REVIEW

A review of the therapeutic properties of dithiocarbamates [version 1; peer review: 1 approved with reservations]

Toluwani Tella[1], Carolina H. Pohl[2], Ayansina Ayangbenro[3]

[1]Biochemistry, North-West University, Mmabatho, North West, 2735, South Africa
[2]Microbiology and Biochemistry, University of the Free State, Bloemfontein, Free State, 9301, South Africa
[3]Food Security and Safety, North-West University, Mmabatho, North West, 2735, South Africa

v1 **First published:** 28 Feb 2022, **11**:243
https://doi.org/10.12688/f1000research.109553.1
Latest published: 28 Feb 2022, **11**:243
https://doi.org/10.12688/f1000research.109553.1

Abstract

The persistence of infectious diseases that continue to plague the world, as well as the formation of harmful substances within the human body, such as free radicals and reactive oxygen species (ROS) have sparked new research. Thus, the need for innovative approaches for developing new or modification of existing therapeutic agents. The design of biologically important metal complexes of dithiocarbamates (DTCs) has been made possible by recent advancements in innovative research. Dithiocarbamates are reduced thiuram disulfides with excellent complexing capabilities and have various applications. They are potent and work in tandem with the core metal ions of coordinating compounds to produce synergistic effects. Dithiocarbamates have many uses, including as antidotes for metal poisoning, cisplatin or carboplatin toxicity, and clinical trials for cancer, Lyme disease, human immunodeficiency virus and antibiotics. They exert anti-oxidant effect in cells. The understanding of the mechanisms of action of this therapeutic agent is important in drug repurposing. This review highlights the protective and therapeutic properties of dithiocarbamate compounds in biological systems.

Keywords

Dithiocarbamate, Biological properties, Antioxidant properties, Apoptosis, Reactive oxygen species

Open Peer Review

Approval Status ?

	1
version 1 28 Feb 2022	? view

1. **Christian K. Adokoh**, University of Cape Coast, Cape Coast, Ghana

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Ayansina Ayangbenro (sinasegun@gmail.com)

Author roles: Tella T: Conceptualization, Data Curation, Investigation, Writing – Original Draft Preparation, Writing – Review & Editing; **Pohl CH**: Project Administration, Resources, Writing – Review & Editing; **Ayangbenro A**: Data Curation, Investigation, Resources, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

How to cite this article: Tella T, Pohl CH and Ayangbenro A. **A review of the therapeutic properties of dithiocarbamates [version 1; peer review: 1 approved with reservations]** F1000Research 2022, **11**:243 https://doi.org/10.12688/f1000research.109553.1

First published: 28 Feb 2022, **11**:243 https://doi.org/10.12688/f1000research.109553.1

Introduction

Dithiocarbamates (DTCs) have lately reappeared as possible therapeutic agents because of their metal chelating properties and affinity for thiol groups (Kaul *et al.*, 2021). Only a few studies have shown the growing DTCs' importance in medicine and the promise for various medicinal applications. DTC moieties have been studied as antimicrobial agents, cancer therapies, and neurology and cardiology applications. New chemical compounds containing DTC moieties have also been developed and investigated for anti-cancer, neurological, and antimicrobial uses (Kaul *et al.*, 2021).

Dithiocarbamates are biologically active chemical compounds with the -N(C=S)S- moiety that is made by reacting amines or their corresponding derivatives with carbon disulfide in the presence of a base. They are a type of soft sulfur donor ligand (mono-anionic 1,1-dithiolate), capable of forming stable metal complexes (Adeyemi & Onwudiwe, 2020). These ligands are mono-anionic 1,1-dithiolate. DTC ligands have a significant metal binding potential because of the presence of two sulfur atoms in their structure that are available for complexation, which are effective in enzyme inhibition in biological systems (Adeyemi & Onwudiwe, 2020; Yeo *et al.*, 2021). DTC ligands are lipophilic and can act as mono- or bi-dentate bridging ligands for metal ions (Hogarth, 2005). Their widespread use and applications are due to the relative simplicity of H^+ replacement from the -SH group inside their molecules, as well as the potential for complex formation. DTCs can suppress bacterial growth in biological systems by modifying the metabolic processes of the organism. The existence of carbon–sulfur bonds has been attributed to most biological features exhibited by dithiocarbamate molecules. This helps with the synthesis of organic intermediates with interesting chemistry (Movassagh & Shokri, 2012). In research, their strong nucleophilic attributes and unique characteristics to perform a redox reaction have been credited with their application in enzyme catalysis, redox signaling and protein folding (Lal, 2014). They also demonstrate anticancer capabilities and the potential for usage in treating various ailments, including viral infections and inflammation. Key proteins involved in apoptosis, degradation, oxidative stress, and transcription can be altered to help achieve these goals (Buac *et al.*, 2012).

The antioxidant behavior of dithiocarbamate includes scavenging the superoxide radical and eliminating hydrogen peroxide (Mankhetkorn *et al.*, 1994), peroxynitrite and the hydroxyl radical (Liu *et al.*, 1996) and peroxyl radical, a product of lipid peroxidation (Zanocco *et al.*, 1989). Excessive generation of free radicals causes damage to DNA, lipids, and proteins, which promote aging, cancer, and various brain and cardiac problems (Onwudiwe & Ekennia, 2017). Dithiocarbamate thiyl radicals are formed when DTCs react with nitrogen species and reactive oxygen, and then dimerize to form thiuram disulfides (Zanocco *et al.*, 1989), the oxidized form of DTCs. Thiuram disulfides, which are characterized by their intense oxidation of GSH and protein thiols, are responsible for much of the pro-oxidant effects of DTCs. (Nobel *et al.*, 1995). The oxidation of diethyldithiocarbamate and PDTC by copper (II) is an example of thiuram disufide production that is metal-dependent (Burkitt *et al.*, 1998).

