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Preclinical evidence of cannabis-induced oxidative stress: A systematic review and meta-analysis

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ABSTRACT

Although cannabis exposure is linked to oxidative stress, no systematic analysis has evaluated its effects on ROS production, lipid peroxidation, and antioxidant defenses. We conducted a systematic review and meta-analysis of recent *in vivo* and *in vitro* studies. Of 9775 records identified across six databases, 51 met inclusion criteria and 49 were quantitatively analyzed (23 *in vitro*, 26 *in vivo*).

In vitro studies exposed cell lines to phytocannabinoids and measured ROS, MDA, and GSH. In vivo studies included 1258 animals, mainly rats (52.7%) and mice (27%), treated with THC, CBD, THC + CBD, crude extracts, or synthetic cannabinoids via intraperitoneal, oral, or aqueous routes. Assessed biomarkers included MDA/TBARS, CAT, SOD, GSH, and GPx.

Meta-analyses showed cannabis exposure was associated with ROS production *in vitro* (SMD = 0.04, 95% CI 0.02–0.06), a small, context-dependent effect, and *in vivo* (SMD = 0.93, 95% CI 0.10–1.75), along with increased lipid peroxidation in both systems. Cannabis reduced GSH and antioxidant enzymes, decreasing GR and CAT *in vitro* and SOD and GPx *in vivo*.

Overall, cannabinoid exposure was associated with changes in oxidative stress markers in preclinical models. These findings suggest a possible biological pathway but do not provide definitive evidence of a consistent effect.

1. Introduction

Oxidative stress is defined as "an imbalance between oxidants and antioxidants in favor of oxidants, resulting in disrupted redox signaling, impaired molecular regulation, and/or oxidative damage." It is also referred to as free radical dyshomeostasis (Sies, 2015). Initially regarded as mere byproducts of metabolism, free radicals play an essential role as signaling molecules in maintaining cellular homeostasis and regulating key biological processes such as cell proliferation and differentiation (Averill-Bates, 2024; Nugud et al., 2018; Tauffenberger and Magistretti, 2021). However, a breakdown in redox allostasis can lead to excessive production of reactive oxygen species (ROS), including superoxide anion ($O_2^{\bullet-}$), hydroxyl radical ($^{\bullet}OH$), hydroperoxyl radical ($HOO^{\bullet}$), and hydrogen peroxide (H_2O_2) (Huang and Li, 2020). When present at elevated levels, ROS cause damage to cellular components, including DNA, lipids, and proteins, ROS cause damage to cellular components, including (Chaudhary et al., 2023). ROS also contribute to mitochondrial dysfunction, which may trigger cell death through apoptotic or autophagic pathways. This process often involves the opening of the mitochondrial permeability transition pore (mPTP) and dysregulation of the mitochondrial calcium (Ca^{2+}) uniporter (MCU), both of which are critical regulators of mitochondrial integrity and Ca^{2+} homeostasis. (Filomeni et al., 2015; Redza-Dutordoir and Averill-Bates, 2016; Üremiş and Üremiş, 2025). Furthermore, redox homeostasis is modulated by multiple factors, among which the antioxidant defense system plays a central protective role. This system comprises several enzymatic antioxidants, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR). SOD catalyzes the dismutation of superoxide radicals into oxygen and hydrogen peroxide, which is subsequently detoxified by CAT and GPx into water and oxygen. The glutathione system also plays a crucial role in maintaining thiol redox balance and repairing oxidative damage (Birben et al., 2012; Lushchak, 2014). Dysregulation or impairment of these key enzymes leads to excessive ROS accumulation, thereby intensifying oxidative stress and contributing to various pathological conditions (Forman and Zhang, 2021; Hajam et al., 2022). These

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oxidative processes are implicated in the pathophysiology of various neuropsychiatric disorders, including anxiety disorders, depression, psychosis, and bipolar disorder (Pérez et al., 2023; Preuss et al., 2021; Vallersnes et al., 2016).

Recreational drug abuse represents a significant global public health challenge and is increasingly recognized as a major contributor to oxidative stress. According to the United Nations Office on Drugs and Crime (UNODC), approximately 296 million people aged 15–64 used psychoactive substances in 2021, with an estimated 39.5 million meeting criteria for drug use disorders (United Nations, 2020). There is substantial evidence linking the use of substances such as cocaine, amphetamines, ketamine, and benzodiazepines to mitochondrial dysfunction and excessive ROS production (Wang et al., 2025).

Among recreational drugs, cannabis is the most widely consumed substance globally (Degenhardt et al., 2018; United Nations, 2023). Its use has steadily increased in recent years, particularly among adolescents and young adults who are vulnerable to drug-related neuropsychiatric effects (Danpanichkul et al., 2025). Historically, cannabis has been associated with adverse neuropsychiatric outcomes primarily due to the pro-oxidative and psychoactive properties of Δ9-tetrahydrocannabinol (THC), its principal phytocannabinoid. Substantial evidence implicates chronic THC exposure in the development of psychiatric symptoms, including anxiety, psychosis, and mood disturbances (Hindley et al., 2020; Wolff et al., 2015). In contrast, cannabidiol (CBD), the second major phytocannabinoid in cannabis, has demonstrated antioxidant and neuroprotective effects. It shows therapeutic promise in a range of conditions, including epilepsy, Parkinson's disease, and chronic pain (Bilbao and Spanagel, 2022; Lattanzi et al., 2018; Villanueva et al., 2022). However, the safety profile of CBD remains controversial due to the absence of standardized usage guidelines and limited long-term data. Emerging evidence has highlighted potential hepatotoxic effects (Lo et al., 2023)and significant drug-drug interactions (Brown and Winterstein, 2019; Qian et al., 2024), raising concerns about its clinical risk profile (Black et al., 2019; Patel et al., 2020). Concurrently, synthetic cannabinoids continue to appear on the illicit drug market and are frequently associated with severe and unpredictable toxicological outcomes (Alipour et al., 2019). Furthermore, quality control issues persist within the commercial CBD industry, with numerous products found to be contaminated with THC, heavy metals, microorganisms, or pesticides, posing additional health risks to consumers (Dryburgh et al., 2018).

Although numerous studies have reported associations between cannabis exposure and oxidative stress, no systematic effort has been made to comprehensively assess its specific effects on ROS production, lipid peroxidation, and the disruption of antioxidant defense systems. We hypothesized that a systematic synthesis of the available evidence would reveal a significant association between cannabis exposure and oxidative stress biomarkers across preclinical studies. To address this gap, we conducted a systematic review and meta-analysis to evaluate the pro-oxidative effects of cannabis and its derivatives, drawing on recent *in vivo* and *in vitro* studies. Specifically, we quantify cannabis-induced oxidative damage by examining its impact on redox homeostasis. By integrating these data, our analysis offers a comprehensive mechanistic insight into cannabis-mediated oxidative stress and highlights its potential toxicological and health implications.

2. Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020; PRISMA, 2020; Page et al. (2021). The full review protocol was prospectively registered in the PROSPERO (CRD420251020006) database for systematic reviews.

