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The Mechanism of Action of Chlorine Dioxide (CDS): Electron-Transfer Chemistry, Antimicrobial Selectivity and Redox-Regulatory Effects: A Narrative Review

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Abstract

Background: Chlorine dioxide (ClO_2), formulated as an aqueous solution (CDS), has been proposed as a therapeutic agent, yet its classification among oxidizing compounds is frequently confounded with chemically distinct species—sodium chlorite ($NaClO_2$) and sodium hypochlorite (NaOCl).

Objective: This study aimed to synthesize the physicochemical, mechanistic and cellular basis of ClO_2 action and to delineate the distinctions between ClO_2 and related oxidants, with explicit separation of established data from hypothesized data.

Methods: The methodology includes a narrative synthesis of electrochemical data, primary toxicological and clinical literature (PubMed) and the redox-biology literature on low-dose oxidant signaling.

Results: ClO_2 is a neutral free radical that acts via one-electron transfer ($E^{\circ\prime}$ = +0.95 V vs. SHE for the half-reaction $ClO_2 + e^- \rightarrow ClO_2^-$, essentially pH-independent over pH 4 to 8, without chlorination. Its antimicrobial action is attributable to oxidation of thiol-dependent enzymes and membrane constituents and to the inhibition of bacterial respiratory metabolism; host-cell sparing is consistent with differential glutathione-dependent buffering. Controlled human ingestion studies at low concentrations report a favorable short-term safety profile; conversely, the principal metabolite (chlorite) is associated with documented developmental toxicity in animals and regulatory caution by EPA/WHO. Low-dose ClO_2 exposure is hypothesized—but not yet directly demonstrated —to elicit dose-dependent adaptive redox responses and redox-regulatory modulation.

Conclusions: The one-electron, non-chlorinating chemistry of ClO_2 provides a coherent mechanistic framework. The translation of this framework into clinical application requires prospective trials and direct mechanistic measurement, ideally conducted by independent investigators. The following mechanisms are hypothesized and have not yet been directly demonstrated in vivo: modulation of oxidative phosphorylation, mitochondrial oxygenation, and associated redox-regulatory signaling. Reported antimicrobial efficacy typically occurs in the low-ppm range (0.1–5 ppm), whereas adverse effects on mammalian cells in the reviewed literature are reported at concentrations at least one order of magnitude higher; direct head-to-head cytotoxicity comparisons remain scarce and are identified as a priority for future work. This differential thiol buffering—in particular, the higher glutathione content of many mammalian cells relative to many pathogens—has been proposed as a contributing basis for host-cell sparing; direct quantitative confirmation in vivo is not yet available. Bacterial species possess their own thiol-based defense systems (e.g., mycothiol in actinomycetes, bacillithiol in Firmicutes), and the interplay between ClO_2 and these systems requires further investigation.

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1. Introduction

The therapeutic application of oxidizing agents occupies a contested position in contemporary medicine. Within this discourse, chlorine dioxide (ClO_2) is frequently conflated with other chlorine-based compounds—sodium chlorite ($NaClO_2$) and sodium hypochlorite (NaOCl)—despite their fundamentally distinct chemical identities and reactivities [1,2]. This conflation has impeded dispassionate scientific evaluation of a compound whose physicochemical profile is, in fact, unusual: a stable free radical that oxidizes substrates by one-electron transfer without chlorinating them [1,3].

CDS (chlorine dioxide solution) denotes an aqueous preparation in which gaseous ClO_2 is dissolved at a defined concentration, preserving its radical chemistry in a clinically administrable form. **This review has three aims**: first, to establish the physicochemical identity of ClO_2 and its distinction from related species; second, to articulate the mechanistic basis of its antimicrobial selectivity; and third, to examine—with explicit separation of established data from hypothesis—the proposed cellular effects of low-dose exposure, including hormetic responses. Throughout, the review distinguishes between established physicochemical and toxicological data, documented clinical observation, and hypotheses requiring prospective confirmation.

