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Scope of Flavonoid-Thiosemicarbazone Hybrids and Their Coordination Complexes of Copper (II) and Gold (III) For in Vitro Anti-Cancer and Anti- Alzheimer's Activity

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Overview of treatments for cancer and Alzheimer's disease

The interest in metal-based drugs has increased due to their better performance against various types of cancers and Alzheimer's diseases, where the existing therapeutics are not feasible [1]. Generally, cancer can be treated by chemotherapy [2], surgery, and targeted therapy [3]. Cancer treatments can induce many side effects such as anemia, sexual health issues in men and women, hair loss, and nerve problems [4]. Introduction of metal ions into the biological system is useful for both diagnostic and therapeutic purposes [5]. In general, cellular functions are assisted by metals. They are associated with enzyme catalysis and are involved in a series of biological processes. Metals like cobalt, silver, strontium, and vanadium are required in trace amounts to activate the catalytic processes of many biochemical reactions [6]. On the other hand metals such as nickel, chromium, and arsenic are carcinogenic [7] and hence it is hazardous to our body. Moreover, platinum-based compounds for cancer therapy can trigger several side effects and develop cancer resistance [8]. Due to this, recently the chemistry of copper and gold-based compounds has achieved special attention because of their ability to act as an alternative to cisplatin, due to their inimitable cytotoxic and potential anti-cancer properties. In particular complexes of copper (II) with thiosemicarbazone and gold (III), peptidomimetics have shown strong tumor cell growth inhibition effects [9]. So designing and developing a new metal-based drug with enhanced biological activities and minimal side effects is a challenging task. The efficiency of a metallodrug can be improved by designing a new ligand system with enhanced biological activity. Based on the literature to date, different complexes of thiosemicarbazones and

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flavonoids show a broad spectrum of anticancer [10] and anti-Alzheimer's [11] activities. Thiosemicarbazones hybrid derivatives can be further developed by combining flavonoids or biotin with the enhanced anti-cancer, anti-Alzheimer's activities. A combination of bioactive thiosemicarbazones and flavonoids leads to the formation of a hybrid possessing additional modes of action when compared with their parental molecules [12].

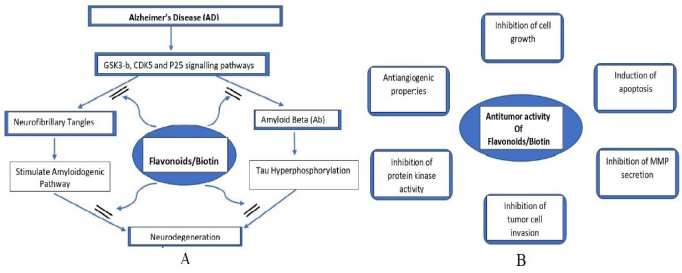

Figure 1: Mechanism of action of anti-Alzheimer's activity of flavonoid/biotin **(A)** and antitumor activity of flavonoid/biotin **(B)**.

Previous works on the different biological applications of thiosemicarbazone hybrids

The various group have investigated different biological applications of thiosemicarbazones and especially focused on antitumor activity. Betul et al introduced the synthesis of thiosemicarbazone derivative Schiff bases and their inhibitory activity against monoamine oxidase [13]. Furthermore the complexes were examined for their monoamine oxidase A and monoamine oxidase B inhibitory activities. From the experimental results, it is observed that many of the compounds were dominant over monoamine oxidase A enzyme rather than monoamine oxidase B enzyme. Also, the nature of the interaction between compounds of thiosemicarbazones and monoamine oxidase A was classified by molecular docking studies.

Bacher et al demonstrated that new water-soluble copper (II) complexes bearing morpholine-thiosemicarbazone hybrid show enhanced anticancer and antibacterial activity [14]. They have mentioned that the thiosemicarbazone hybrids initiate themselves as one of the most eminent players for selective demolition of the cancer cell line.

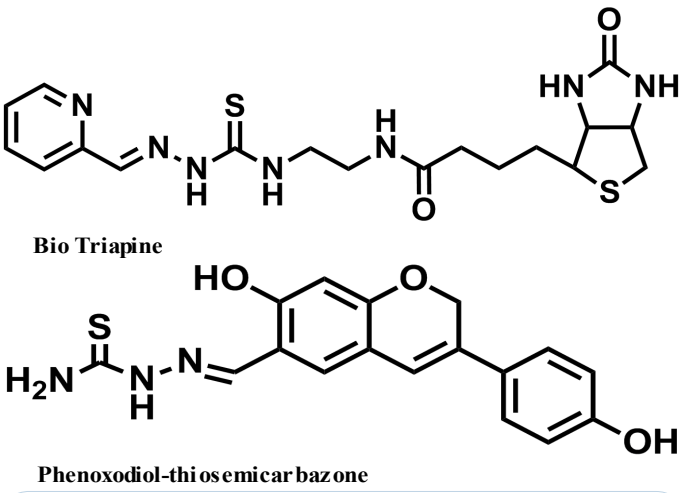

Figure 1: Examples of different thiosemicarbazone hybrids.