2.1. Data sources and collection strategy

Data were collected from multiple bibliographic sources including PubMed, Mendeley, Embase, Web of Science (WOS), Nursing and Allied Health Literature (CINAHL), and Scopus. The objective of the search was to identify available literature from both *in vitro* and *in vivo* preclinical studies that examined the effects of cannabis on oxidative stress. The search covered publications from January 1, 2015, to January 1, 2025. To ensure a comprehensive and accurate search strategy, the following keywords were employed across the different databases: ("cannabis" OR "marijuana" OR "THC" OR "CBD" OR "Synthetic cannabinoids") AND ("Oxidative Stress" OR "ROS" OR "ROS production" OR "mitochondria" OR "mitochondrial disfunction" OR "oxidative damage") AND ("Catalase" OR "Glutathione" OR "Lipid peroxidation" OR "malondialdehyde (MDA)" OR "TBARS" OR "GSH/GSSG ratio" OR "Superoxide dismutase" OR "Antioxidant enzymes" "OR "total antioxidant activity (TAC)" OR "total oxidant activity (TOC)"). Study selection was conducted in two stages: initial screening of titles and abstracts, followed by a full-text review. Two independent reviewers (A.S.*P. and* T.P.P.) performed data extraction and analysis, with a third reviewer (E.G.B.) resolving any discrepancies. Publications that were duplicates or did not meet the inclusion criteria were excluded.

2.2. Selection criteria

Studies were included if they met the following criteria: (1) preclinical studies (*in vitro* and *in vivo*); (2) use of any animal model; (3) publications date between January 1, 2015, and January 1, 2025; (4) use of cannabis or its derivatives (e.g., cannabis extract, THC, CBD, CBG, or synthetic cannabinoids); and (5) investigation of oxidative stress and/or pro-oxidative effects; (6) reporting of relevant oxidative stress markers, including "ROS", "CAT", "GSH", "GPx", "GSH/GSGG ratio", "MDA" or "TBARS", "TAC" and/or "TOC"; (7) published in English or Spanish.

Studies were excluded if they met any of the following criteria: (1) non-original research (e.g., reviews, commentaries, abstracts, or clinical trials); (2) involvement of human subjects or patient data; (3) focus on the antioxidant effects of cannabis; (4) absence of oxidative stress data; (5) insufficient or irrelevant information; (6) inability to extract quantitative data; or (7) duplication of previously included studies.

2.3. Quality of bias assessment

To minimize the potential for misleading results, risk of bias was independently assessed by two reviewers for both *in vitro* and *in vivo studies.* The *ToxRTool* (Toxicological data Reliability Assessment Tool) (Schneider et al., 2009) was used to evaluate the risk of bias in *in vitro* studies. This tool assesses the reliability of toxicological data based on the following five criteria: (1) Test substance identification (chemical name, CAS number, purity, source, and relevant physico-chemical properties); (2) Test system characterization (description of cells/tissues, origin, cultivation conditions, and maintenance); (3) Study design (administration method, dose/concentration details, exposure duration, controls [negative/positive where required], and replicates); (4) Results documentation (clear endpoints, transparent reporting of all outcomes, and appropriate statistical methods); and (5) Plausibility of design/results (appropriateness of the test system, dose ranges, and reliability of quantitative data). Data is summarized in Table 1. A final score in provided (0-18) for assessment of total risk of bias for each study being: "reliable without restrictions", 15–18 points; "reliable with restrictions", 11–14 points, "not reliable" and "not assignable" if do not give sufficient experimental details.

For the *in vivo* studies, the SYRCLE's risk of bias tool (Hooijmans et al., 2014)was used, as it is an adaptation of Cochrane RoB tool specifically designed for animal research. This tool evaluates 6 types of bias and 10 domains consisting of 10 questions: (1) Selection bias, includes:

Table 1
ToxRtool analysis for *in vitro* studies. Risk of bias assessment.

Authors	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Total Score	Reliability
Akar et al. (2023).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	17	Reliable without restrictions
Almada, M et al. (2020).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	18	Reliable without restrictions
Bachari, A et al. (2024).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	17	Reliable without restrictions
Cerretani, D et al. (2020).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	17	Reliable without restrictions
de la Harpe, A et al. (2022).	✓	X	X	✓	✓	X	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	14	Reliable with restrictions
Fonseca et al. (2019).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	18	Reliable without restrictions
Goenka, S. (2022).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	17	Reliable without restrictions
Hamad, H and Olsen, B.B. (2021).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	17	Reliable without restrictions
Kim, N. Y et al. (2024).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	17	Reliable without restrictions
Li, J et al. (2023).	✓	✓	✓	✓	✓	✓	X	X	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	15	Reliable without restrictions
Loubaki, L et al. (2022).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	18	Reliable without restrictions
Misri, S et al. (2022).	✓	X	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	15	Reliable without restrictions
Mould, RR et al. (2021).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	17	Reliable without restrictions
Omer, S et al. (2024).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	17	Reliable without restrictions
Oztas, E et al. (2019).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	17	Reliable without restrictions
Podinic, T et al. (2024).	✓	X	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	16	Reliable without restrictions
Salbini, M et al. (2021)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	18	Reliable without restrictions
Schultze et al. (2017).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	17	Reliable without restrictions
Sezer, Y et al. (2020).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	18	Reliable without restrictions
Soto-Mercado, V et al. (2020).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	17	Reliable without restrictions
Staton Laws III and Smid (2024).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	18	Reliable without restrictions
Tazi, N et al. (2022).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	18	Reliable without restrictions
Wu, HY et al. (2018).	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	17	Reliable without restrictions

1-“Was the allocation sequence adequately generated and applied?“, 2-“Were the groups similar at baseline or were they adjusted for confounders in the analysis?“, 3- “Was the allocation to the different groups adequately concealed during?“; (2) Performance bias: 4- “Were the animals randomly housed during the experiment?“, 5- “Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?“; (3) Detection bias: 6-“Were animals selected at random for outcome assessment?“, 7- “Was the outcome assessor blinded?“; (4) Attrition bias: 8- “Were incomplete outcome data adequately addressed?“; (5) Reporting bias: 9- “Are reports of the study free of selective outcome reporting?“; (6) Other: 10-“Was the study apparently free of other problems that could result in high risk of bias?“. The results of the *in vivo* risk of bias assessment are presented in Table 2. In line with the SYRCLE authors' recommendations, no overall summary score was calculated, as this may obscure domain-specific risks and compromise interpretability.

2.4. Data extraction and analysis

The initial data screening focused on extracting descriptive information directly from the study texts. For *in vitro* studies, the following variables were collected: author and year, study aims, sample description, total sample size (intervention group), disease/condition model, treatment component, treatment details (dose and duration), control group information, biochemical assays, techniques, and outcomes. For *in vivo* studies, the same variables were extracted, with the addition of the administration route. These data are summarized in Tables 3 and 4.