In studies of DTC activity, the antioxidant properties of these compounds have been emphasized, whereas their pro-oxidant properties have received less attention.

Types and structure of dithiocarbamates

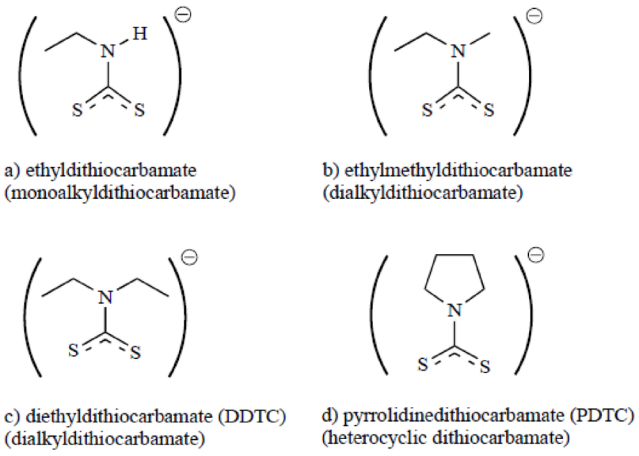
Dithiocarbamates are divided into four groups:

a) Monoalkyldithiocarbamates *e.g.* ethyldithiocarbamate

b) Asymmetric (dialkyldithiocarbamate) *e.g.* ethylmethyldithiocarbamate

c) Symmetric (dialkyldithiocarbamate) *e.g.* diethyldithiocarbamate

d) Heterocyclic dithiocarbamates *e.g.* pyrrolidinedithiocarbamate



Free radicals, reactive oxygen species and oxidative stress

Molecules or molecular fragments with one or more unpaired electrons in atomic or molecular orbitals are known as free radicals (Halliwell & Gutteridge, 2006). The free radical usually has a lot of reactivity because of the unpaired electron(s). The most common type of radical species produced in living systems is radicals originating from oxygen (Miller *et al.*, 1990). The electrical arrangement of molecular oxygen (dioxygen) is unusual, making it a radical.

When one electron is added to dioxygen, the superoxide anion radical ($O_2^{\cdot -}$) is generated (Miller *et al.*, 1990). Superoxide anion is the "primary" ROS, formed either using metabolic processes or after physical irradiation "activates" oxygen. It can then combine with other molecules to generate five "secondary" ROS, either directly or through enzyme or metal-catalyzed processes (Valko *et al.*, 2005). The most prevalent ROS include superoxide anion, hydrogen peroxide, peroxyl radicals, and highly reactive hydroxyl (OH^-) radicals.

Although, oxygen is required by cells, its metabolites such as the ROS are lethal to cells (de Lamirande & Gagnon, 1995). As a result of its toxicity to cells, ROS must continually be inactivated to keep only a small amount necessary to maintain normal

cell function. "Oxidative stress" (OS) is a condition associated with an increased rate of cellular damage induced by oxygen and oxygen-derived oxidants (Sikka *et al.*, 1995). The imbalance between ROS and the antioxidant defense mechanism of the cell also causes oxidative stress (Sikka, 2001). Carcinogenesis, aging, infection, physical injury, acquired immunodeficiency syndrome, and toxin exposure have all been linked to ROS (Joyce, 1987). It's also been hypothesized that oxidative stress plays a role in many disorders linked to reproductive dysfunction (Sharma & Agarwal, 1996).

Dithiocarbamates in treatment and prevention of organ damage

Pyrrolidine dithiocarbamate (PDTC) is an antioxidant and an inhibitor of NF-κB. In cells treated with IL-1, LPS, phorbol ester, and TNF-α, micromolar levels of PDTC inhibited the release of the inhibitory subunit IκB from the latent cytoplasmic form of NF-κB (Schreck *et al.*, 1992). Hepatic fibrosis, triggered by hepatocyte damage results in the recruitment of inflammatory cells and the subsequent release of cytokines and growth factors (Muriel, 2007a; Muriel, 2007b) that are thought to link the inflammatory and reparative phases of fibrosis by activating hepatic stellate cells (HSC) (Parsons *et al.*, 2007). HSC is triggered by oxidative stress and responds to IL-1β and TNF-α therapy, resulting in NF-κB nuclear translocation and I-κBα breakdown. Activated HSCs are the primary source of extracellular matrix synthesis, and the expression of adhesion molecules and cytokines contributes to liver injury (Hellerbrand *et al.*, 1998).

In experimental models of liver damage, activation of NF-κB has been linked to the pathophysiology of cell injury. In a rat model of thioacetamide-induced liver failure, Bruck *et al.* (2002) investigated whether PDTC could reduce hepatic damage. They discovered that giving thioacetamide-treated animals PDTC intraperitoneally reduced immediate liver damage and increased survival. Reduced oxidative stress, reduced hepatic hydroxyproline levels, inhibition of NF-κB, reduced spleen weight and fibrosis score, as well as inhibition of HSC activation, reduced collagen content, and tissue inhibitor of metalloproteinase-2 and collagen α1(I) gene expression in the liver of PDTC-treated rats, could all contribute to this effect.

Eren *et al.* (2010) reported that PDTC reduced biochemical and structural derangement of diabetic lungs. Another finding revealed that in the rat aorta, pyrrolidine dithiocarbamate inhibits the loss of contractile responsiveness caused by interleukin-1-mediated stimulation of inducible nitric oxide synthase (Schini-Kerth *et al.*, 1994).

Borghi *et al.* (2018) reported that in the kidney, PDTC inhibited diclofenac-induced morphological changes, oxidative stress, NF-κB activation, pro-inflammatory cytokine production and increased antioxidant defenses and anti-inflammatory cytokine (IL-10). Additionally, N-benzyl-D-glucamine dithiocarbamate (BGD) protects against renal toxicity in rats during repeated cisdiamminedichloroplatinum administrations (Hidaka *et al.*, 1995).