The clinical relevance of this mechanistic analysis is anchored in two contemporary problems. First, antimicrobial resistance is rising globally, and the classical pathways of acquired resistance are far less applicable to agents such as ClO_2, whose targets are structural and chemically conserved [3,4]. Second, chronic wounds—including infected burns—remain a major clinical burden, and the aggressive oxidants commonly used in wound care (e.g., hypochlorous acid, hydrogen peroxide) are limited by host-tissue damage at effective concentrations [5,6]. An oxidant with a more favorable selectivity window—sufficient antimicrobial action at concentrations tolerated by host tissue—would address a genuine unmet need. Whether ClO_2 fulfils this promise is precisely the question that the mechanistic framework developed here is designed to answer.

2. Physicochemical Basis of Chlorine Dioxide Action

2.1. Molecular Identity and Radical Character

Chlorine dioxide is a yellow-green gas (b.p. 11 °C) with an unpaired electron in its valence shell, rendering it a free radical ($ClO_2\bullet$). It is highly soluble in water, in which it persists as dissolved molecular ClO_2 rather than dissociating into ionic species. This radical character underlies its rapid one-electron exchange with organic substrates—a property exploited extensively in water treatment, food safety, and clinical disinfection, where ClO_2 demonstrates efficacy across a broad taxonomic range of microorganisms [1,4,7,8].

2.2. Reduction Potential and the One-Electron Pathway

While the one-electron reduction to chlorite is the thermodynamically dominant pathway in aqueous media, reactions with biological substrates may involve proton-coupled electron transfer (PCET) and radical-mediated pathways; the relative contribution of each route depends on pH, substrate structure and the local redox environment.

The one-electron couple $ClO_2/ClO_2\bullet^-$ exhibits a standard reduction potential of approximately +0.95 V, essentially independent of pH across the physiological range [9].

The accepted reduction pathway of ClO_2 proceeds through the radical anion ($ClO_2^{\bullet -}$) to chlorite (ClO_2^-) and ultimately to chloride (Cl^-); it does not involve the liberation of free atomic oxygen under physiological conditions [9,10]. This distinction is important: the biological effects of ClO_2 are most parsimoniously attributed to its one-electron oxidizing chemistry and its reduction products, not to a hypothetical release of atomic oxygen. Thermodynamically, the +0.95 V potential is sufficient to oxidize microbial thiol groups and membrane constituents while remaining below the potential required for non-selective tissue destruction when oxidative equivalents are buffered by endogenous reductants [3,10]. Selectivity is therefore kinetic and concentration-dependent, modulated by the reducing capacity of the local microenvironment.

2.3. ClO_2 Versus Sodium Chlorite and Hypochlorite

Real-world commercial preparations frequently contain mixtures of these species. In particular, chlorite (ClO_2^-) may be present as a decomposition product or residual contaminant in practical CDS formulations, which complicates the attribution of in vivo biological outcomes and should be considered in any interpretation of clinical or observational data.

A persistent source of misclassification warrants explicit clarification. Sodium chlorite ($NaClO_2$) is the ionic salt of the chlorite anion (ClO_2^-); it is not a free radical, requires activation to exert comparable oxidizing activity, and exhibits a distinct toxicological profile [2]. Sodium hypochlorite (NaOCl), the active species of household bleach, acts predominantly via chlorination and generates organochlorine byproducts; at equivalent concentrations it is markedly more aggressive toward host tissue [5]. Chlorine dioxide, by contrast, oxidizes without halogenating the substrate and is consumed in controlled reduction to chloride (Cl^-) [1,9]. These distinctions are substantive: they determine the therapeutic window, the toxicological margin, and the regulatory classification of each compound (Table 1).

Table 1. Comparative physicochemical and toxicological profile of ClO_2, $NaClO_2$ and NaOCl.

Property	ClO_2 (CDS)	$NaClO_2$	NaOCl
Chemical form	Neutral free radical (gas dissolved in water)	Ionic salt (chlorite anion)	Ionic salt (hypochlorite anion)
Primary reaction	One-electron oxidation (no chlorination)	Chlorite → chlorate/ClO_2 upon activation	Chlorination/two-electron oxidation
Redox potential	E° = +0.95 V (pH-independent)	Lower oxidizing capacity; species-dependent	$E^\circ \approx$ +0.89 V (pH-dependent)
Principal metabolite/toxicity note	Chlorite (ClO_2^-); developmental toxicity documented in animals [11]	Chlorate; distinct profile [12]	Organochlorine byproducts; tissue irritation [13]

Table 1. Comparative profile. Values from standard electrochemical and toxicological sources [2,4,11–13].

