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THE ANTI-NEOPLASTIC ACTIVITY OF THE COORDINATIVE COMPOUNDS, THIOSEMICARBAZIDE DERIVATES

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Summary
Background. Thiosemicarbazide derivates are considered potential compounds of the antitumor drugs, with a large spectrum of biological properties. The aim of the research was to reflect the actual progress in studies on thiosemicarbazide derivates, their complexes with metals and their mechanisms of activities.
Material and methods. A systematic literature review was conducted for which the open electronic sources, through the PubMed web interface and HINARI collection of health literature were evaluated. Printed publications were found using the Universal Decimal Classification (UDC).
Conclusions. Thiosemicarbazide derivates are chemical compounds of drugs with vast therapeutic potential. The improvement of their chemical structure could contribute to the development of new classes of drugs with better acceptability for in vivo experiments.
Keywords: Thiosemicarbazide derivates, coordination complexes, metal-ligands, anti-neoplastic activity

Introduction

Nowadays, oncological diseases represent an actual problem of modern medicine [1]. The research for new drugs with anti-neoplastic activity is one of the main tasks of modern medical chemistry [1, 2]. One of the most important problems in the treatment of neoplastic diseases is the high toxicity of chemotherapeutic agents [2]. So far, there are known several hundreds of effective antitumor drugs agents used to treat various malignant pathologies, and almost all of these agents, used in clinical practice, are highly toxic and nonselective [3, 4].

The anti-neoplastic drugs, doxorubicin, cisplatin, vinblastine, methotrexate, and other drugs are widely used in clinical oncology [3]. They have a low selectivity in relation to healthy tissues, which leads to severe side effects, the need to reduce the therapeutic doses of chemotherapy and, consequently, develop resistance to chemotherapy [2]. Consequently, in the last decade, along with the task of finding new antitumor drugs, the problem of increasing the selectivity and reducing the toxicity of the new agents already used, as well as creating new strategies regarding the synthesis of some drugs in relation to tumor tissues, appeared. One of the possibilities to reduce the general toxicity of the antitumor drugs is to introduce into the molecule a fragment responsible for the targeted delivery of a therapeutic agent that would stop the proliferation of tumor cells. Increasing the selectivity towards tumor tissues is possible in several ways: a) by increasing the affinity of the drug for the folic acid or biotin receptor, of which expression was increased on the surface of the majority of tumoral tissues [4], or b) to introduce fragments of some peptides in the structure of the antitumor drug with big affinity for integrins, their expression is increased on the surface of some tumors, as being associated with the angiogenesis and metastasis, [5] or c) to develop new antitumor drugs, which will contain specific antibodies that will be able to recognize the tumoral cells [6, 7].

Special attention in recent years was attributed to Schiff bases, which are important chemical compounds that have wide applications in various fields such as organic, analytical and medicinal chemistry, due to their ability to create numerous stable complexes when coordinated with various transition-metal ions. Schiff bases refer to the imine bonds formed by the nucleophilic attack of amine to the aldehyde group. They are aldehyde or ketone-like compounds, in which the carbonyl group is replaced by an imine or azomethine group. Their active group contains electrons, making them ideal candidates for the development of new antitumor drugs implemented in therapeutic chemistry [7, 8]. Among the organic substances used as ligands, an important role belongs to thiosemicarbazones (TSC), compounds with valuable pharmacological and therapeutic antimicrobial, antitumoral, antimycotic, antitoxic, antioxidant, and antidiabetic properties [9-11]. Thiosemicarbazones represent a versatile class of Schiff-based lignans with sulfur and nitrogen as donor atoms [12]. They are prepared by the condensation reaction between aldehydes or ketones with thiosemicarbazide [11]. The first therapeutic applications of thiosemicarbazones were against tuberculosis and leprosy infection in 1950's. During the sixties, the anti-viral properties were established and methisazone and Marboran were implemented to treat smallpox than were used to treat the variola virus [13].

The first results about the thiosemicarbazone antitumoral activity was published in the same period and Tripine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone) was presented. Actually, the drug reached phase II trials in several types of cancer, and its antitumor activity was established to be broad depending on the type of tumor cells [14].