Dithiocarbamates in sepsis treatment and apoptosis

Sepsis is a severe systemic inflammation caused by dysregulated host response to pathologic infection (Singer *et al.*, 2016), a report estimated its global incidence at 19 million people each year (Fleischmann *et al.*, 2016). Free-oxygen radicals, lipid and protein oxidation have been implicated in sepsis pathogenesis (Goodee & Webster, 1993; Prauchner, 2017). Lipopolysaccharides activate nuclear factor kappa B (NF-kB), activation of NF-kB results in the expression of pro-inflammatory mediators and increased biosynthesis in sepsis, which has been linked to multiple organ injury (Ang *et al.*, 2011). Pyrrolidine dithiocarbamate has been reported to be an effective medication for sepsis treatment (Gezmis *et al.*, 2019; Liu *et al.*, 1999).

Due to their pleiotropic effects on cells, dithiocarbamates may both prevent and trigger apoptosis (Orrenius *et al.*, 1996). They prevent apoptosis induced by a range of stimuli in short-term incubations. This has been interpreted to mean that ROS plays a function in apoptosis (Wolfe *et al.*, 1994). Others, on the other hand, believe that dithiocarbamate prevention of apoptosis is due to oxidation of key thiols rather than broad scavenging of oxygen radicals (Nobel *et al.*, 1997a). Thus, disulfiram inhibits caspase-3, caspase-1 (whose sensitivity to disulfiram varies in vitro), and most likely additional members of the caspase family (Nobel *et al.*, 1997a). Dithiocarbamate induce apoptosis via intracellular uptake of copper by triggering the formation of ROS and proteasome inhibition (Hogarth & Onwudiwe, 2021; Nobel *et al.*, 1995). The precise molecular processes underlying their anticancer effect are unknown, although mechanistic investigations have revealed that they can operate as proteasome inhibitors (Milacic *et al.*, 2006), DNA intercalators (Ronconi *et al.*, 2006), nuclear factor kappa B (NF-kB) inhibitors, and inactivators of various metal-containing enzymes (Nobel *et al.*, 1997b). In the presence of copper ions, disulfiram acts as an anticancer agent. With copper (Cu), it does not form a stable complex, but reacts rapidly. They are most likely transformed to thiuram disulfides, which are powerful glutathione oxidants, using a copper-catalysed process (Burkitt *et al.*, 1998). Park *et al.* (2003) has postulated a mechanism that involves the initial reduction of Cu(II) to Cu(I) and the creation of bitt-4 2^{+}, the oxidized form of disulfiram, at the same time. The bitt-4 2^{+} molecule is unstable and decomposes catastrophically, resulting in the generation of 30 electrons per molecule and oxidative stress in cells (Cen *et al.*, 2004). The significant cell death observed when exposed to disulfiram-copper combinations is most likely due to this (Chen *et al.*, 2006).

Disulfiram and Cu(II) also induce cellular apoptosis in prostate and human breast cancer cells (Daniel *et al.*, 2005; Daniel *et al.*, 2007), suggesting that they could be used to treat resistant neuroblastoma in children (Hogarth & Onwudiwe, 2021). Based on IC50 values, Zhang *et al.* (2008) found that this combination suppressed the growth of BE (2)C cells (a human neuroblastoma cell line) and was more potent than cisplatin. These DTC salts reduce cancer cell migration and invasion by decreasing cell proliferation and inducing apoptosis and autophagy.

Dithiocarbamates in the fight against microbial pathogens

Antimicrobial resistance and the subsequent lack of effective antimicrobials to combat infectious diseases has remained a global health challenge. Understanding the mechanisms of resistance, which enables new diagnostic and therapeutic approaches, antimicrobial resistance drivers in the environment, will help in combating this threat. Pathogens have evolved defensive mechanisms, such as preventing drug entry or export, altering the drug target or generating enzymes that degrade or modify the antimicrobial. As a result, antimicrobial resistance could be thought of as a Darwinian competition from antimicrobial compounds originating from natural microorganisms (Holmes *et al.*, 2016).

This challenge has resulted in fewer treatment options for patients and an increase in morbidity and mortality. As a result, we now have more serious infections that require comprehensive treatment, as well as lengthier illness causes that frequently necessitate protracted hospitalization. The costs of treating these illnesses have skyrocketed because of this. As a result, despite multiple discoveries and antimicrobial medicines already accessible for therapeutic use, continued hunt for novel drugs to combat rapidly evolving pathogens remains critical.

According to the World Health Organization, antimicrobial-resistant illnesses are expected to result in the death of 10 million people by 2050. This is due in part to an increase in microbial drug resistance, as well as a slower rate of discovery of new antimicrobials (Kaul *et al.*, 2021). Thus, there is an obvious need to discover new and effective antibiotics. A practical strategy is to focus on metallodrugs, which provide novel drug discovery prospects due to their increased potency and different modes of action (Yeo *et al.*, 2021). DTCs have been studied as antibacterial possibilities, with activity against viruses, bacteria, fungi, and parasites, leading to clinical trials in some cases. With the recognized therapeutic usage and promise of DTC derivatives and a growing understanding of the role of metal-based medications, it seems only logical that DTC derivatives be investigated as possible antimicrobial agents. Interference with cell wall (by affecting cell permeability), metabolic interference with cellular enzymes, cellular damage owing to protein denaturing, and disruption of normal cell processes as a result of hydrogen bonding with active cellular constituents through the azomethine group (Adeyemi & Onwudiwe, 2018). The permeability of these compounds through the cell membrane/wall of either Gram-positive or Gram-negative organisms was considered to guide these activities. Gram-negative bacteria pose a greater challenge because of the complex outer-lipid membrane, which is made of lipopolysaccharide. This outer membrane contributes to their antigenic specificity and makes them less penetrable than Gram-positive bacteria with simpler cell membrane (Jabbar *et al.*, 2012).