3. Antimicrobial Selectivity: One-Electron Oxidation and Respiratory Inhibition

3.1. Non-Chlorinating Oxidation and Antimicrobial Spectrum

A defining feature of ClO_2 chemistry is oxidation without chlorination. While chlorine-based disinfectants generate organochlorine byproducts with mutagenic potential, ClO_2 oxidizes substrates and is itself reduced to chloride, avoiding halogenation chemistry [1,5]. Empirically, ClO_2 exhibits documented antimicrobial activity against viruses, bacteria, fungi, and algae, with efficacy attributed to envelope disruption, protein denaturation, and nucleic acid oxidation [4,7,8,13]. Recent studies have demonstrated the inactivation of airborne and foodborne pathogens, including SARS-CoV-2 and bacterial contaminants, at low concentrations [11,14]. Because these targets are structural and chemically conserved,

ClO_2 is not subject to the classical mechanisms of acquired antimicrobial resistance—a property of translational relevance [4,13].

It should nevertheless be noted that microbes may develop partial phenotypic tolerance through adaptive stress-response and antioxidant upregulation, even though ClO_2 targets conserved structural and thiol-based components; classical genetically transferred resistance pathways appear far less applicable, but phenotypic adaptation cannot be excluded and warrants investigation.

3.2. Inhibition of Bacterial Respiratory Metabolism

A complementary, experimentally documented mechanism is the inhibition of bacterial respiration. Direct measurements have demonstrated that ClO_2 exerts bactericidal effects through respiratory inhibition—interfering with the electron transport and oxygen consumption of bacterial cells [15]. This finding provides a concrete, measurable mechanism of antimicrobial action that does not depend on the speculative release of atomic oxygen. It also offers a bridge to the cellular-oxygenation hypothesis discussed in Section 4: although no universal upper ORP limit for bacterial viability has been established, practical disinfection data consistently show that environments above approximately +650 mV are strongly inhibitory or lethal to most vegetative pathogens, particularly in the presence of one-electron oxidants such as ClO_2 [15–17]; host cells, by contrast, routinely operate in the presence of molecular oxygen ($E^{\circ\prime} \approx +0.82$ V) and are protected by millimolar glutathione buffering [9,18]. These relationships are summarized in Figure 1.