The second screening phase involved quantitative data extraction. When available, means and standard deviations were directly obtained from the text. If quantitative values were presented only in graphical format, a web-based plot digitizer tool (https://automeris.io) was used to extract the data. The measurement of effect was the standardized mean differences (SMDs) and the effect sizes (ES) accompanied by the 95 % confidence interval (CI). All standardized mean differences were calculated using the package “esc” for the Practical Meta-Analysis Effect Size Calculator (Lüdecke, 2022). SMDs and ES were extracted for all redox variables (ROS, CAT, SOD, GPx, GSH, GR, MDA, TAC and TOC). A meta-analysis was conducted using a random effects model adjusted with the restricted maximum likelihood (REML) approach. To evaluate variability across studies, two complementary approaches were employed. The Q-test served as a formal assessment of whether heterogeneity was present, whereas the I^2 statistic measured its extent. The I^2 value, expressed as a percentage, reflects the proportion of total

Table 2
SYRCLE's analysis for *in vivo* studies. Risk of bias assessment.

Author and year	1	2	3	4	5	6	7	8	9	10
Mowaad et al. (2024).	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear	Low
Mobisson, SK et al. (2022).	Low	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Low
Kopjar, N et al. (2019).	Low	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Low
Ajayi et al. (2024).	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Khadrawy, AY et al. (2017).	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Lafzi et al. (2024).	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Carvalho, RK et al. (2022).	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Alzu'bi et al. (2024a)	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Low
Xu, B et al. (2024).	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Alzu'bi, A et al. (2022).	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Low
Alzu'bi, A et al. (2024b).	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Low
Çetinkaya and Polat (2018).	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Low
Mobisson et al. (2024).	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Abdel-Salam et al. (2018).	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Alagbonsi and Olayaki (2017).	Low	Low	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Zhang, Z. et al. (2020).	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
El-Shamarka, M.E et al. (2020).	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Nafea, O. E et al. (2016).	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Žunec, S et al. (2023).	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Polanska et al. (2023).	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Oluwasola et al. (2023).	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Kruk-Slomka et al. (2016).	Unclear	Low	Unclear	Uncear	Unclear	Unclear	Unclear	Low	Low	Low
Lucić Vrdoljak et al. (2018).	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear

variation attributable to differences between studies rather than chance. Higher I^2 values suggest stronger heterogeneity, with conventional thresholds guiding interpretation: 0–40 % (minimal), 30–60 % (moderate), 50–90 % (substantial), and 75–100 % (considerable) (Higgins and Thompson, 2002). To investigate underlying causes of heterogeneity, subgroup analyses were performed by targeting: Type of Molecule employed in the treatment (THC, CBD, both, synthetic cannabinoids and others), *in vitro* treatment administration method (injected intraperitoneally, oral or inhaled), dose concentration (*in vitro*: ≤10 μM, 10–50 μM, >50 μM; *in vivo*: ≤2 mg/kg, >2 mg/kg y ≤ 7 mg/kg, >7 mg/kg y ≤ 30 mg/kg, >100 mg/kg), treatment duration (*in vitro*: min-12 h, 24 h, >48 h; *in vivo*: ≤7 days, >7 days y ≤ 28 days, >28 days), animal model (mice, rats, fish), tissue (cardiac, hepatic, plasma, nervous, renal, respiratory reproductive), cancerous/not cancerous cells.

To explore potential sources of heterogeneity, subgroup analyses were conducted separately for *in vitro* and *in vivo* studies. In vitro subgroup variables included cannabinoid type (THC, CBD, combined THC/CBD, synthetic cannabinoids, others), exposure concentration (≤10 μM, 10–50 μM, >50 μM), exposure duration (minutes–12 h, 24 h, >48 h), cell type (cancerous vs. non-cancerous), and tissue or cellular origin. In vivo subgroup variables included cannabinoid type, route of administration (intraperitoneal, oral, inhalation), dose (≤2 mg/kg, >2–7 mg/kg, >7–30 mg/kg, >100 mg/kg), treatment duration (≤7 days, >7–28 days, >28 days), animal model (mice, rats, fish), and tissue analyzed (cardiac, hepatic, plasma, nervous, renal, respiratory, reproductive).

When sufficient information was available, sensitivity analyses were performed by eliminating outliers from the meta-analysis and reviewing the impact on the overall score.

Publication bias was assessed using Egger's test (Egger et al., 1997), which examined the statistical significance of observed asymmetry. This evaluation was conducted only for outcomes reported in a minimum of 10 studies. If studies were based on a minor quantity of studies, qualitative comparisons were established.

Statistical analysis was performed using Stata software, version 18.0. (StataCorp, 2023).

3. Results

3.1. Search results

A total of 9748 records were initially retrieved from 6 different databases, with an additional 27 new records identified through citation searching. A total of 4418 records were excluded from screening as were duplicated. 5330 records from databases and 27 from citations were analyzed first by title, second by abstract, and third by further analysis, resulting in a total of 51 studies and 49 suitable for meta-analysis. The flow diagram strategy is presented in Fig. 1.

3.2. Characteristics of the studies

A total of 23 *in vitro* studies were included in the analysis. These studies involved a wide range of cell lines representing various tissue types: cancer cell lines included oral (Ca9-22, GMSM-K), breast (MCF-7, MDA-MB-231/361), prostate (PC3), brain (U87, U373), lung (A549, H460, H69, H1299), colorectal (HT-29), melanoma (MM418-C1, MM329, MM96L), neuronal (PC12, SH-SY5Y), skin (HaCaT), reproductive (BeWo), immune (PBLs) and hematopoietic cancers (Jurkat); Non-cancerous cell lines included: skin (HEMn-LP/DP), reproductive (St-T1b, HdF), immune (THP-1, PBMCs), and cardiac (H9c2) cells. Treatment concentrations ranged from 1 to 200 μM. The interventions evaluated across studies included cannabinoids: THC and CBD (4 studies), CBD alone (8 studies), CBG (1 study), CBN (1 study), and CBDP/CBDB (1 study), synthetic analogs (9 studies) such as AKB48, CP55940, and UR-144), terpenes: β-caryophyllene and humulene (1 study), cannabis mixture (1 study), and cannabis smoke (1 study). Oxidative stress markers quantified across studies included ROS (21 studies), MDA (3 studies), CAT (2 studies), SOD (1 study), GSH (5 studies), GPx (2 studies), GSH/GSSG (4 studies), and GR (2 studies). A complete summary of the *in vitro* characteristics of included studies is presented in Table 3.

Moreover, this systematic review included 26 preclinical *in vivo* studies investigating cannabinoid-induced oxidative stress, involving a total of 1258 experimental animals across three model organisms. Rodents comprised most animal models used, with rats accounting for 52.7 % of animals (n = 663 across 16 studies) and mice comprising 27 % (n = 340 across 8 studies), while piscine models accounted for the remaining 20.3 % (n = 255 across 2 studies). Among the murine studies, BALB/c (5 studies), Swiss (2 studies), and NSG (1 study) strains were employed. Rat models included Wistar (8 studies), Sprague-Dawley (2 studies), and various albino strains (4 studies). The fish models included both AB strain transgenic zebrafish and the neotropical species *Brycon amazonicus*. Pharmacological interventions involved both

Table 3
In vitro studies outcomes.