Several metal–dithiocarbamate complexes have shown moderate-to-high antibacterial activity against Gram-negative and Gram-positive bacterial pathogens on the World Health Organization's global priority list of antibiotic-resistant species. Disulfiram (DSF), a DTC derivative, inhibits Gram-positive bacterial growth in recent research, especially methicillin-resistant *Staphylococcus aureus* (MRSA) (Frazier *et al.*, 2019; Sheppard *et al.*, 2018). Diethyldithiocarbamate (DDC), the bestknown DTC derivative, on the other hand, did not show any substantial inhibition of Gram-positive bacterial growth when used alone (Frazier *et al.*, 2019). Periodontitis-causing organisms such as *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis* were inhibited by PDTC, which had a medium action against *S. aureus* and low sensitivity to *Escherichia coli* (Kang *et al.*, 2008).

DTC derivatives (PDTC and DDC) have been reported to be highly effective against both growing and non-growing *Mycobacterium tuberculosis* persisters. These derivatives improved the efficacy of existing tuberculosis drugs (Byrne *et al.*, 2007). Dalecki *et al.* (2015) on the other hand, reported that the bactericidal activities of DSF and DDC in *M. tuberculosis* are solely dependent on Cu^{+}. This indicates a synergistic antibacterial activity of DSF and Cu^{+}. This allows the complex to penetrate M. tuberculosis's cellular defenses and its drug resistance machinery. As a result, M. tuberculosis is vulnerable to chemical attacks, and copper-interacting compounds are identified as a unique family of bacterial inhibitors. Liegner (2019) presented a case of three patients, who were treated with DSF for Lyme disease and relapsing babesiosis caused by *Borrelia burgdorferi.* Patients who previously required intense open-ended antibiotic therapy for Lyme disease were able to quit treatment after completing a finite course of treatment alone with DSF and were clinically healthy for periods of observation ranging from 6–23 months (Liegner, 2019).

The metal chelation properties of DTC complexes depend on the polarity of the metal. Due to partial positive charge sharing with donor groups and the potential for n-electron delocalization over the entire chelate ring, the polarity of the metal is greatly reduced during complexation (Adeyemi & Onwudiwe, 2020; Manoussakis *et al.*, 1987). In this process, the complexes' permeability triumphs over the bacteria's lipophilic membrane, through chelation with DTC ligands, this mechanism of action was thought to block biological activities within the organism by suppressing physiologically important metals like Zn and Cu (Manoussakis *et al.*, 1987; Vuksanović *et al.*, 2013).

Another mechanism is thought to be exploited by DTCs is the formation of a hydrogen bond with the active centers of the bacterium cell constituents *via* the -N-C(S)SH group, which disrupts normal cell processes (Manoussakis *et al.*, 1987). A well-known DTC derivative, potassium-3-dithiocarboxy-3-aza-5-aminopentanoate, has been postulated to react with metalloenzymes in bacteria, killing them (Vuksanovi *et al.*, 2013).

In a study by Khan *et al.* (2007), the antifungal activities of DSF against *Aspergillus*, *Candida* and yeast isolates that cause life-threatening infections in immunocompromised patients were reported. Similarly, a series of DTCs were investigated against β-class carbonic anhydrase from *Malassezia globosa*, a fungal pathogen causing dandruff (Vullo *et al.*, 2017).

Compared to the typical sulfonamide medication acetazolamide, several DTCs were found to be more effective in suppressing *M. globosa.* These studies show the antifungal properties of DTCs and its derivatives in combating fungal infections.

The antiviral properties of DTC and its derivatives have also been reported in the literature. Several studies and DTC drugs are in preclinical and clinical stages against coronaviruses and human immunodeficiency virus (Kaul *et al.*, 2021). However, certain DTCs have been reported to be effective against other viruses. The antiviral activities of PDTC against influenza A (Wiesener *et al.*, 2011), enterovirus 71 (Lin *et al.*, 2015), herpes simplex 1 and 2 (Qiu *et al.*, 2013), and dengue virus 2 (Duran *et al.*, 2017) have been reported.

The blockage of influenza virus-induced apoptosis is responsible for PDTC's antiviral action against influenza virus (Uchide *et al.*, 2002). In primary cultured chorion cells generated from human fetal membranes, influenza virus increased ROS generation and apoptotic fragmentation of DNA as genetic material. The anti-influenza properties of PDTC were demonstrated by inhibition of induction of DNA fragmentation, ROS overproduction and the release of influenza particles from infected cells. Furthermore, PDTC suppressed the synthesis of complementary (cRNA and mRNA) RNAs, viral (vRNA), and influenza virus hemagglutinin up to 6 hours after infection, as well as delaying and deceasing hemagglutinin protein synthesis. PDTC did not affect apoptosis or influenza virus formation, but did inhibit ROS overproduction, suggesting that PDTC inhibited apoptosis by decreasing viral macromolecule synthesis rather than through its antioxidant impact (Uchide *et al.*, 2002).

The mechanism of PDTC on influenza virus gene replication and transcription is by chelating divalent metal ions and rapid recruitment of copper and zinc ions into cells from the extracellular medium (Kim *et al.*, 1999). The activity of viral RNA-dependent RNA polymerase is inhibited by zinc or copper ions. Bathocuproine–copper or bathocuproine–zinc complexes have a higher inhibitory impact than bathocuproine alone (Oxford & Perrin, 1974). Thujaplicin–copper complex, a metal chelator, prevents influenza virus multiplication (Miyamoto *et al.*, 1998). As a result, it's possible that PDTC suppresses viral gene replication and transcription by increasing intracellular copper and zinc ions, or intracellular PDTC–copper and PDTC–zinc complexes, by inhibiting RNA-dependent RNA polymerase activity. If PDTC worked just as a replicative enzyme inhibitor, the viral RNA production that PDTC halted would not resume in its presence; also, earlier exposure of cells to PDTC would not amplify its action (Takizawa *et al.*, 1993).