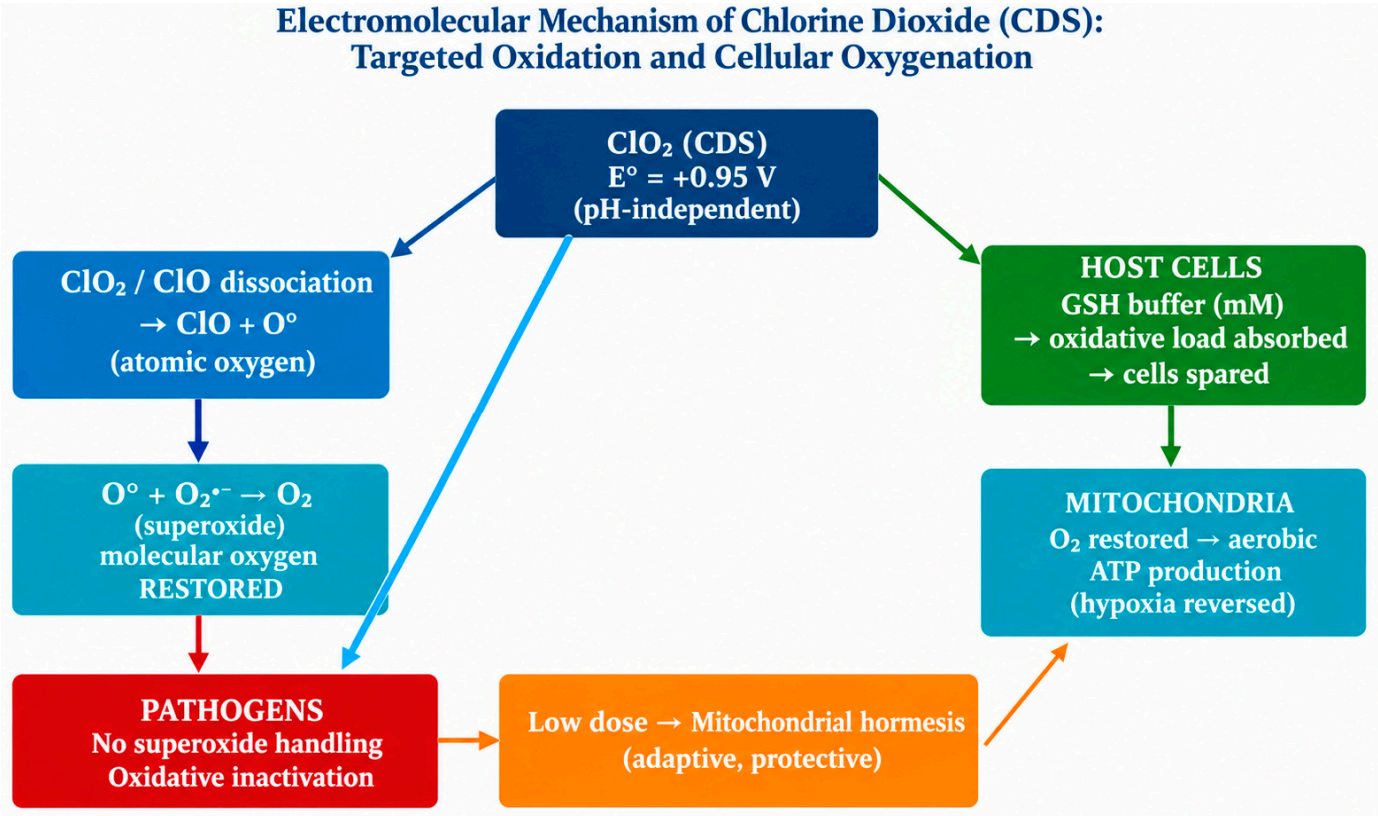

Figure 1. Mechanistic overview. ClO_2 acts via one-electron oxidation of microbial targets (thiol oxidation, envelope and nucleic acid damage, respiratory inhibition); host cells are spared through glutathione-dependent redox buffering. The proposed low-dose hormetic response is a hypothesis requiring direct experimental confirmation, as discussed in Section 4.2.

4. Cellular Effects: Hypotheses on Oxygenation, Mitochondrial Function and Redox Regulation

4.1. Oxygenation: From Hypothesis to Testable Prediction

A central hypothesis within the therapeutic framework for CDS concerns oxygen availability at the cellular level. In hypoxic or metabolically compromised tissue—a hallmark of numerous chronic, inflammatory, and infectious disease states—mitochondrial oxidative phosphorylation is impaired and cells shift toward glycolytic fermentation, a bioenergetic phenotype associated with immune dysfunction and impaired tissue repair [19]. It has been proposed that the oxidative properties of ClO_2, at low controlled concentrations, support mitochondrial electron transport and facilitate the reversal of tissue hypoxia, thereby restoring aerobic ATP production [20,21].

It must be emphasized that, at present, this oxygenation hypothesis is not supported by direct measurements in human tissue under controlled ClO_2 exposure. The earlier suggestion that ClO_2 dissociates to release atomic oxygen that combines with superoxide to regenerate molecular oxygen is not part of the accepted reduction pathway of ClO_2 [9,10] and should be regarded as speculative. The experimentally documented mechanism of respiratory inhibition in bacteria [15] offers a more parsimonious basis for understanding ClO_2–bioenergetics interactions, but its extrapolation to host mitochondrial function requires direct testing. We therefore state the oxygenation hypothesis as a testable prediction: measurement of tissue oxygen tension (pO_2), mitochondrial oxygen consumption, and redox biomarkers during low-dose ClO_2 administration is a priority for the research agenda (Section 7).