Author and year	Study aims	Sample description	Cell seeding	Experimental model	Treatment	Treatment (concentration and duration)	Controls	Biochemical Assay	Technique
Schultze et al. (2017)	Impact on mitochondrial functions	THP-1 monocytic cell line	1x105 cells/well	Toxicity	CBD	10.68 and 21.64 μM for 24h	Treated with vehicle 0.03% ethanol	ROS	Fluorescence intensity assay
Wu, HY et al. (2018)	Cellular mechanisms underlying CBD-induced oxidative stress and apoptosis in primary monocytes	Peripheral blood mononuclear cells (PBMC)	2x105 cells/well	Apoptosis	CBD	16 μM for 5 min−2 h	Treated with vehicle 0.05% ethanol	ROS, SOD	Spectrophotometric methods
Fonseca et al. (2019)	Study the influence of synthetic cannabinoids in women's fertility.	Human decidual fibroblasts (HdF) and human endometrial stromal cell line (St-T1b)	1 × 104 cells/well	Human endometrium remodeling process	WIN 55,212-2, JWH-122 and UR-144	0.01-25 μM for 5 min and 48h	Not treated	ROS, GSH/GSSG	Spectrophotometric and fluorometric methods
Oztas, E et al. (2019)	Investigate the possible toxicity mechanisms of AKB48	Human neuroblastoma SH-SY5Y cell line	5x105 cells/well ROS 1x106 cells/well GSH	Toxicity	AKB48	25, 50, 100 or 200 μM for 24h	Treated with 1% v/v DMSO	ROS and GSH	Spectrophotometric and fluorometric methods
Almada, M et al. (2020)	Understanding of the impact of cannabinoids on particularly sensitive groups, such as pregnant women.	Human choriocarcinoma BeWo cell line	1.5 × 104 and 4 × 104 cells/well	Pregnancy	JWH-018, JWH-122 and UR-144	JWH-018: 10 μM, JWH-122: 10 μM, UR-144: 10 μM and THC: 15 μM for 48h	Not treated	ROS	Fluorescence intensity assay
Cerretani, D et al. (2020)	Investigate the effects of cannabinoids on human colorectal carcinoma	Human colorectal HT-29 cell line	2x105 cells/well	Toxicity	THC, CBD and CB83	CB83: 1 μM for 24h CBD: 30 μM for 24h THC: 30 μM for 24h	Not treated	GSH/GSSG, MDA, GR, GPx and CAT	Spectrophotometric methods
Sezer, Y et al. (2020)	Investigate the in vitro neurotoxicity of JWH-018 in SH-SY5Y cells.	Human neuroblastoma SH-SY5Y cell line	1 x 104	Toxicity	JWH-018	5, 10, 25, 50, 100, or 150 μM concentration for 24 h	1% DMSO-treated cells were negative control, and 0.1% Triton X-100-treated cells were the positive control.	GR, GPx, CAT, MDA and GSH	Spectrophotometric methods
Soto-Mercado, V et al. (2020)	Evaluate the cytotoxic effect of CP55940	Human peripheral blood lymphocytes (PBL) and on T-ALL cells (Jurkat)	1 × 106 cells/well	Toxicity	CP55940	0−20 μM for 24h	Not treated	ROS	Fluorescence intensity assay
Hamad, H and Olsen, B.B. (2021)	Study the anti-cancer effects of cannabis.	NSCLC cell lines: A549, H69 and H1299	1 x 103	Lung cancer	CBD	10 μM for 24h	Not treated	ROS	Fluorescence intensity assay
Mould, RR et al. (2021)	Assess the effects of CBD on mitochondrial metabolism and morphology	Human breast cancer MCF7 cell line	3x104 cells/well	Toxicity	CBD	1, 5, 10, and 20 μM CBD for 24h	Treated with 0.005% v/v DMSO	ROS	Fluorescence intensity assay
Salbini, M et al. (2021)	Effects in human breast carcinoma cells.	Breast cancer cell lines: MCF-7, MDA-MB-361 and MDA-MB-231	2x105 cells/well	Breast cancer	CBDB and CBDP	10 μM for 24h.	Medium with vehicle control	ROS	Fluorescence intensity assay
de la Harpe, A et al. (2022)	Studythe effects of cannabinoids on Ca^{2+} influx, ROS production, and ER stress-induced cell death	Breast cell lines: MCF7, MDA-MB-231 (cancer), and MCF10A (normal)	1x104 cells/well	Toxicity	CBD, THC, CGB and CBN	20 μM for 48 h	Tunicamycin (TNC), and Thapsigargin (TG) treated cells	ROS	Fluorescence intensity assay
Goenka, S. (2022)	Investigate and compare the effects of THC as well as CBD on melanogenesis	Human epidermal melanocytes: HEMn-LP and HEMn-DP cells	6 × 104 HEMn-LP cells/well or 4 × 104	Human epidermal melanogenesis	THC and CBD	1, 2 and 4 μM for 6 days.	Treated with 0.4% v/v DMSO	ROS	Fluorescence intensity assay

(*continued on next page*)

Table 3 (*continued*)

Author and year	Study aims	Sample description	Cell seeding	Experimental model	Treatment	Treatment (concentration and duration)	Controls	Biochemical Assay	Technique
	and oxidative stress in vitro		HEMn-DP cells/well						
Loubaki, L et al. (2022)	Investigate the cytotoxic effect of a cannabinoid mixture (CM) in oral cells.	Human oral epithelial cells: Ca9-22 (cancer) and GMSM-K (normal)	3x105 cells/well	Oral cancer	Cannabinoid Mixture-8 component solution	1 μg/ml for 24h	Non-treated cells	ROS, SOD, GSH	Flux cytometry
Misri, S et al. (2022)	Provide novel insights into the anti-tumor effects mediated by CBD	Non-small-cell lung cancer cell lines H460 and A549	1 x 104	Lung cancer	CBD	H460- 15.8 μM and A549-16 μM. 1 h for ROS generation.	Treated with vehicle (PBS).	ROS	Fluorescence intensity assay
Tazi, N et al. (2022)	Investigate the effects on the adhesion, growth, and signaling pathways.	Human oral epithelial cells: GMSM-K	1x106 cells/well	Gingival epithelial cell damage	Cannabis smoke condensate	Each cannabis cigarette contained 1.7 mg of THC and less than 0.1 mg of CBD. cells were exposed/not exposed to CSC at 1%, 5%, 10%, and 20% concentrations for 1 h.	non-CSC-exposed cells	ROS	Fluorescence intensity assay
Akar et al. (2023)	investigates the cardiotoxic mechanisms of UR-144	Rat cardiomyoblastic H9c2 cell line	2.5 x 105 cells/well	Cardiotoxicity	UR-144	50 and 200 μM for 48h	Treated with 1% DMSO	ROS and TAC	Spectrophotometric and fluorometric methods
Li, J et al. (2023)	Demonstrate the cell death mechanism of CBD in the PC3 prostate cancer	prostatic adenocarcinoma PC3 cell line	1x104 cells/well	Prostate cancer	CBD	10 μM for 48h	Non-treated cells	ROS, GSH, GSSG	Fluorescence intensity assay
Bachari, A et al. (2024)	Explore the mechanisms underlying the effects of cannabinoids on melanoma cells.	Melanoma (MM418-C1, MM329, MM96L), and keratinocyte-derived cells HaCaT	4 × 105 cells per well	Melanoma	PHEC66	MM418-C1: 4.25 and 8.25 μg/mL for 24h MM329: 4.25 and 8.50 μg/mL for 24h MM96L: 3.70 and 7.40 μg/mL for 24h	Treated with vehicle 0.05% v/v DMSO.	ROS	Fluorescence intensity assay
Kim, N. Y et al. (2024)	Demonstrate that CBD can impart anticancer function	Human gliobastomaGBM U87 and U373 cells	1 × 104 cells/well	Glioblastoma	CBD	30 μM for 12/24h	Not treated	ROS and GSH-GSH/GSSG	Spectrophotometric and fluorometric methods
Omer, S et al. (2024)	Demonstrate the anti-cancer effects	T-cell lymphoma (TCL)	1x104 cells/well	Lymphoma	CBD, THC and WIN 55-212-22	1 μM, and 50 μM concentrations for 24 and 48 h.	Cells were treated with the vehicle (Ethanol/DMSO)	MDA, ROS, GSH	Spectrophotometric and fluorometric methods
Podinic, T et al. (2024)	Characterize the effects of CBD on trophoblast cell function and highlight its impacts on mitochondrial function and respiration	Human choriocarcinoma BeWo cell line	3x103 cells/well	Pregnancy	CBD	20 μM CBD over six days	0.1% methanol, and the ST co-treated with epidermal growth factor and forskolin	ROS	Fluorescence intensity assay
Staton Laws III and Smid (2024)	Neuroprotection versus neurotoxicity	Rat pheochromocytoma PC12 cell line	3x104 cells/well	Neurotoxicity	β-caryophyllene Humulene	200 μM for 4h and 24h.	Vehicle-treated <1% ethanol v/V	ROS	Fluorescence intensity assay