Limitations of dithiocarbamates as therapeutic agents

Dithiocarbamate and its metal complexes have been shown in numerous studies to be effective biological agents, particularly at the cellular level. However, most of these complexes are not clinically resolved. A few of the metallo-complexes have been linked to negative consequences on biological systems. These are frequently related to either the metal's toxicity or the instability of the ligand moiety (Adeyemi & Onwudiwe, 2018). Metal complexation, on the other hand, is hypothesized to have a modulating effect on the metal ion's toxicity while also allowing the ligand to become more stable, thus, reducing its availability for additional side reactions. Adokoh (2020) reported that these complexes have low stability in biological systems under physiological conditions as therapeutic agents. This property continues to be a major stumbling block in the development of this type of drug. Another challenge associated with the use of DTC complexes, particularly gold complexes, is the likelihood of oxidation state shift (Adokoh, 2020). Because most gold (III) compounds are largely unstable under physiological conditions and are frequently transformed into more thermodynamically stable gold (I) complexes, part of this compound's utility has been limited. Despite numerous publications suggesting that these gold (I) complexes have a more promising potential than most currently used anticancer medicines, the instability of gold (III) complex oxidation impedes the development of innovative therapeutic agents (Adokoh, 2020).

Conclusions

There has been limited information about the protective and therapeutic properties of dithiocarbamate compounds and the mechanisms of action is yet unknown. Recent research, on the other hand, has revealed information about DTC interactions with enzymes, intracellular metal concentrations, and oxidative processes, all of which are important targets in many diseases. This review gives comprehensive information about the protective effect of DTC compounds on ameliorating damage done to various organs and its use against microbial pathogens. In vitro tests on DTC and its derivatives have yielded promising results, prompting additional in vivo testing. The utilization of these complexes in drug design could have a tremendous impact on human health and provides alternative to currently available drugs that is both cheaper and more effective. Because of their biological potentials, DTC complexes could be effective in the fight against antibiotic resistance. However, understanding their precise mechanism of action and side effects requires a significant amount of effort. Regardless of the limitations, these complexes can provide a platform 12 for the development of novel therapeutic drugs, hence fresh approaches as well as detailed studies are required to overcome their drawback. Uncovering the possibilities and drawbacks of DTCs as revolutionary medical treatments is an interesting journey ahead.

Data availability

Underlying data

There are no data associated with this article.

References

Adeyemi JO, Onwudiwe DC: **Organotin(IV) dithiocarbamate complexes: chemistry and biological activity.** *Molecules.* 2018; **23**(10): 2571.
PubMed Abstract | Publisher Full Text | Free Full Text

Adeyemi JO, Onwudiwe DC: **The mechanisms of action involving dithiocarbamate complexes in biological systems.** *Inorg Chim Acta.* 2020; **511**: 119809.
Publisher Full Text

Adokoh CK: **Therapeutic potential of dithiocarbamate supported gold compounds.** *RSC Adv.* 2020; **10**: 2975–2988.
Publisher Full Text

Ang SF, Moochhala SM, MacAry PA, *et al.*: **Hydrogen sulfide and neurogenic inflammation in polymicrobial sepsis: involvement of substance P and ERK-NF-κB signaling.** *PLoS One.* 2011; **6**(9): e24535.
PubMed Abstract | Publisher Full Text | Free Full Text

Borghi SM, Fattori V, Ruiz-Miyazawa KW, *et al.*: **Pyrrolidine dithiocarbamate inhibits mouse acute kidney injury induced by diclofenac by targeting oxidative damage, cytokines and NF-κB activity.** *Life Sci.* 2018; **208**: 221–231.
PubMed Abstract | Publisher Full Text

Bruck R, Aeed H, Schey R, *et al.*: **Pyrrolidine dithiocarbamate protects against thioacetamide-induced fulminant hepatic failure in rats.** *J Hepatol.* 2002; **36**(3): 370–377.
PubMed Abstract | Publisher Full Text

Buac D, Schmitt S, Ventro G, *et al.*: **Dithiocarbamate-based coordination compounds as potent proteasome inhibitors in human cancer cells.** *Mini Rev Med Chem.* 2012; **12**(12): 1193–1201.
PubMed Abstract | Publisher Full Text | Free Full Text

Burkitt MJ, Bishop HS, Milne L, *et al.*: **Dithiocarbamate toxicity toward thymocytes involves their copper-catalyzed conversion to thiuram disulfides, which oxidize glutathione in a redox cycle without the release of reactive oxygen species.** *Arch Biochem Biophys.* 1998; **353**(1): 73–84.
PubMed Abstract | Publisher Full Text

Byrne ST, Gu P, Zhou J, *et al.*: **Pyrrolidine dithiocarbamate and diethyldithiocarbamate are active against growing and nongrowing persister *Mycobacterium tuberculosis*.** *Antimicrob Agents Chemother.* 2007; **51**(12): 4495–4497.
PubMed Abstract | Publisher Full Text | Free Full Text

Cen D, Brayton D, Shahandeh B, *et al.*: **Disulfiram facilitates intracellular Cu uptake and induces apoptosis in human melanoma cells.** *J Med Chem.* 2004; **47**(27): 6914–6920.
PubMed Abstract | Publisher Full Text

Chen D, Cui QC, Yang H, *et al.*: **Disulfiram, a clinically used anti-alcoholism drug and copper-binding agent, induces apoptotic cell death in breast cancer cultures and xenografts via inhibition of the proteasome activity.** *Cancer Res.* 2006; **66**(21): 10425–10433.
PubMed Abstract | Publisher Full Text