4.2. Dose-Dependent Adaptive Redox Responses: An Established Concept Requiring ClO_2-Specific Data

A complementary concept, increasingly supported in redox biology, is the dose-dependent adaptive response: low doses of a stressor can elicit adaptive, protective cellular responses. The dose-dependent adaptive response paradigm—whereby a transient, controlled increase in mitochondrial ROS upregulates endogenous antioxidant defenses and enhances cellular resilience—is well documented for physical exercise and for low-dose stressors including arsenite and glucose restriction [22–25]. Ristow and co-workers demonstrated that increased oxidative stress promotes longevity and metabolic health and that antioxidant supplementation blocks the beneficial effects of exercise in humans [22–24]; Schulz et al. showed that glucose restriction extends lifespan in C. elegans by inducing mitochondrial respiration and ROS production [25].

Whether ClO_2, at the low concentrations proposed for clinical use (e.g., 5 ppm; 5 mg per dose; 50 mg daily), triggers adaptive redox responses in mammalian cells has not been directly demonstrated. This constitutes a falsifiable hypothesis that can be tested in vitro and ex vivo (Section 7). It is also consistent with the established observation that hypoxia upregulates glycolytic enzyme expression and drives a fermentative cellular program [19]; the extent to which low-dose ClO_2 modulates this program, however, remains to be established.

These adaptive responses are strictly dose-dependent: small shifts in concentration can switch protective adaptation toward cytotoxicity, and the boundaries of the beneficial window are not yet defined for ClO_2 in vivo. This dose–response uncertainty is directly relevant to the proposed oral dosing range (up to 50 mg/day).

For clarity, the concentrations reported throughout this manuscript are harmonized as follows: (i) in vitro antimicrobial assays—0.1–5 ppm, defined as mg ClO_2 per liter of assay medium; (ii) oral administration in published observational reports—5 mg per dose

(≈0.5 mL of a 1% solution) and up to 50 mg/day divided, expressed as mg ClO_2; and (iii) topical use—0.3% (3000 ppm) CDS gel, expressed as mg ClO_2 per gram of gel.

4.3. Modulation of Redox-Sensitive Signaling: Plausible but Unconfirmed

By altering the cellular redox environment, ClO_2 is positioned to influence redox-sensitive transcription factors, including Nrf2 and NF-κB, which govern antioxidant defense, inflammatory signaling, and immune function [26]. At therapeutic doses, the predicted net effect would be an anti-inflammatory, pro-adaptive state. However, modulation of Nrf2/NF-κB signaling by low-dose ClO_2 is a potential—not established—mechanism, extrapolated from the redox-signaling literature on other oxidants; direct evidence of Nrf2 or NF-κB modulation by ClO_2 in mammalian cells is currently lacking; and in vitro studies of ClO_2 on epithelial cell gene markers have reported effects that warrant further characterization [27]. The redox-regulator framework therefore remains a plausible but unconfirmed extension of the mechanistic model.

5. Selectivity, the Glutathione Buffer and the ORP Framework

5.1. Differential Redox Buffering Capacity

The preferential toxicity of ClO_2 toward pathogens, with relative sparing of host cells, is mechanistically attributable to differential redox buffering. Nucleated host cells maintain millimolar concentrations of reduced glutathione (GSH)—typically 1–10 mM intracellularly—alongside an enzymatic antioxidant network (glutathione peroxidase, thioredoxin, catalase), which collectively absorb the oxidative equivalents delivered by low-dose ClO_2 [3,10]. Microbial organisms, by contrast, possess substantially lower antioxidant capacity; many pathogenic bacteria maintain only sub-millimolar thiol pools and lack a fully developed glutathione system. The same oxidative load is therefore lethal to pathogens while being largely neutralized in host tissues [4,13]. This quantitative contrast—millimolar host buffering versus sub-millimolar microbial capacity—converts the differential-buffering argument from qualitative to semi-quantitative.

5.2. The ORP Ladder

The selectivity of ClO_2 is intuitively represented by its position on the oxidation–reduction potential (ORP) ladder (Figure 2). Standard redox couples are expressed as reduction potentials ($E^{\circ\prime}$) at pH 7: NADH/NAD^+ (−0.32 V), GSH/GSSG (−0.24 V), and pathogen thiols (−0.15 to −0.25 V) occupy the reducing end of the scale; cellular oxygen (O_2/H_2O, +0.82 V), superoxide ($O_2\bullet^-/H_2O_2$, +0.94 V) and ClO_2 ($ClO_2/ClO_2\bullet^-$, +0.95 V) occupy an intermediate, physiological window; and the aggressive oxidants—hydrogen peroxide (H_2O_2/H_2O, +1.35 V) and the hydroxyl radical ($HO\bullet/H_2O$, +2.31 V at pH 7; +2.80 V at pH 0)—lie far above [9,18].