Table 4
In vivo studies outcomes.

Author and year	Study aims	Sample description	Total sample (intervention)	Experimental model	Treatment	Treatment (dose and duration)	Administration	Controls	Biochemical Assay	Technique
Kruk-Slomka et al. (2016)	Investigating the impact of CB1 and CB2 receptor ligands on the long-term memory stages	Swiss mice	Each experimental group consisted of 8–12 animals	Memory disorders	WIN 55,212-2, AM 251, JWH 133 and AM 630	WIN 55,212-2: 0.25, 0.5, and 1.0 mg/kg AM 251: 0.25, 0.5, 1.0, and 3.0 mg/kg JWH 133: 0.25, 0.5, 1.0, and 2.0 mg/kg AM 630: 0.25, 0.5, 1.0, 2.0, and 3.0 mg/kg	Injected intraperitoneally	Received saline solution with Tween 80	TAC, SOD and MDA	Spectrophotometric methods
Nafea, O. E et al. (2016)	Study the neurotoxic effects of tramadol and cannabis.	Albino rats	132 male rats: 22 per group.	Neurotoxicity	Hashish extract: 5% of THC, 6.2% CBD and 4.16% cannabidiolic acid.	92, 184 and 368 mg/kg/day in the first, second and third, ten days of the study respectively	Oral	Three groups: -negative control regular diet and tap water -normal saline group 1 ml of normal saline 0.9% NaCl - olive oil group received 1 ml of olive oil	MDA and CAT	Spectrophotometric methods
Alagbonsi and Olayaki (2017)	Investigating the role of oxidative stress in CS-associated spermatotoxicity	Albino rats	44 male rats: 6 per group	Infertility	*Cannabis sativa* leaves	2 mg/kg for 30 days.	Oral	Treated with 1 ml/kg normal saline and 10% ethanol	TAC and ROS	Spectrophotometric and fluorometric methods
Khadrawy, AY et al. (2017)	To investigate the effect of Cannabis extract on the depressive-like rats	Wistar rats	24 male rats: n = 6 for each group.	Depression	THC	10 mg/kg daily for 15 days	Injected intraperitoneally	Received the vehicle till the end of experiment	MDA, GSH	Spectrophotometric methods
Abdel-Salam et al. (2018)	The effect of *Cannabis sativa* extract was examined on brain oxidative stress	Sprague-Dawley rats	7-8 male rats each group	Epilepsy	*Cannabis sativa* 20% THC	20 mg/kg once every 48 h for 12 times alone.	Injected intraperitoneally	Treated with 0.9% saline	MDA and GSH	Spectrophotometric methods
Çetinkaya and Polat (2018)	Obtain information about predicted damages caused by synthetic drugs in tissues and organs.	Wistar albino rats	20 male rats: n = 10 for each group.	Toxicity	JWH-200	5 mg/kg for 8 h	Injected intraperitoneally	No implementation was applied to the control group	TAS and TOS	Spectrophotometric methods
Lucić Vrdoljak et al. (2018)	Study THC and iriotecan heptotoxicity	Wistar rats	60 male rats: 5 per group	Liver toxicity	THC	7 mg/kg for 1, 3 and 7 days	Oral	Vehicle sesame oil	MDA, SOD and CAT	Spectrophotometric methods
Kopjar, N et al. (2019)	Establish the magnitude of THC exposure.	Wistar HsdBroHan rats	30 male rats n = 5 for each group.	Neurotoxicity	THC	7 mg/kg b.w. for 1, 3 and 7 days.	Oral	Administered the same volume of vehicle sesame oil once a day	TBARS, GSH, SOD, CAT	Spectrophotometric methods
El-Shamarka, M.E et al. (2020)	Study the neurotoxic effects of nandrolone and cannabis.	Wistar rats	60 male rats: n = 15 per group.	Neurotoxicity	Cannabis extract with 10% THC	20 mg/kg, s.c daily for one month	Injected intraperitoneally	Rats received normal saline and peanut oil/benzyl alcohol at 90:10 v/v subcutaneously (s.c.)	MDA and GSH	Spectrophotometric methods
Zhang, Z. et al. (2020)	Investigate whether systemic administration with THC would cause toxic effects on retinas.	BALB/c mice	20 mice: n = 10 per group.	Retinal damage	THC	treated with THC at 1 or 2 mg/kg daily for 61 days.	Injected intraperitoneally	Treated with vehicle	SOD, CAT, GSH and MDA	Spectrophotometric methods

(*continued on next page*)

Table 4 (*continued*)