It should be noted that the biological activity of thiosemicarbazones in its free state is less pronounced than that of the coordinating compounds of ligands with the metals [10, 11]. These compounds are usually obtained by the condensation reaction between aldehydes or ketones with thiosemicarbazones (Figure 1):

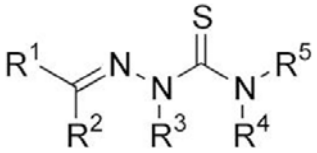

Figure 1. *General structure of TSC. R1, R2, R3, R4, R5 = H, or an organic substituent.*

Synthetic macrocyclic chelates of transition metals have attracted attention in coordination and supramolecular chemistry. Apart from thiosemicarbazones complexes, stronger antitumor agents than cisplatin were established the metal ion groups of complexes of semicarbazones. The metal ion complexes inhibit tumor cell proliferation by arresting the S phase of the cell cycle [10]. Some of the chelates formed by thiosemicarbazones complexes have received considerable attention as anticancer compounds. Copper and iron-containing coordination compounds were demonstrated to be valuable antitumor therapeutic agents, more active than the free semicarbazone and thiosemicarbazone, and able to disturb the cell metabolism and signaling pathways, which can be considered an attractive approach in cancer. It was observed that the cytotoxic activity depends not only on the metal ion but also on the position of the substituent group on the aromatic ring [15-20]. Recently, trivalent iron and bivalent nickel complexes with S-methyl-thiosemicarbazones of 2-hydroxy-R-benzaldehyde showed maximum cytotoxic potential when the methoxy group (-OCH3) was placed in the aromatic ring of the side chain [10] (Figure 2).

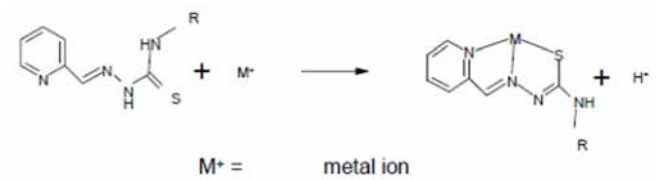

Figure 2. *Metal ion coordination to a thiosemicarbazone ligand induces structural changes in the complex*

The aim of the research was to reflect the actual progress in studies on thiosemicarbazide derivates, their complexes with metals, and their mechanisms of activities.

Material and methods

A systematic literature review was conducted for which the open electronic sources published till 2022, through the PubMed web interface and HINARI collection of health literature were used. Printed publications were found using the Universal Decimal Classification (UDC).

Results

Molecular mechanisms responsible for antitumor, antiproliferative effect, and cytotoxic activity of thiosemicarbazone and their transition metal complexes are following: a) inhibition of the ribonucleoside diphosphate reductase; b) inhibition of topoisomerase II and DNA interactions; c) inhibition of the cellular proteasome; d) generation of reactive oxygen species and other mechanisms. However, the most important is the inhibition of DNA biosynthesis by blocking the enzyme ribonucleotide diphosphate reductase, as well, as binding of DNA or RNA to the nitrogenous bases, which prevents or blocks their replication. A secondary mechanism consists in creating lesions in the DNA strands through induced oxidative stress [17, 18].

The inhibitory activity on the ribonucleoside diphosphate reductase is attributed to the tyrosyl radical. Inhibition of this enzyme was determined to blockage in the synthesis phase of the cell cycle and the apoptosis of the cell [19-24]. Pyrazine carboxaldehyde thiosemicarbazone and 1-formylisoquinoline thiosemicarbazone, which are α (N)-heterocyclic thiosemicarbazones, demonstrated a higher activity making them better chelators [25]. Certain formyl-pyridyl thiosemicarbazones were identified as potent inhibitors of ribonucleoside diphosphate reductase [26]. The mechanism of action consists of the exposure of ribonucleoside diphosphate reductase to these molecules. The tyrosyl free radical of the enzyme is targeted by the drug and is destroyed. In this mode, the thiosemicarbazone complex inhibits the enzyme by destroying the tyrosyl radical [25, 26]. The mechanism requires oxygen, is reversible, and demonstrates the role of thiosemicarbazones as iron chelators [26]. Iron chelate of 1-formylisoquinoline thiosemicarbazone is one of the most potent inhibitors of the ribonucleoside diphosphate reductase in mammalian cells [24]. Tyrosine radical and ribonucleoside diphosphate reductase activity can be increased by the extraction of the compound and incubation of the enzyme with dithiothreitol [27]. Higher inhibitory activity of 1-formylisoquinoline thiosemicarbazone than 2-formylpyridine thiosemicarbazone was confirmed by the presence of a hydrophobic pocket in the enzyme with which the aromatic system interacts. The methylation of the aromatic ring in 2-formylpyridine thiosemicarbazone increased its activity [22-24].