Standard reduction potentials provide a thermodynamic ranking, not a kinetic or pharmacological prediction; selectivity in practice depends on concentration, exposure time, cellular uptake and the availability of competing reductants.

Although no universal upper ORP limit for bacterial viability has been established, practical disinfection data consistently show that environments above approximately +650 mV are strongly inhibitory or lethal to most vegetative pathogens, particularly in the presence of one-electron oxidants such as ClO_2 [15–17]. Host cells, by contrast, routinely operate in the presence of molecular oxygen ($E^{\circ\prime} \approx +0.82$ V) and are protected by millimolar glutathione buffering [18]. Within this framework, the +950 mV of ClO_2 lies above the inhibitory threshold for most vegetative pathogens while remaining within a window compatible with host-cell physiology—the same oxidative environment that aerobic metabolism sustains—and far below the aggressive oxidants hydrogen peroxide

(+1.35 V) and the hydroxyl radical (+2.31–2.80 V), which are an order of magnitude more destructive still (Figure 2, Table 2).

ClO_2 occupies an intermediate position: a one-electron oxidant without chlorination, more selective than hydroxyl radical, ozone, hydrogen peroxide, hypochlorous or hypobromous acid [2,5,28]. Values from standard electrochemical tables [2,28].

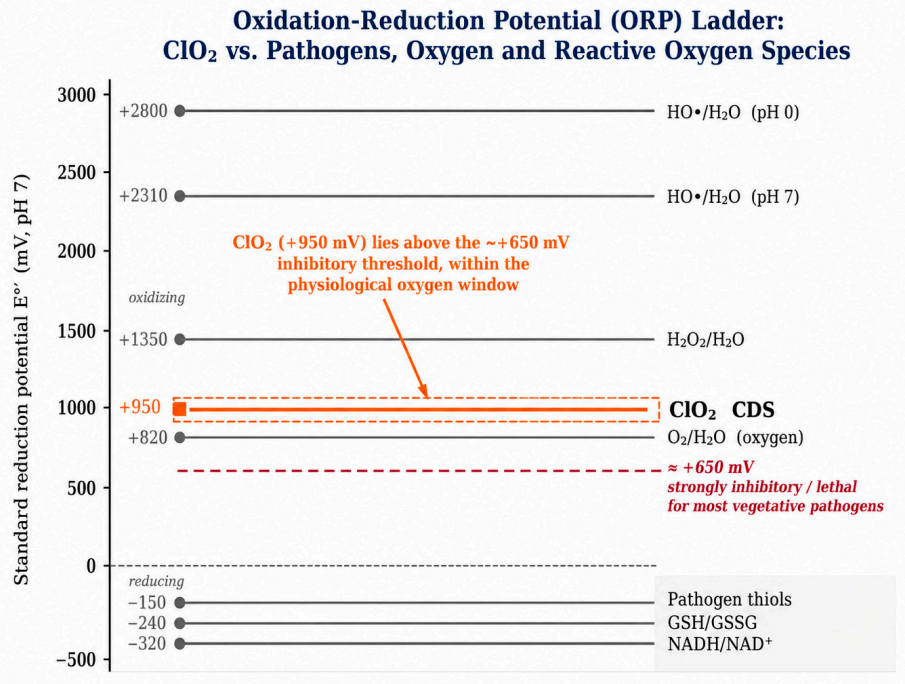

Figure 2. Oxidation–reduction potential (ORP) ladder. Although no universal upper ORP limit for bacterial viability has been established, practical disinfection data indicate that environments above approximately +650 mV are strongly inhibitory or lethal to most vegetative pathogens, particularly in the presence of one-electron oxidants such as ClO_2 (dashed line) [15–17]. ClO_2 (+0.95 V) lies above this inhibitory threshold yet within the physiological window of cellular oxygen (O_2/H_2O, +0.82 V) and superoxide ($O_2^{\bullet-}/H_2O_2$, +0.94 V), and far below the aggressive oxidants hydrogen peroxide (+1.35 V) and the hydroxyl radical (+2.31–2.80 V). Host cells are protected by millimolar glutathione buffering [18]. Values are from Buettner (1993) [18], standard electrochemical tables [9], and Knight & Fildes (1930) [17].