Author and year	Study aims	Sample description	Total sample (intervention)	Experimental model	Treatment	Treatment (dose and duration)	Administration	Controls	Biochemical Assay	Technique
Alzu'bi, A et al. (2022)	Impact of acute administration of the synthetic cannabinoid XLR-11 n the liver.	BALB/C mouse animal model	10 males: n = 5 per group.	Acute Hepatic Injury	XLR-11	3 mg/kg, i.p. for 5 consecutive days	Injected intraperitoneally	Treated with DMSO	MDA	Spectrophotometric methods
Carvalho, RK et al. (2022)	Therapeutic use of CBD and its possible genotoxic activity and interactions	Swiss mice	44 male mice: n = 11 for each group.	Sperm Toxicity	CBD	15 mg/kg/30 mg/kg for 34 consecutive days	Intragastric administration	Control group received sunflower oil	CAT, SOD, MDA	Spectrophotometric methods
Misri, S et al. (2022)	Provide novel insights into the anti-tumor effects mediated by CBD	NSG mice	6 females	Lung cancer	CBD	H460- 15.8 μM and A549- 16 μM. 1 h for ROS generation.	Injected intraperitoneally	Treated with vehicle (PBS).	ROS	Fluorescence intensity assay
Mobisson, SK et al. (2022)	Ascertain the reproductive impact.	Wistar rats	15 malerats: n = 5 for each group.	Reproductive system alteration	THC and CBD	7.5 mg/kg b.w. and 15 mg/kg b.w. for 28 days.	Oral	Were given feed and 0.5 ml of normal saline as a vehicle all through the experimental period.	CAT, GSH, GPx, SOD and MDA	Spectrophotometric methods
Okorie, N et al. (2022)	Evaluate the acute and chronic histopathological effect, oxidative stress indices and some of the hematological parameters.	Albino rats	21 male rats: n = 7 per group	Toxicity	Marijuana	Exposed to smoke of burnt wrapped 2 mg marijuana in the morning and evening for 21 and 42 days.	Inhaled	No exposition to smoke	CAT, SOD, GSH, GPx and MDA	Spectrophotometric methods
Mobisson et al. (2024)	The cognitive impact of CBD oil treatment on cadmium-induced toxicity.	Wistar rats	40 male rats: n = 5 per group	Toxicity	CBD oil	0.1 and 0.2 mg/kg bw for 14 days	Oral	Feed +0.5 ml of normal saline	CAT, SOD, GSH, GPx and MDA	Spectrophotometric methods
Lafzi et al. (2024)	To investigate the toxic effects of the synthetic cannabinoid	Sprague Dawley rats	56 male rats: n = 7 for each group.	Toxicity	CUMYL-4CN-BINACA	Three doses (0.5, 1.0, and 2.0 mg/kg, body weight) administered for 2 days in the acute exposure groups and 14 days in the subacute exposure groups	Injected intraperitoneally	Treated with vehicle solution (2% ethanol, 2% Tween 80 and 96% saline)	CAT, SOD, MDA	ELISA kit
Oluwasola et al. (2023)	Investigate the acute effects of an ethanolic extract of *Cannabis sativa* (EECS) on oxidative stress biomarkers	Wistar rats	20 male rats and 20 female rats: 5 per group	Toxicity	Ethanolic extract of *Cannabis sativa* (EECS) leaves	2 mg/kg, 4 mg/kg, and 6 mg/kg for 21 days	Oral	Treated with 1 mL distilled water	MDA, SOD, CAT, GPx, GSH	Spectrophotometric methods
Polanska et al. (2023)	*In vivo* safety evaluation and the effect of CBD and CBG on the redox status	SPF Wistar rats	40 male rats: n = 10 per group.	Toxicity	CBD and CBG	CBD Dose: 0.66 mg/kg/day CBG Doses: 0.66 mg/kg/day and 1.33 mg/kg/kg/kg/day. For 90 days.	Intragastric administration	Received 50 μL of pure helianthus oleum (vehicle) daily for 90 days	TAC, MDA and ROS	Spectrophotometric and fluorometric methods
Žunec, S et al. (2023)	Elucidate the biochemical changes produced by THC in cancer.	BALB/c mice	60 male rats: n = 15 per group.	Cancer	Dronabinol	7 mg/kg daily for 7 days.	Injected intraperitoneally	Not treated	ROS, GSH, CAT, SOD and GPx	Spectrophotometric and fluorometric methods
Ajayi et al. (2024)	Examine the effect of skoochies, an illicit cocktail drink, on testicular and sperm function in male rats.	Wistar rats	25 male rats: n = 5 per group.	Fertility	cannabis extract (mostly dronabinol) and "cannabis	2 mg/kg daily for 28 days	Oral	Normal saline vehicle	MDA, GSH, SOD, CAT and GPx	Spectrophotometric methods

(*continued on next page*)

Table 4 (*continued*)

Author and year	Study aims	Sample description	Total sample (intervention)	Experimental model	Treatment	Treatment (dose and duration)	Administration	Controls	Biochemical Assay	Technique
					cocktail" Skoochies					
Alzu'bi, A et al. (2024b)	Evaluate the *in vivo* effects of chronic administration of AB-FUBINACA on the hippocampus	BALB/C mouse animal model	30 adult males: n = 10 per group	Neurotoxicity	AB-FUBINACA	0.3 mg/kg for 4 consecutive weeks	Injected intraperitoneally	Treated with vehicle solution (consisting of 5 % ethanol, 5 % Tween 80, and 90 % saline)	MDA	Spectrophotometric methods
Fernandes, S. L. A. et al. (2024).	Investigate how activation of cannabinoid receptors (CB1+CB2 vs. CB2 alone) modulates oxidative stress in the liver and blood	*Brycon amazonicus* (Neotropical freshwater fish)	45 juvenile fish: n = 15 per group	Toxicity	WIN 55,212-2 and HU-308	WIN 55,212-2: 1 mg/kg for 24h HU-308: 1 mg/kg for 24h	Injected intraperitoneally	Treated with 0.5 mL of 2.5% DMSO in sterile saline	CAT, GPx, SOD, GR, LPO, GSH/GSSG	Spectrophotometric methods
Mowaad et al. (2024)	Evaluate the biochemical and histopathological changes related to the hypertrophic effects of stanozolol and/or cannabis in conditions of exercise practice or sedentary conditions.	Wistar rats	48 male rats: 8 different groups: n = 6 for each group.	Physical performance and the potential for adverse health effects	Cannabis resin	10 mg/kg for 56 days	Injected intraperitoneally	-Trained: treated with saline -Sedentary: treated with saline	MDA and GSH	Spectrophotometric methods
Xu, B et al. (2024)	Evaluate the toxicity of MDA-19, focusing on morphological and neural development	AB strain and transgenic (hb9-GFP) zebrafish	30 larvae for ROS staining. 60 for CAT, SOD and MDA.	Neural development	MDA-19	Exposure concentrations of MDA-19 (1, 10, and 20 mg/L). Exposure continued for 5 days.	Aqueous solution	Treated with 0.1% v/v DMSO	ROS, SOD, CAT and MDA	Spectrophotometric and fluorometric methods
Alzu'bi et al. (2024a)	Investigate the nephrotoxic effect of synthetic cannabinoids	Balb/c mice	20 adult mice: n = 10 for each group.	Nephrotoxicity	AB-FUBINACA	3 mg/kg for 5 days	Injected intraperitoneally	Vehicle solution (consisting of 5% ethanol, 5% Tween 80, and 90% saline)	MDA	Spectrophotometric methods