Dalecki AG, Haeili M, Shah S, *et al.*: **Disulfiram and copper ions kill *Mycobacterium tuberculosis* in a synergistic manner.** *Antimicrob Agents Chemother.* 2015; **59**(8): 4835–4844.
PubMed Abstract | Publisher Full Text | Free Full Text

Daniel KG, Chen D, Orlu S, *et al.*: **Clioquinol and pyrrolidine dithiocarbamate complex with copper to form proteasome inhibitors and apoptosis inducers in human breast cancer cells.** *Breast Cancer Res.* 2005; **7**(6): R897–908.
PubMed Abstract | Publisher Full Text | Free Full Text

Daniel KG, Chen D, Yan B, *et al.*: **Copper-binding compounds as proteasome inhibitors and apoptosis inducers in human cancer.** *Front Biosci.* 2007; **12**: 135–44.
PubMed Abstract | Publisher Full Text

de Lamirande E, Gagnon C: **Impact of reactive oxygen species on spermatozoa: a balancing act between beneficial and detrimental effects.** *Hum Reprod.* 1995; **10 Suppl 1**: 15–21.
PubMed Abstract | Publisher Full Text

Duran A, Valero N, Mosquera J, *et al.*: **Gefitinib and pyrrolidine dithiocarbamate decrease viral replication and cytokine production in dengue virus infected human monocyte cultures.** *Life Sci.* 2017; **191**: 180–185.
PubMed Abstract | Publisher Full Text

Eren G, Cukurova Z, Hergunsel O, *et al.*: **Protective Effect of the Nuclear Factor Kappa B Inhibitor Pyrrolidine Dithiocarbamate in Lung Injury in Rats with Streptozotocin-Induced Diabetes.** *Respiration.* 2010; **79**(5): 402–410.
PubMed Abstract | Publisher Full Text

Fleischmann C, Scherag A, Adhikari NK, *et al.*: **Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations.** *Am J Respir Crit Care Med.* 2016; **193**(3): 259–272.
PubMed Abstract | Publisher Full Text

Frazier K, Moore J, Long T: **Antibacterial activity of disulfiram and its metabolites.** *J Appl Microbiol.* 2019; **126**(1): 79–86.
PubMed Abstract | Publisher Full Text

Gezmis A, Balkan B, Yektas AK: **Protective Effect of Pyrrolidine Dithiocarbamate to Liver Injury in a Sepsis Model with Cecum Ligation and Perforation - An Animal Study.** *Ann Clin Lab Res.* 2019; **7**(1): 294.
Reference Source

Goode HF, Webster NR: **Free radicals and antioxidants in sepsis.** *Crit Care Med.* 1993; **21**(11): 1770–1776.
PubMed Abstract | Publisher Full Text

Halliwell B, Gutteridge JMC: **Free Radicals in Biology and Medicine, Ed 4.** Clarendon Press, Oxford. 2006.

Hellerbrand C, Jobin C, Licato LL, *et al.*: **Cytokines induce NF-kappaB in activated but not in quiescent rat hepatic stellate cells.** *Am J Physiol.* 1998; **275**(2): G269–G278.
PubMed Abstract | Publisher Full Text

Hidaka S, Funakoshi T, Shimada H, *et al.*: **Protective effect of N-benzyl-D-glucamine dithiocarbamate against renal toxicity in rats during repeated cis-diamminedichloroplatinum administrations.** *Ren Fail.* 1995; **17**(5): 539– 550.
PubMed Abstract | Publisher Full Text

Hogarth G, Onwudiwe DC: **Copper Dithiocarbamates: Coordination chemistry and applications in materials science, biosciences and beyond.** *Inorganics.* 2021; **9**(9): 70.
Publisher Full Text

Hogarth G: **Transition metal dithiocarbamates: 1978-2003.** *Progress in Inorganic Chemistry.* 2005; **53**: 71–561.
Publisher Full Text

Holmes AH, Moore LSP, Sundsfjord A, *et al.*: **Understanding the mechanisms and drivers of antimicrobial resistance.** *Lancet.* 2016; **387**(10014): 176–187.
PubMed Abstract | Publisher Full Text

Jabbar S, Shahzadi I, Rehman R, *et al.*: **Synthesis, characterization, semi-empirical study, and biological activities of organotin (IV) complexes with cyclohexylcarbamodithioic acid as biological active ligand.** *Journal of Coordination Chemistry.* 2012; **65**: 572–590.
Publisher Full Text

Joyce DA: **Oxygen radicals in disease.** *Adverse Drug Reaction Bull.* 1987; **127**: 476–479.
Reference Source

Kang MS, Choi EK, Choi DH, *et al.*: **Antibacterial activity of pyrrolidine dithiocarbamate.** *FEMS Microbiol Lett.* 2008; **280**(2): 250–254.
PubMed Abstract | Publisher Full Text

Kaul L, Süss R, Zannettino A, *et al.*: **The revival of dithiocarbamates: from pesticides to innovative medical treatments.** *iScience.* 2021; **24**(2): 102092.
PubMed Abstract | Publisher Full Text | Free Full Text

Khan S, Singhal S, Mathur T, *et al.*: **Antifungal potential of disulfiram.** *Nihon Ishinkin Gakkai Zasshi.* 2007; **48**(3): 109–113.
PubMed Abstract | Publisher Full Text

Kim CH, Kim JH, Hsu CY, *et al.*: **Zinc is required in pyrrolidine dithiocarbamate inhibition of NF-Kappab activation.** *FEBS Lett.* 1999; **449**(1): 28–32.
PubMed Abstract | Publisher Full Text

Lal N: **Dithiocarbamates: a versatile class of compounds in medicinal chemistry.** *Chemistry and Biology Interface.* 2014; **4**: 321–340.