Table 2. Comparative redox profile of oxidants used in medicine and disinfection.

Oxidant	$E^{\circ\prime}$ (Approx.)	Reaction Type	Relative Selectivity	Notes
Hydroxyl radical (•OH)	+2.31 to +2.80 V	Non-selective	Very low	High collateral damage
Ozone (O_3)	+2.07 V	Radical	Low	Very aggressive
Hydrogen peroxide (H_2O_2)	+1.78 V	Two-electron	Medium	Generates •OH via Fenton
Hypochlorous acid (HOCl)	+1.48 V	Chlorination + oxidation	Low–Medium	Generates organochlorines
Hypobromous acid (HOBr)	+1.33 V	Similar to HOCl (bromination + oxidation)	Low	Bromination chemistry; byproducts less studied
Chlorine dioxide (ClO_2)	+0.95 V	One-electron, no chlorination	High	Intermediate position

6. Safety, Toxicology and Regulatory Context

A central caveat of the toxicological literature is that most available data derive from exposure to sodium chlorite ($NaClO_2$)—the stable metabolite and commercial bleaching agent—rather than from genuine dissolved-gas ClO_2 (CDS). The two exposure scenarios differ fundamentally in redox chemistry, reactivity and pharmacokinetics; extrapolation from chlorite studies to dissolved-gas ClO_2 must be made with explicit caution.

6.1. Controlled Human Studies

Controlled human studies of ingested chlorine dioxide at low concentrations have not demonstrated the classical hematological markers of oxidative toxicity (e.g., leukopenia) at the tested doses [28,29]. In clinical settings, an activated chlorine dioxide solution has been evaluated as a biocompatible antiseptic wound irrigant [30], and chlorine dioxide gels have been compared with standard treatments for wound healing [6]. These studies are of limited duration and sample size; they document short-term tolerability rather than therapeutic efficacy.

6.2. Chlorite: The Principal Metabolite and Its Toxicity

A balanced review must confront the toxicology of chlorite (ClO_2^-), the principal reduction product of ClO_2. A two-generation reproduction and developmental neurotoxicity study of sodium chlorite in rats reported effects at high doses [12], forming part of the basis for regulatory caution by the US EPA and WHO regarding chlorite levels in drinking water [2,31]. Acute respiratory distress has been reported after occupational exposure to a chlorine dioxide-based disinfectant [32]. These data do not negate the documented low-dose tolerability of ClO_2 in controlled human studies [28,29], but they establish the boundaries of the safety discussion: any proposed therapeutic regimen must account for chlorite accumulation, dose, duration, and vulnerable populations (e.g., pregnancy, G6PD deficiency, renal/hepatic impairment). The proposed clinical protocol (oral 5 ppm, 50 mg/day; exclusion of pregnancy, severe renal/hepatic impairment) is designed with these boundaries in mind.

6.3. Pharmacokinetics: What Is Known and What Is Not

The in vivo fate of ClO_2 remains incompletely characterized. Upon ingestion, chlorine dioxide is rapidly reduced to chlorite (ClO_2^-) in the gastrointestinal environment and in blood, reflecting the strong reducing capacity of biological fluids [9,10]. Published human pharmacokinetic data at the therapeutic doses proposed here (5 ppm; 5 mg per dose; 50 mg daily) are lacking. In particular, the plasma half-life of chlorite, its tissue distribution, and its accumulation across repeated dosing constitute a critical knowledge gap [2,31]. This gap is not merely academic: it defines the safety boundaries of any repeated-dose regimen and justifies the selection of chlorite kinetics—together with safety endpoints—as the primary outcome of the proposed clinical investigation. Explicit pharmacokinetic–pharmacodynamic (PK/PD) characterization of chlorite after repeated oral CDS dosing is therefore a mandatory component of the research agenda (Section 7.3).