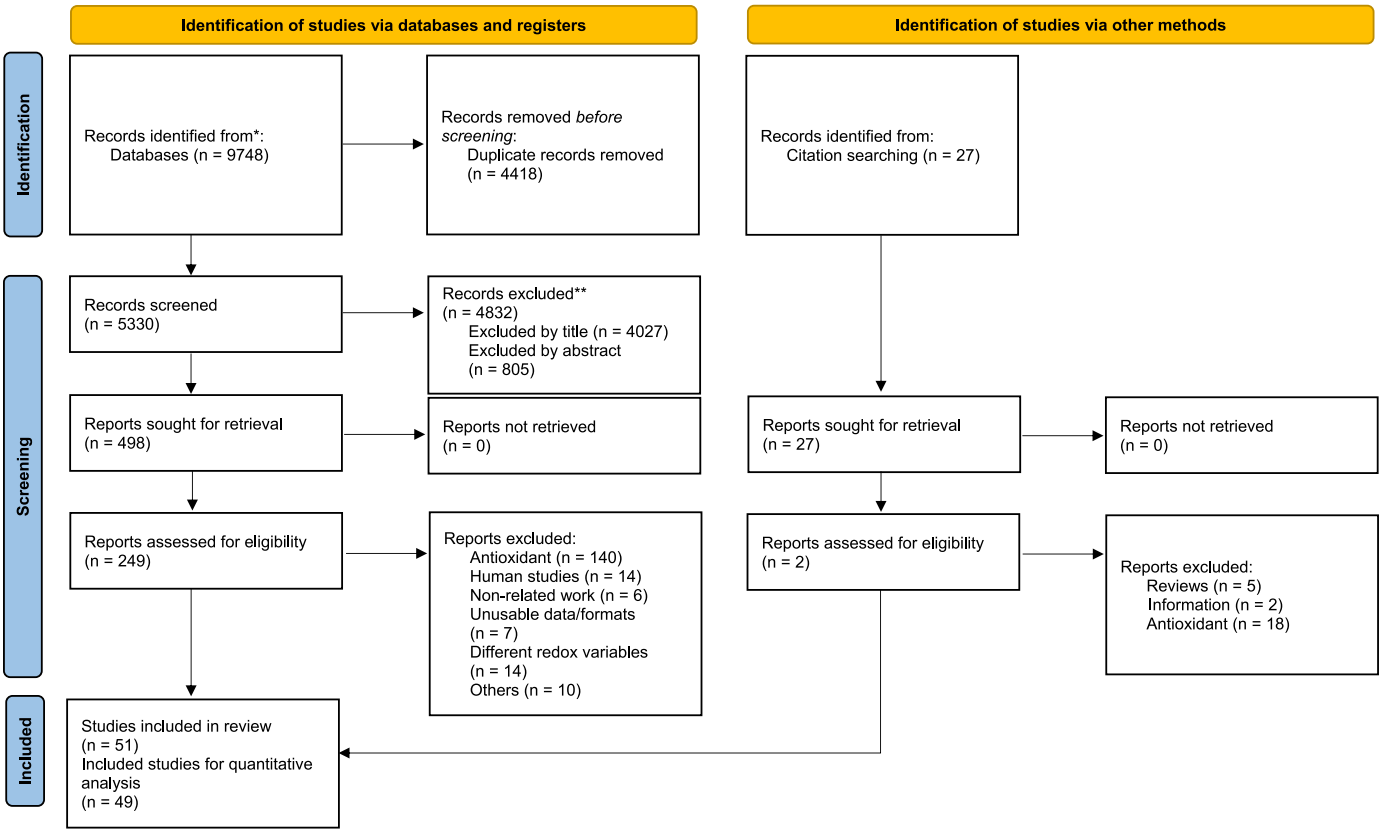


Fig. 1. PRISMA flow diagram of studies of interest for the quantitative synthesis.

phytocannabinoids and synthetic analogs. The former included Δ9-tetrahydrocannabinol (THC/dronabinol; 8 studies), cannabidiol (CBD; 4 studies), combined THC + CBD formulations (4 studies), crude *Cannabis* leaf extracts (2 studies), and cannabigerol (CBG; 1 study). Synthetic cannabinoids were used in 9 studies and included compounds such as JWH-133, AB-FUBINACA, and WIN 55,212-2. Endpoints were categorized by organ systems and pathological processes, with the majority of studies assessing toxicity. These included general systemic toxicity (6 studies), neurotoxicity/behavioral effects (9 studies), and hepatotoxicity (2 studies). Additional studies investigated reproductive toxicity (4 studies), oncological (2 studies), and single studies exploring ocular, renal, and exercise physiology outcomes. Dosages ranged from 0.25 mg/kg to 364 mg/kg, with considerable variability in administration protocols reflecting the heterogeneity of experimental designs. The most common route of administration was intraperitoneal injection (14 studies, 53.8 %), followed by oral gavage (8 studies, 30.8 %), intragastric administration (2 studies, 7.7 %), and aqueous exposure (1 study, 3.8 %). Oxidative stress biomarkers were commonly assessed, with MDA or thiobarbituric acid reactive substances (TBARS) measured in 20 studies. CAT and SOD were each reported in 12 studies, glutathione (GSH) in 10 studies, GPx in 6 studies, total antioxidant capacity (TAC) in 4 studies, and the GSH/GSSG ratio or GR in 1 study. Table 4 presents characteristics of *in vivo* studies included.

3.3. Quality of studies

Table 1 presents the results of *in vitro* quality assessment conducted according to the ToxRTool1 guidelines. A total of 23 studies were included and none of them presented a high risk of bias. Nevertheless, one study represented a moderate risk with a score of 14, meaning that it is reliable with restrictions (de la Harpe et al., 2022). The rest of the studies are reliable without restrictions. Approximately half of the included studies failed to meet criterion 12 as most of them do not include positive controls (Bachari et al., 2024; Cerretani et al., 2020; de la Harpe et al., 2022; Goenka, 2022; Kim et al., 2024; Li et al., 2023; Mould et al., 2021; Omer et al., 2024; Oztas et al., 2019; Schultze et al., 2017; Soto-Mercado et al., 2020; Wu et al., 2018). Moreover, three studies failed in two of the four items in Test substance identification, as they did not report information about the purity and origin of the substance (de la Harpe et al., 2022; Misri et al., 2022; Podinic et al., 2024). Table 2 summarizes the *in vivo* risk of bias results based on SYRCLE's guidelines. Unlike the ToxRTool1 assessment, SYRCLE's approach does not generate an overall score. Nevertheless, many studies exhibited "unclear" results, as authors did not specify in those items. The most commonly unclear items were the 5th, 6th and 7th items as they did not present information about blind investigators, randomly selected animals for each outcome assessment and continuity of the previous processes. The 3rd item also frequently received an "unclear" rating; however, one study presented a "low" score as is the only one that mentions different allocation for the different groups (Alagbonsi and Olayaki, 2017).

3.4. Quantitative outcomes

3.4.1. Cannabis and ROS production

A meta-analysis was conducted on 19 *in vitro* studies assessing cannabis-induced ROS production. Due to variability in treatment conditions, 67 estimable data points were included. The pooled analysis suggested a statistically association in ROS levels production and cannabis exposure compared to controls (SMD = 0.04, 95 % CI [0.02 to 0.06]; I^2 = 99.86 %, $p < 0.001$). The *in vivo* meta-analysis included 5 studies, contributing 8 estimable data points. Results also indicated a significant association in ROS production in treated groups relative to controls (SMD = 0.93, 95 % CI [0.1 to 1.75]; I^2 = 92.17 %, p = 0.03) (Fig. 2).