Liegner KB: **Disulfiram (Tetraethylthiuram Disulfide) in the treatment of lyme disease and babesiosis: report of experience in three cases.** *Antibiotics (Basel).* 2019; **8**(2): 72.
PubMed Abstract | Publisher Full Text | Free Full Text

Lin L, Qin Y, Wu H, *et al.*: **Pyrrolidine dithiocarbamate inhibits enterovirus 71 replication by down-regulating ubiquitin-proteasome system.** *Virus Res.* 2015; **195**: 207–216.
PubMed Abstract | Publisher Full Text

Liu SF, Ye X, Malik AB: **Pyrrolidine dithiocarbamate prevents I-kappaB degradation and reduces microvascular injury induced by lipopolysaccharide in multiple organs.** *Mol Pharmacol.* 1999; **55**(4): 658–667.
PubMed Abstract

Liu J, Shigenaga MK, Yan L, *et al.*: *Free Radicals Res.* 1996; **24**: 461–472.

Mankhetkorn S, Abedinzadeh Z, Houee-Levin C: *Free Radicals Biol Med.* 1994; **17**: 517–527.

Manoussakis G, Bolos C, Ecateriniadou L, *et al.*: **Synthesis, characterization and anti-bacterial studies of mixed-ligand complexes of dithiocarbamato–Thiocyanato and iron(III), nickel(II), copper(II) and zinc(II).** *Eur J Med Chem.* 1987; **22**(5): 421–425.
Publisher Full Text

Milacic V, Chen D, Ronconi L, *et al.*: **A novel anticancer gold(III) dithiocarbamate compound inhibits the activity of a purified 20S proteasome and 26S proteasome in human breast cancer cell cultures and xenografts.** *Cancer Res.* 2006; **66**(21): 10478–10486.
PubMed Abstract | Publisher Full Text

Miller DM, Buettner GR, Aust SD: **Transition metals as catalysts of "autoxidation" reactions.** *Free Radic Biol Med.* 1990; **8**(1): 95–108.
PubMed Abstract | Publisher Full Text

Miyamoto D, Kusagaya Y, Endo N, *et al.*: **Thujaplicin-copper chelates inhibit replication of human influenza viruses.** *Antiviral Res.* 1998; **39**(2): 89–100.
PubMed Abstract | Publisher Full Text

Movassagh B, Shokri B: **A facile and efficient one-pot regioselective synthesis of 2-hydroxyalkyl dithiocarbamates under catalyst-free conditions.** *Int J Org Chem (Irvine).* 2012; **2**(3): 248–253.
Publisher Full Text

Muriel P: **Some experimental models of liver damage.** In *Hepatotoxicity: from Genomics to in Vitro and in Vivo Models.* Sahu S (ed.). Wiley: Chichester; 2007a; 119–137.
Publisher Full Text

Muriel P: **Cytokines in liver diseases.** In *Hepatotoxicity: from Genomics to in Vitro and in Vivo Models.* Sahu S (ed.). Wiley: Chichester; 2007b; 371–389.

Nobel CI, Kimland M, Lind B, *et al.*: **Dithiocarbamates induce apoptosis in thymocytes by raising the intracellular level of redox-active copper.** *J Biol Chem.* 1995; **270**(44): 26202–8.
PubMed Abstract | Publisher Full Text

Nobel CS, Kimland M, Nicholson DW, *et al.*: **Disulfiram is a potent inhibitor of proteases of the caspase family.** *Chem Res Toxicol.* 1997a; **10**(12): 1319–1324.
PubMed Abstract | Publisher Full Text

Nobel CS, Burgess DH, Zhivotovsky B, *et al.*: **Mechanism of dithiocarbamate inhibition of apoptosis: thiol oxidation by dithiocarbamate disulfides directly inhibits processing of the caspase-3 proenzyme.** *Chem Res Toxicol.* 1997b; **10**(6): 636–43.
PubMed Abstract | Publisher Full Text

Onwudiwe DC, Ekennia AC: **Synthesis, characterization, thermal, antimicrobial and antioxidant studies of some transition metal dithiocarbamates.** *Res Chem Intermed.* 2017; **43**: 1465–1485.
Publisher Full Text

Orrenius S, Nobel CS, van den Dobbelsteen DJ, *et al.*: **Dithiocarbamates and the redox regulation of cell death.** *Biochem Soc Trans.* 1996; **24**(4): 1032–1038.
PubMed Abstract | Publisher Full Text

Oxford JS, Perrin DD: **Inhibition of the particle-associated RNA-dependent RNA polymerase activity of influenza viruses by chelating agents.** *J Gen Virol.* 1974; **23**(1): 59–71.
PubMed Abstract | Publisher Full Text

Park JH, Afzaal M, Kemmler M, *et al.*: **The deposition of thin films of $CuME_2$ by CVD techniques (M = In, Ga and E = S, Se).** *J Mater Chem.* 2003; **13**(8): 1942–1949.
Publisher Full Text

Parsons CJ, Takashima M, Rippe RA: **Molecular mechanisms of hepatic fibrogenesis.** *J Gastroenterol Hepatol.* 2007; **22 Suppl 1**: S79–S84.
PubMed Abstract | Publisher Full Text

Prauchner CA: **Oxidative stress in sepsis: pathophysiological implications justifying antioxidant co-therapy.** *Burns.* 2017; **43**(3): 471–485.
PubMed Abstract | Publisher Full Text

Qiu M, Chen Y, Cheng L, *et al.*: **Pyrrolidine dithiocarbamate inhibits herpes simplex virus 1 and 2 replication, and its activity may be mediated through dysregulation of the ubiquitin-proteasome system.** *J Virol.* 2013; **87**(15): 8675–8686.
PubMed Abstract | Publisher Full Text | Free Full Text