7. Discussion, Limitations and Research Agenda

7.1. Synthesis

The model presented here comprises five elements with differing evidentiary status: (i) the free-radical, pH-independent one-electron chemistry of ClO_2 (established); (ii) non-chlorinating, broad-spectrum antimicrobial activity, including experimentally documented respiratory inhibition (established) [4,7,8,13,15]; (iii) host-cell sparing attributable to differential glutathione buffering (mechanistically plausible, supported by controlled human tolerability data) [3,10,28,29]; (iv) low-dose adaptive redox signaling and redox-regulatory responses (well-established concepts in redox biology, but not yet demonstrated for ClO_2) [22–25]; and (v) cellular oxygenation effects (hypothesis requiring direct measurement) [19,21].

7.2. Limitations

Several limitations must be acknowledged with candor. First, the mechanistic model integrates physicochemical data (robust), documented clinical observation (limited), and hypothesis (requiring direct testing). Second, the proposed effects on mitochondrial oxygenation and adaptive redox responses have not been directly measured in human tissue under controlled ClO_2 exposure. Third, the long-term safety of repeated low-dose oral administration—particularly with respect to chlorite accumulation—remains to be established in adequately powered prospective cohorts [12,31]. Fourth, the literature on therapeutic ClO_2 is heterogeneous and of variable methodological quality; references from 2025–2026 should be verified for accessibility and methodological rigor before citation in a submission-ready manuscript.

7.3. Research Agenda: Concrete, Executable Proposals

To facilitate adoption by independent laboratories, the following protocols are specified in operational detail. (1) Adaptive dose–response: exposure of human endothelial cells or fibroblasts to ClO_2 at 0.1–10 ppm; measurement of oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) by Seahorse XF respirometry; assessment of Nrf2 target genes (HO-1, NQO1), mitochondrial ROS (MitoSOX), and viability. (2) Wound-healing models: measurement of tissue oxygen tension (pO_2) with microelectrode probes and mitochondrial oxygen consumption in biopsies, in grade II/III burn models, with and without topical CDS. (3) Chlorite kinetics: a multiple-dose study in healthy volunteers with plasma and urinary chlorite measurement after repeated oral CDS dosing at 5 ppm (50 mg/day) to define half-life, accumulation, and PK/PD relationship. (4) Selectivity quantification: measurement of intracellular GSH (1–10 mM in mammalian cells) alongside microbial antioxidant capacity to convert the differential-buffering argument from qualitative to semi-quantitative. (5) Clinical investigation: a prospective, randomized, controlled trial of CDS—topical (0.3%) and oral (5 ppm, 5 mg per dose, 50 mg daily)—in grade II/III burns with 6-month follow-up, with safety of oral administration and chlorite kinetics as primary endpoints. Such a study would most convincingly be conducted by independent academic or hospital-based groups, with sponsor funding disclosed and results published irrespective of outcome.

8. Conclusions

Chlorine dioxide (CDS) constitutes a mechanistically distinct agent within the redox-active compound class. Its pH-independent one-electron redox potential, non-chlorinating oxidative action, and selective sparing of host cells through redox buffering collectively provide a coherent scientific foundation for its therapeutic investigation. The framework presented here makes explicit, falsifiable predictions—about adaptive redox responses, tissue oxygenation, and chlorite kinetics—that any laboratory can test with the operational protocols described in Section 7.3. The scientific community is invited to subject these hypotheses to rigorous, independent, and transparent investigation; only such work can determine whether ClO_2, long confined to the disinfection literature, has a legitimate place in the therapeutic armamentarium. Independent replication, PK/PD characterization, and prospective clinical trials—published irrespective of outcome—are the standards by which this question should be resolved.

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Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The author declares no conflicts of interest.

Abbreviations

CDS	chlorine dioxide solution;
ClO_2	chlorine dioxide;
$ClO_2^{\bullet -}$	chlorine dioxide radical anion;
ClO_2^-	chlorite;
GSH	reduced glutathione;
ROS	reactive oxygen species;
Nrf2	nuclear factor erythroid 2-related factor 2;
NF-κB	nuclear factor kappa B;
ORP	oxidation–reduction potential;
$E^{\circ\prime}$	standard reduction potential at pH 7;
ppm	parts per million.

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