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Short Communication

Advances in Glioma Treatment with Utilization of Enzyme - Stimulated Chemodynamic Therapy - Through a Peptides - H2S Donor Conjugate Complexed with Fe^{2+} -- A Short Communication

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Abstract

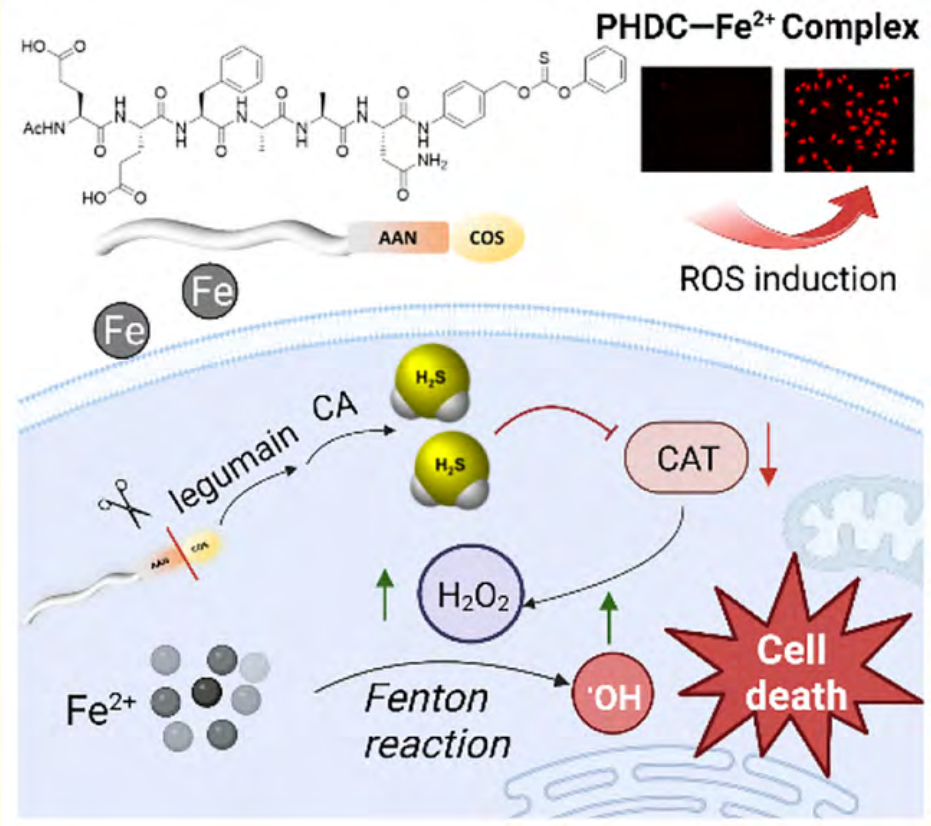
It has been reasoned out that induction of greater quantities of Reactive oxygen (ROS) with in the tumor cells is a cancer treatment strategy known as Chemodynamic therapy (CDT). Depending on the administration of Fenton reaction facilitators like Fe^{2+}, CDT benefits from the fact that over generated ROS amongst the tumor microenvironment. Production of a peptides- H2S donor conjugate (PHDC) which was complexed with Fe^{2+} known as AAN-PTC- Fe^{2+} was achieved by Zhu., *et al*. This AAN-tripeptide was particularly cleaved by legumain, an enzyme which was over expressed in glioma cells for liberation of carbonyl Sulfide (COS). Whereas COS hydrolysis by enzyme carbonic anhydrase (CA) which generated H2S, a hampering agent of catalase (CAT), an enzyme which leads to detoxification of H2O2. Fe^{2+} in combination with H2S escalated intracellular ROS quantities as well as diminished viability in C6 glioma cells in contrast to controls having absence of either Fe^{2+}, AAN sequence or capacity of production of H2S. AAN-PTC-Fe^{2+} worked better compared to temozolomide whereas demonstrating no cytotoxicity against cardiomyocytes. Hence this study illustrated an H2S-augmented, enzyme responding manifesto regarding synergistic cancer treatment.

Keywords: H2S donor; Reactive Oxygen;

Graphical Abstract

Courtesy ref no-15- By combining an enzyme estimulated hydrogen sulfide (H2S) donor with the Fenton reaction promoter Fe^{2+}, a peptide–H2S donor conjugate–Fe^{2+} complex was generated that quantities escalated of cytotoxic reactive oxygen species in C6 cancer cells, providing an H2S-amplified, enzyme-responsive system for precise cancer treatment.