Published studies confirmed the inhibitory action of thiosemicarbazide complexes on topoisomerase type II and DNA interactions [26-28]. Topoisomerase type II is a eukaryotic cell nuclear enzyme that decatenates DNA coils, passing one helix through another to prevent supercoiling during DNA replication [19, 20]. It is required for DNA synthesis and cellular division and tumor cells, as rapidly proliferating cells contain high level of this enzyme [19]. Thiosemicarbazones inhibit topoisomerase type 2 and

respectively cells proliferation [2].

The relationship between *in vitro* and *in vivo* activity of ^{64}Cu-labelled thiosemicarbazide complexes and the expression of topoisomerase type II was investigated [28]. Four 4N-azobicyclo-[3.2.2]-nonane thiosemicarbazide ligands were prepared and marked with ^{64}Cu. Four ligands (1-4) were examined and ligand three demonstrated a significantly higher growth inhibitory activity when compared with non-radioactive copper [29]. Several tridentate thiosemicarbazide complexes were evaluated with various nitrogen-based heterocycles [29]. A ligand bearing a quinoline group was identified to have particularly high cytotoxicity due to inhibitory action on the topoisomerase type II. The mechanism of inhibition of the enzyme is mediated through adenosine triphosphate hydrolysis [28]. The study demonstrated that topoisomerase II is effectively inhibited by Cu complexes [29]. Cu-thiosemicarbazone complexes have significantly higher growth inhibitory activity than the uncomplexed ligand and have lower half maximal inhibitory concentration (IC50) [29]. Antitumor activity of 1,2 naphthoquinone-2-thiosemicarbazone and its metal complexes of Cu (II), Pd (II) and Ni (II) were investigated against breast cancer (MCF-7) cell line and was established a high antitumor activity. The complex with Ni (II) was confirmed to be the most effective based on IC50 [29]. Further study of the thiosemicarbazide complexes established that they can stabilize the single-strand DNA, but not double-strand breakage intermediates. The metal complexes were found to have an antagonizing effect on the activity of topoisomerase II, compared with the free ligands. In a study, Cu (II) complexes of 4-hydroxy-3-methyl-1,2-naphthoquinone-1-thiosemicarbazone demonstrated higher cytotoxicity on mammary tumoral cells compared to those of Fe(II), Ni(II), Pd(II) and Pt(II) metal complexes with the same ligand. It was explained by the generation of Cu(I) species during intracellular enzymatic reduction or greater binding affinity of Cu(I) to an estrogen receptor protein complex [30]. The binding prevents the protein complex from functioning properly during its interaction with DNA. Other studies determined that the metal complexes stabilize the cleavable complex formed by DNA and Topo-II [29]. Studies have shown that iron and copper complexes are more active in cell destruction and inhibition of DNA synthesis than the uncomplexed thiosemicarbazone [28-30]. It was shown that 5-hydroxy-2-formyl thiosemicarbazone causes lesions in DNA [31]. It was demonstrated that the tridentate composition and the high formation constant is necessary for increased activity by comparing the activity of pyrazine thiosemicarbazone derivatives and an analog derived from acetophenone. It was confirmed that these complexes prevent iron uptake from the serum transferrin by disturbing the iron homeostasis. A study on Cu (II) (thiosemicarbazone) complexes confirmed a higher catalytical inhibition on topoisomerase-II compared with thiosemicarbazone ligands alone [32]. The cooper complexes have also shown inhibitory action towards the proliferation of breast cancer cells which are expressing high levels of topoisomerase-II. The copper complex of acetylpyridine methylthiosemicarbazone also inhibits the topoisomerase-II. Studies of the complexes of the ligands with palladium(II) and platinum(II) demonstrated that the mechanism of the inhibition of the topoisomerase type II is due to the same chemical composition - square planar around the metal [35]. A series of acetylpyridine thiosemicarbazone ligands, and their Cu(II) and Pd(II) metal complexes have been synthesized and studied. The results demonstrated that the Pd (II) complexes have the same anti-proliferative activity as the Cu (II) complexes [10, 11, 15, 17].

