth compounds. The other studies reported the cytotoxicity and antitumor activity of a range of bismuth compounds including organobismuth compounds. It was postulated that activity might be related to partially hydrolyzed species and therefore the inactive Ph_3Bi could be traced to its insolubility in an aqueous solution.⁸²

Organobismuth as Gastroprotective Agents

Bismuth therapy has shown efficacy against two major gastrointestinal disorders that is peptic ulcer disease and diarrhea.⁸³⁻⁸⁵ 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.^{86,87} 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.⁸⁸⁻⁹⁵ In the recent past, it was reported by some researchers that organobismuth compounds like amides, derivatives of amides, isatins and their derivatives, carboxylates and some other complexes of bismuth play an important/potent role in gastric disorder and use as a gastroprotective agent and effective against *H. pylori*.⁹⁶

Eradication Therapy

Eradication of *H. pylori* is the less expensive approach for curing ulcer disease,⁹⁷ it also helps in the healing of both duodenal and gastric ulcers. Eradication also results in a dramatic decrease of relapse rate and maintains protein concentration in the stomach to normal. It also eliminates the need for maintenance therapy.⁹⁸ *H. pylori* infection is associated with gastric carcinogenesis and eradication can reduce the lifetime risk of gastric cancer. Recommendation of *H. pylori* eradication is given for those patients who were suffering from PUD, gastric MALT lymphoma, atrophic gastritis, after gastric cancer resection, first-degree relative patients of gastric cancer, investigated non-ulcer dyspepsia, users of NSAIDs, unexplained iron deficiency anemia etc. A different regimen of drugs including different categories of antibiotics, proton pump inhibitors, bismuth-based drugs etc. are available for the eradication of *H. pylori*.⁹⁹

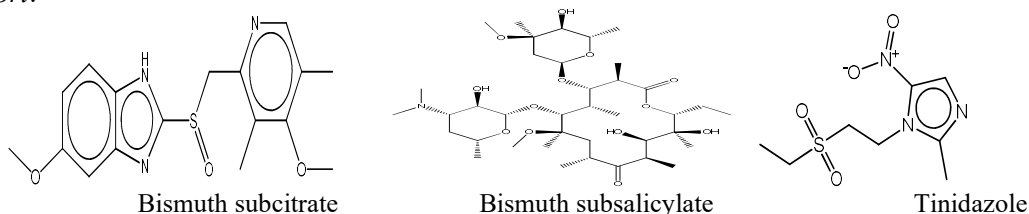


Fig.-1: Reported Structures of Drugs in *H. pylori* eradication

Failure in Eradication Therapy

The failure in eradication therapy of *H. pylori* is observed due to major reasons like (a) Rapid metabolism of PPI; (b) Antibiotic resistance, most commonly used antibiotic is Clarithromycin, which develops resistance but is unevenly distributed worldwide and there resistance rates are higher in developed countries than in developing countries. Another important antibiotic used is levofloxacin for which resistance is also of concern. The development of resistance to these two important antibiotics can decrease the standard level of eradications from 90% to less. Other antibiotics used are metronidazole, amoxicillin, tetracycline and rifampicin etc. Greater consumption of these antibiotics may also develop resistance which may result in decreased eradication rates. (c) Failure also results due to the lack of patient compliance due to non-avoidable side effects of drugs. (d) Behind this *H. pylori* can assume a resting coccoid form that is not susceptible to antibiotic treatment. *H. pylori* may be remains in a protective environment like the stomach mucus layer or even inside the epithelial cells so that they were not affected by drugs also. So, finding an alternative drug therapy that overcomes these problems is necessary. Various alternatives like plant material,¹⁰⁰ probiotics,¹⁰¹ peptides,¹⁰² polysaccharides,¹⁰³ microorganisms vaccines¹⁰⁴ and many more are explored. In this context organobismuth drugs also exerts an important role through a different mechanism of action like binding to proteins and enzymes interacting networks which provide prevention of *H. pylori* associated diseases. So, it is required to explore more about organobismuth drugs which improve their solubility and other pharmacokinetic and pharmacodynamics properties so that they can be easy to use.

Alternative therapies of Organobismuth

Bismuth containing triple or quadruple therapy is an alternative first choice of treatment for *H. pylori* infection¹⁰⁵ because these are safe and exert local effects¹⁰⁶ and resistance towards bismuth drugs has not been reported yet¹⁰⁷ for *H. pylori* or any other pathogenic microorganism. Bismuth can act as an antimicrobial agent toward *H. pylori* by suppressing them but do not eliminate it properly when

administered with antibiotics provide synergistic effects to the antibiotics. So, use of these drugs may also reduce the resistance risk of other co-administered antibiotics like clarithromycin, metronidazole etc. and slow down the relapse rate of *H. pylori* infection also. A number of different bismuth based preparations are available, such as colloidal bismuth subcitrate¹⁰⁸ (CBS-it used for dyspepsia, duodenal ulcer, gastric ulcer), bismuth subsalicylate (BSS-used for Traveler's diarrhea, dyspepsia, *H. pylori*), bismuth-subnitrate (for gastric disorders, constipation, irritable colon), the newer ranitidine bismuth citrate^{109,110} (RBC-for *H. pylori*, duodenal ulcer, gastric ulcer). In addition, many new bismuth compounds with different structures and activities as well as bismuth nanotubes have been synthesized and are active toward the eradication of *H. pylori* by exerting different mechanism of actions. No single report of bismuth intoxication has appeared probably due to the low dosage (below 0.5 g/day) of bismuth used and its application in the colloidal form that reduced its absorption from the gut and excluded potential neurotoxicity.¹¹¹ In serum bismuth form strong complexes with lactoferrin and transferrin and this is also an important factor for low toxicity.¹¹² Bismuth containing medicaments are available in form of colloidal suspensions, ointments, injectables, liquids, salves and tablets.

Mechanisms of Action

Bismuth disrupts multiple biological pathways of *H. pylori* like tricarboxylic acid cycle, cell redox homeostasis, nickel homeostasis, protein folding and iron homeostasis.¹¹³⁻¹¹⁵ The mechanisms of bismuth action against *H. pylori* have been reviewed and it is assumed that it may produce antimicrobial action by different complex mechanisms like- Inhibition of various enzymes produced by *H. pylori* including urease, alcohol dehydrogenase (ADH), fumarase reductase, fumarase and proteases such as pepsin and phospholipase C & A2^{116,117} which affects the local environment of the organism for its growth, inhibition of adhesion of *H. pylori* to surface epithelial cells¹¹⁸, inhibition of ATP synthesis¹¹⁹, inhibition of protein, cell wall synthesis and membrane function¹²⁰ through the complex formation and a reduction in capsular polysaccharide production.¹²¹ On the other side, it is also assumed that it inhibits gastric acid secretion¹²² and provides cytoprotective¹²³ like properties which result in ulcer healing.

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