The escalated intracellular quantities of Reactive oxygen (ROS) might be possessing the capacity of killing cancer with greater specificity, with ROS stimulated oxidative injury to lipids, DNA as well as proteins [1]. Chemodynamic therapy (CDT), a therapeutic approach towards treatment of tumors generated in 2016 by Bu, Suetal. [2], utilized benefits of ROS stimulated cytotoxicity by basically depending on the greater quantities of ROS in the tumor microenvironment (TMA) in contrast to normal tissue environment



Graphical Abstract

[2]. A frequently used CDT pattern, makes use of the reaction with involvement of metal salts (for instance Fe^{2+}) with over generated H2O2 in the TMA for facilitating the formation of extensively cytotoxic hydroxyl radicals (*OH) by the Fenton reaction (Fe^{2+} + H2O2---→ Fe^{3+} + *OH +OH^-) [3]. Inspite of probability of selectivity in addition to appropriate targeting of this innovative tumor treatment approaches, its effectiveness is intrinsically restricted by H2O2 quantities [4]. A probable way out to get out of this restriction or stoppage is to promote hampering of catalase (CAT), which is 1 of the main antioxidant enzymes in cells that catalyzes the degradation of H2O2 into water as well as oxygen.

A hampering agent of CAT that has been recently isolated portrays a signaling gas (gastrotransmitter) Hydrogen Sulfide (H2S) [5,6]. Initially developed in the form of a gastro transmitter in 1996 [4], H2S is involved in various signaling functions over numerous cell kinds. Exogenous H2S administration has been evaluated regarding cancer with mixed outcomes obtained, where it escalates cancer cell proliferation in case of some situations, as well as restricts growth in case of others [7]. Appropriate administration of H2S to cancer cells thus might lead to improvement of CDT results in cancer therapy. Thereby Zhu., *et al*. [15], posited that combination of H2S with any Fenton reaction facilitator like Fe^{2+} might prove to be an efficacious approach to delete tumor cells with selectivity.

Glioma portrays a specifically tough cancer in the context of therapy with restricted successful surgery in addition to, chemotherapy possesses a lesser survival rate. Origination of glioma takes place from the glial cells, occurring in brain in addition to spinal cord, which mirror maximum frequent kinds of the primary brain tumors [9]. It has been acknowledged that gliomas possess great proliferation as well as growth rate along with patients of glioma possess extremely bad prognosis having a 5 year

survival rate of just 7% [10]. Whereas newer glioma cells targets in addition to newer lead agents have been produced recently in the last decade [11-13], a simple possessing effectiveness along with appropriate aim regarding gliomas therapy continues to remain the main objective in treatment of cancer. Intriguingly, particularly legumain (LGMN), a cysteine endopeptidase belonging to the peptidase family C13 which hydrolyses COS particularly substrates aspariginyl bonds. It is maximally portrayed in lysosomes where [14] it works as a lysosomal cysteine protease which carries out cleavage of the C-terminal of the Ala Ala Asn (AAN) peptides sequences ,which gets overexpressed in various kinds of primary human tumor cells, inclusive of glioma cells [15], determines it in the form of plausible targets for facilitating CDT.

Hence here Zhu., *et al*. [16], attempted asssessment of combination of the Fenton reaction (Fe^{2}) with a CAT hampering agent (H2S), in the form of a CDT approach started by legumain. Ferrous Sulfide (FeS) has been assessed in the form of a donor for Fe^{2+} as well as H2S, Nevertheless, this manifesto did not possess the capacity of targeting cancer cells, nor liberate H2S gas in a regulated fashion, that is key for efficacious administration. Thereby Zhu., *et al*. [15], fashioned an innovative production peptides- H2S donor conjugate (PHDC) which they predicted would breakdown in the existence of legumain for formation of carbonyl Sulfide (COS) that possesses the rapid capacity of transformation into H2S by the omnipresent enzyme carbonic anhydrase (CA). Attempting a combination of PHDC) with Fe^{2} Zhu., *et al*. [15], posited that this distinct PHDC- Fe^{2} complex would integrate the advantages gained from H2S as well as a Fenton reaction facilitator giving a correct programme targeting gliomas; thereby resulting in tumor cells demise (Figure 1).