The generation of reactive species of oxygen is a secondary mechanism through which the thiosemicarbazone complexes determine the inhibitory action toward the proliferation of tumor cells. Reactive oxygen species (ROS) are vital for various biological processes in the cell because they act as second messengers in cell signaling pathways [38, 41]. The cancer cells have higher levels of ROS compared to normal cells. ROS are involved in tumor promotion by directly inducing genomic instability through the intensification of DNA synthesis, protein and lipid oxidation, and methylation processes. Increased production of ROS disturbs the regulation of the expression of genes and proteins responsible for restoring the redox balance. Among these, the most important genes are those encoding manganese superoxide dismutase (MnSOD) and catalase (CAT). MnSOD is a mitochondrial protein that is highly efficient in the coaptation of superoxide anions, converting them to hydrogen peroxide, which is further removed by CAT in the cytosol [42]. So, the induced oxidative stress and ROS by the thiosemicarbazone complexes can be used to destroy cancer cells [43].

Proteasome is a protease complex responsible for the hydrolysis of proteins, catalyzing biological reactions. In association with ubiquitin it makes the proteolysis a regulated mechanism in eukaryotic cells [33]. Tumor cells are highly dependent on the functioning of ubiquitin-proteasome system [34]. Proteasome inhibitors are used to treat multiple myeloma and mantle cell lymphoma, and a limited efficacy was established in the treatment of solid tumors [35-37].

The thiosemicarbazone complexes contain redox metal ions and can activate O2 and generate OH- radicals. Complexes [Cu (L)2(Pz)](ClO4) and {[Cu(L)2 (DCA)] (ClO4)} where L=2-formylpyridine thiosemicarbazone complexes, Pz is pyrazine and DCA is dicyanamide were evaluated to establish their biological activity on DNA. The oxidative cleavage of DNA has been assayed in the presence of 3-mercaptopropionic acid as a reducing agent by gel electrophoresis. Both complexes determined single and double-strand breaks in DNA [38-40]. Copper is an essential micronutrient and is involved in redox regulation and angiogenesis [40, 41]. An increased level of intracellular copper will induce cellular apoptosis. The related investigations on Cu (II) complex-mediated cytotoxicity are on the rise [43]. Four novel thiosemicarbazone metal complexes, [Cu(Am4M)(OAc)]•H2O (1), [Zn(HAm4M)Cl2] (2), [Zn2(Am4M)2Br2] (3) and [Zn2(Am4M)2(OAc)2]•2MeOH (4) [HAm4M=(Z)-2-(amino(pyridine-2-yl)methylene)-N-methylhydrazinecarbothioamide], were synthesized and tested against human and animal tumor lines cell- HepG-2 cell. The studies showed lower toxicity and a stronger

inhibition of the viability of HepG-2 cells than cis-platin [42, 43].

Discussions

Thiosemicarbazones are ligands with important biological activity and their ability to chelate metal ions made them antitumor and antiproliferative agents [2, 4, 10]. The metal complexes have an enhanced biological activity [10]. The reason for the higher activity by the metalthiosemicarbazone complexes compared to free ligands is through the diffusive mechanism of their internalization compared with the active transport mechanism across the membranes [26]. The chelation of the metal ion by the polar regions of the ligands determined an easier internalization of the metalthiosemicarbazone complexes by the cell [38]. Only a limited number of *in vivo* studies were done to determine their potential as chemotherapeutic agents [39, 43]. Several studies were done to improve hydrophilicity and reduce the toxic effects by modifying the structure of thiosemicarbazones [18, 19, 40]. Due to their low solubility in aqueous solutions, thiosemicarbazones and their metal complexes show a very low in vivo activity [28]. Anticancer activity of thiosemicarbazone complexes is mainly attributed to inhibition of the ribonucleoside diphosphate reductase activity, topoisomerase 2 activity, and generation of reactive species of oxygen [30, 39]. Studies *in vitro* confirmed that ribonucleotide inhibitors have low anti-proliferation action [26, 27]. Another area that could be studied is metal sequestering, because thiosemicarbazones are versatile chelators, and they can deprive the cell of essential metal ions by forming stable chelates with them. The redox capability of transition metals like copper has an important role in increasing of the activity but it can also determine the Fenton's reactions by producing a significant amount of hydroxyl radicals that can inhibit normal cell functions [23].

Conclusions

Thiosemicarbazide is an important structural agent that has the potential to determine chemical functionality in biologically active molecules.

Thiosemicarbazones and their transition metal complexes containing amide, imine, and thione groups make them potential new antineoplastic agents. Transition metal complexes are much more biologically active than uncoordinated semicarbazone and thiosemicarbazone ligands.

In the future, the success of thiosemicarbazone-based complexes as antineoplastic agents will depend on the possibility to enhance their activity through modifications in their structures which will increase their acceptability and in vivo solubility.

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