Mirela et al demonstrated the complexes of copper (II) with iminodiacetate-thiosemicarbazone hybrids targeting the ribonucleotide reductase inhibitingt their activity [15]. Moreover they have also revealed the antiproliferative activity of the compound of our interest. Similarly, a recent study on thiosemicarbazone and triazole hybrid compounds demonstrated their antidiabetic and antioxidant actions [16].They have developed eight hybrids of thiosemicarbazone and triazole to check their effects on both type 2 diabetes and antioxidant activity. The effects of hybrids on glucose transport genes such as glut-4 and mef2a was carried out using quantitative polymerase chain reaction. It is found that the hybrids have shown high expression of glut-4 gene compared to insulin. Moreover, some of the hybrids exhibited the highest 1-diphenyl-2-picryl-hydrazyl radical foraging ability.

Sulekh Chandra et al from the University of Delhi developed indoxyl N(4)-methyl thiosemicarbazone and thereby introduced its copper (II) complexes and proved the tetragonal structure of copper (II) complexes using various physical and chemical methods [17]. Recently Karvembu et al from NIT Trichy was developed water-soluble ruthenium complexes using thiosemicarbazone and evaluated their anticancer activity and apoptosis studies [18].The gel-electrophoresis method showed the ability of complexes to cleave DNA and higher affinity towards BSA protein. The anti-cancer activity of complexes revealed that binuclear compounds of ruthenium exhibited higher activity with an IC50 value of 11.5 µM. Similarly, Priya et al from the University of Calicut, demonstrated the antitumor and cytotoxic activity of transition metal complexes bearing N(4) substituted thiosemicarbazones derivatives [19]. They exclusively studied seven different metal complexes of N(4)- methyl (phenyl) thiosemicarbazones and their cytotoxic activities. Among these IC50 values, the copper complex was found to be 46 µg/ml. The action of copper complex against the cancer cell line was carried out using Dalton lymphoma ascites cell-induced solid tumor model and Ehrlich's ascites carcinoma cell-induced ascites tumor model. The designed copper complex with various concentrations prevented tumor development in mice and enhanced the life span of tumor-bearing mice. One of the striking features of this work is that only complexes have shown appreciable cytotoxicity and the cytotoxic activity of ligands was observed to be diminished in the absence of a suitable metal. With this national status, it can be concluded that different groups in India are developing various thiosemicarbazone derivatives with the preparation of its metal complexes by varying donor sites and subject to its biological application. But the existing current cancer therapeutics using metal complexes are not shown advanced stages of drug development in cancer treatment. It gives huge interest to the researchers to develop new metal complexes in this unique area of research and also possible to collaborate with the medical community, especially in the oncology unit.

Importance of the development of drugs for cancer and Alzheimer's

The development of a new drug candidate for cancer is one of the challenging tasks as it consumes more time for drug discovery. The existing anti-cancer and anti-Alzheimer's drugs reduce the efficiency of the immune system [20,21] and the live methods in cancer treatment like ionizing radiation [22] and chemotherapy are highly harmful to born marrow and major surgery produces a diminution of lymphocytes, hence affecting natural killer functions [23,24]. So design and development of a drug with high activity and minimum side effects of cancer and Alzheimer's treatments is a serious challenge facing drug researchers. Flavonoids and biotins are important bioactive compounds present in many fruits, vegetables, and nuts [25,26]. They are essential for body functions as they possess antioxidant, antiviral, antibacterial, and anti-inflammatory activities [27]. Also they regulate many cellular functions in the

body.28 Apart from this, flavonoids can inhibit angiogenesis [29], metastasis [30], cell proliferation [31],and also promote programmed cell deaths [32]. Compounds obtained from natural sources such as plants are of great interest due to their large availability, minimal side effects, safety, and most attraction are on cost-effectiveness. A longitudinal study of our reports supports that incorporating bioactive metals with flavonoid-thiosemicarbazone and biotin-thiosemicarbazone hybrids having appreciable biological activity can lift the treatment of cancer and Alzheimer's disease to the next level. The aim of this editorial is to provoke researchers to work in the field of synthesis of various complexes of copper and gold with different flavonoid-thiosemicarbazone and biotin-thiosemicarbazone hybrids with better pharmacokinetic properties, controlled and precise targeting of tumor cells. A targeted metallodrug results in reduced cost of Alzheimer's and cancer treatment with a high-level benefit to the Indian society.

Conclusion

Flavonoids, a group of chemical compounds with various phenolic structures, are found in a wide variety of plants and show various attractive biological activities. These compounds are well known for their antitumor and anti-Alzheimer properties. Recent studies reported that different hybrids of biologically active compounds can exhibit enhanced biological activities than the individual components of the hybrid systems. Here we discussed the scope of different flavonoid-thiosemicarbazone hybrids and their copper (II) and gold (III) complexes as antitumor and anti-Alzheimer agents. From this editorial, it's clear that these biologically active compounds and their hybrids can be considered as one of the best candidates for cancer and Alzheimer's diseases.

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