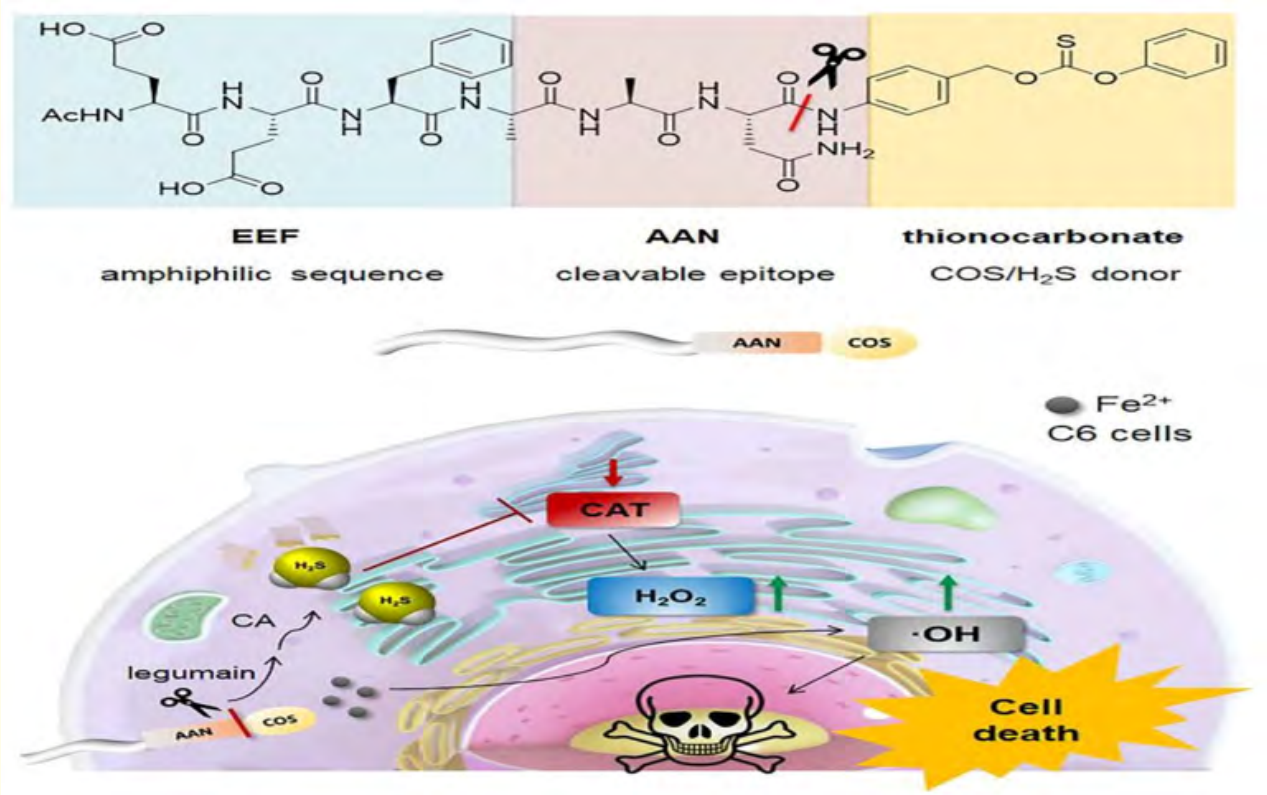
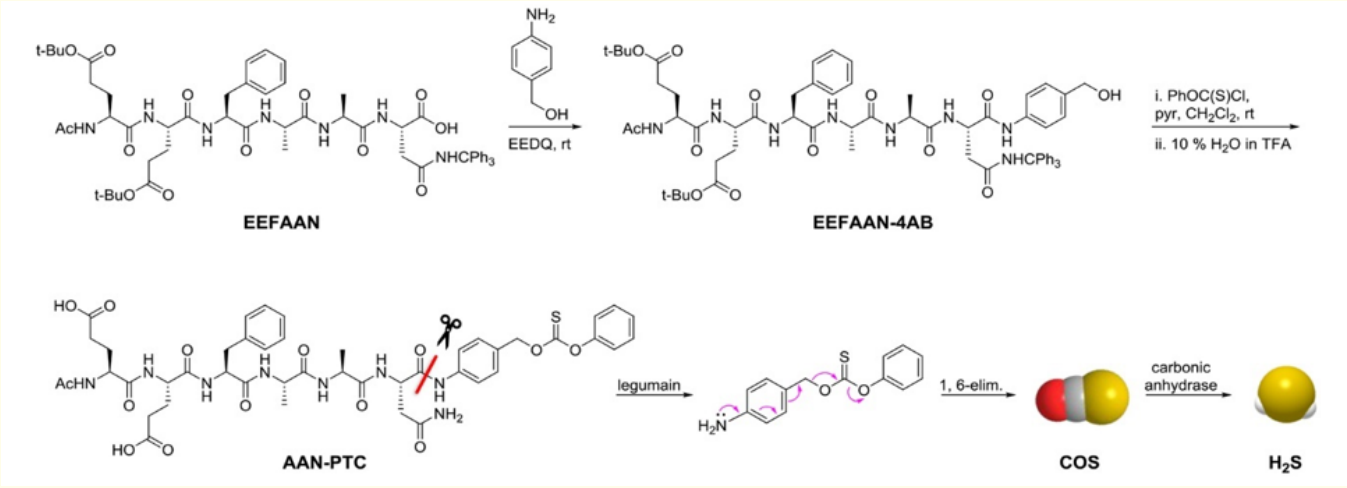


Figure 1: Courtesy ref no-15 - Schematic illustration of PHDC–Fe^{2+} complex chemical structure and therapeutic mechanism in C6 glioma cell line.



Scheme 1: Courtesy ref no-15 - Synthetic route to AAN-PTC and COS/H2S release triggered by legumain and aided by CA.

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