Ronconi L, Marzano C, Zanello P, *et al.*: **Gold(III) dithiocarbamate derivatives for the treatment of cancer: solution chemistry, DNA binding, and hemolytic properties.** *J Med Chem.* 2006; **49**(5): 1648–1657.
PubMed Abstract | Publisher Full Text

Schini-Kerth V, Bara A, Mülsch A, *et al.*: **Pyrrolidine dithiocarbamate selectively prevents the expression of the inducible nitric oxide synthase in the rat aorta.** *Eur J Pharmacol.* 1994; **265**(1–2): 83–87.
PubMed Abstract | Publisher Full Text

Schreck R, Meier B, Männel DN, *et al.*: **Dithiocarbamates as potent inhibitors of nuclear factor kappa B activation in intact cells.** *J Exp Med.* 1992; **175**(5): 1181–1194.
PubMed Abstract | Publisher Full Text | Free Full Text

Sharma RK, Agarwal A: **Role of reactive oxygen species in male infertility.** *Urology.* 1996; **48**(6): 835–850.
PubMed Abstract | Publisher Full Text

Sheppard JG, Frazier KR, Saralkar P, *et al.*: **Disulfiram-based disulfides as narrow-spectrum antibacterial agents.** *Bioorg Med Chem Lett.* 2018; **28**(8): 1298–1302.
PubMed Abstract | Publisher Full Text | Free Full Text

Sikka SC: **Relative impact of oxidative stress on male reproductive function.** *Curr Med Chem.* 2001; **8**(7): 851–862.
PubMed Abstract | Publisher Full Text

Sikka SC, Rajasekaran M, Hellstrom WJ: **Role of oxidative stress and antioxidants in male infertility.** *J Androl.* 1995; **16**(6): 464–468.
PubMed Abstract

Singer M, Deutschman CS, Seymour CW, *et al.*: **The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).** *JAMA.* 2016; **315**(8): 801–810.
PubMed Abstract | Publisher Full Text | Free Full Text

Takizawa T, Matsukawa S, Higuchi Y, *et al.*: **Induction of programmed cell death (apoptosis) by influenza virus infection in tissue culture cells**. *J Gen Virol.* 1993; **74**(Pt 11): 2347–55.
PubMed Abstract | Publisher Full Text

Uchide N, Ohyama K, Bessho T, *et al.*: **Effect of antioxidants on apoptosis induced by influenza virus infection: inhibition of viral gene replication and transcription with pyrrolidine dithiocarbamate.** *Antiviral Res.* 2002; **56**(3): 207–17.
PubMed Abstract | Publisher Full Text

Valko M, Morris H, Cronin MT: **Metals, toxicity and oxidative stress.** *Curr Med Chem.* 2005; **12**(10): 1161–1208.
PubMed Abstract | Publisher Full Text

Vuksanović V, Leka Z, Terzić N: **Antibacterial effect of synthesized dithiocarbamate KDAAP.** *Fresenius Environ Bull.* 2013; **22**: 3803–3807.

Vullo D, Del Prete S, Nocentini A, *et al.*: **Dithiocarbamates effectively inhibit the β-carbonic anhydrase from the dandruff-producing fungus *Malassezia globosa*.** *Bioorg Med Chem.* 2017; **25**(3): 1260–1265.
PubMed Abstract | Publisher Full Text

Wiesener N, Zimmer C, Jarasch-Althof N, *et al.*: **Therapy of experimental influenza virus infection with pyrrolidine dithiocarbamate.** *Med Microbiol Immunol.* 2011; **200**(2): 115–126.
PubMed Abstract | Publisher Full Text

Wolfe JT, Ross D, Cohen GM: **A role for metals and free radicals in the induction of apoptosis in thymocytes.** *FEBS Lett.* 1994; **352**(1): 58–62.
PubMed Abstract | Publisher Full Text

Yeo CI, Tiekink ERT, Chew J: **Insights into the antimicrobial potential of dithiocarbamate anions and metal-based species.** *Inorganics.* 2021; **9**(6): 48.
Publisher Full Text

Zanocco AL, Pavez R, Videla LA, *et al.*: **Antioxidant capacity of diethyldithiocarbamate in a metal independent lipid peroxidative process.** *Free Radic Biol Med.* 1989; **7**(2): 151–156.
PubMed Abstract | Publisher Full Text

Zhang H, Wu JS, Peng F: **Potent anticancer activity of pyrrolidine dithiocarbamate-copper complex against cisplatin-resistant neuroblastoma cells.** *Anticancer Drugs.* 2008; **19**(2): 125–132.
PubMed Abstract | Publisher Full Text

Open Peer Review

Current Peer Review Status: ?

Version 1

Reviewer Report 23 May 2022

https://doi.org/10.5256/f1000research.121066.r125694

?

Christian K. Adokoh
Department of Forensic Sciences, University of Cape Coast, Cape Coast, Ghana

The work of Ayangbenro *et al.* is an interesting and well-written summarized review that describes the therapeutic properties of dithiocarbamates. Mainly it highlights the protective and therapeutic properties of dithiocarbamate compounds in biological systems. It is a topic of great interest and I presume that it will be highly referenced by many authors working in drug discovery, especially those devoted to medicinal chemistry. The scheme followed describing the antioxidant properties of these compounds, treatment and prevention of organ damage, sepsis treatment and apoptosis, its limitations and conclusion is comprehensive and well-structured with up-to-date references containing the most essential data. In summary, a paper that I recommend for indexing. But my approval comes with some reservation due to minor points that should be considered prior to indexing and, under my point of view, would favour the understanding of the review. They refer to small editing changes I have already pointed out in the attached annotated manuscript.

Is the topic of the review discussed comprehensively in the context of the current literature?
No

Are all factual statements correct and adequately supported by citations?
Yes

Is the review written in accessible language?
Yes

Are the conclusions drawn appropriate in the context of the current research literature?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medicinal chemistry

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.