A)

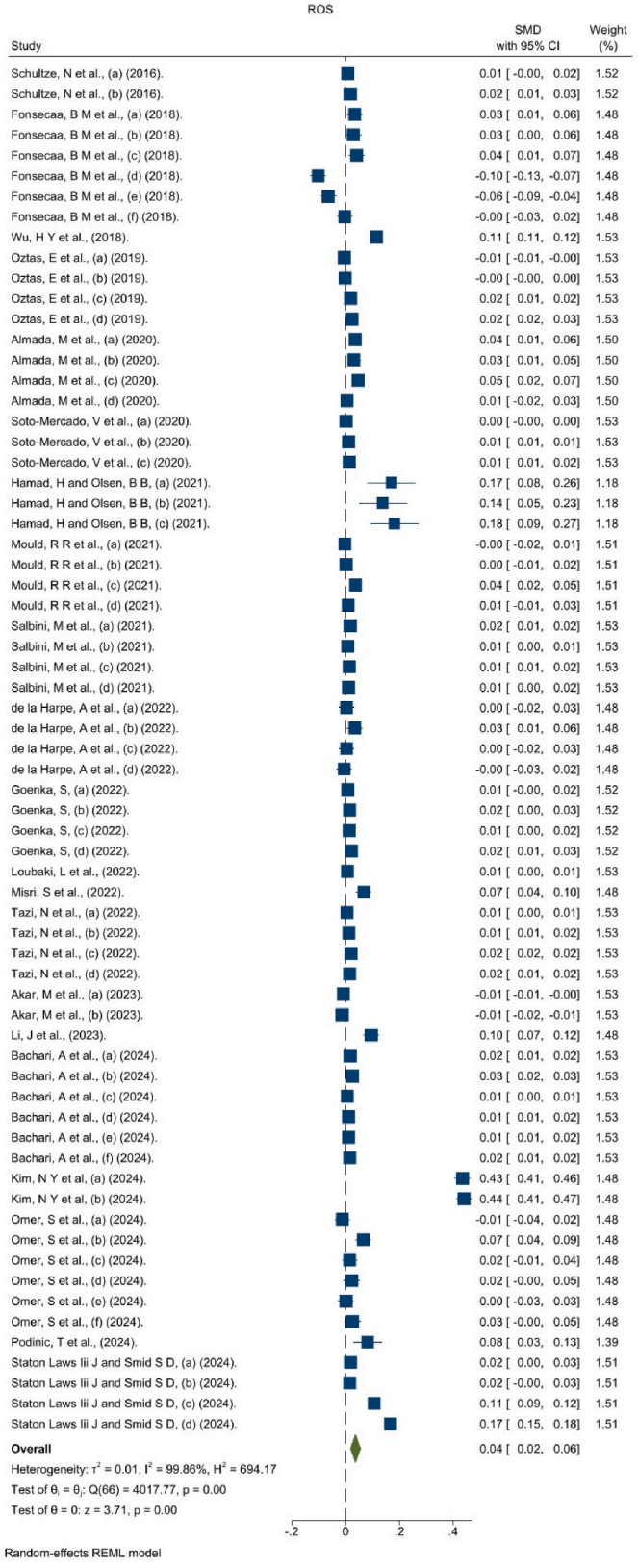


Fig. 2. Forest plot showing the effect size of correlation coefficients between cannabis (natural products and synthetic products) and ROS production. A) *In vitro* and B) *In vivo*

3.4.2. *Cannabis and lipid peroxidation*

To evaluate cannabis-induced oxidative damage, a meta-analysis was performed using MDA levels as a biomarker of lipid peroxidation, as MDA production is directly linked to free radicals activity and

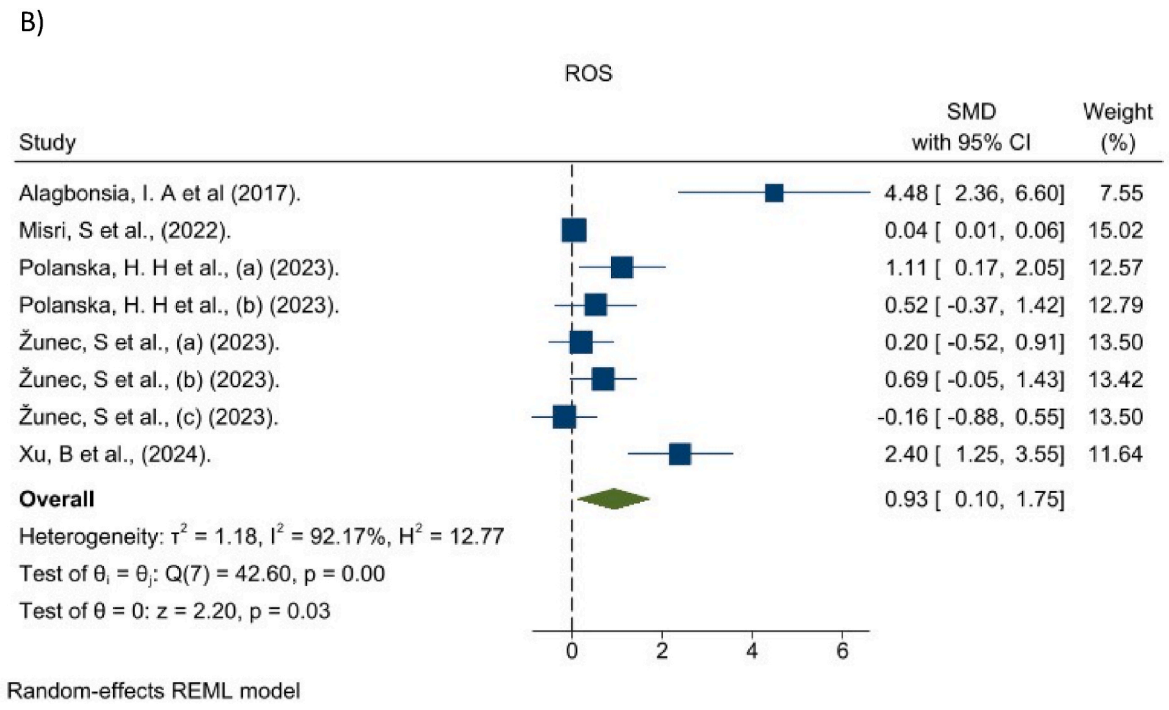


Fig. 2. (*continued*).

membrane damage.

For *in vitro* experiments, pooled data from 3 studies (12 data points) revealed higher MDA levels following cannabis exposure compared to controls (SMD = 0.04, 95 % CI [0.01 to 0.07]; $I^2 = 97.82$ %, $p < 0.001$).

In *in vivo* models, the meta-analysis included 21 studies, contributing 59 data points. The results similarly linked an increase in lipid

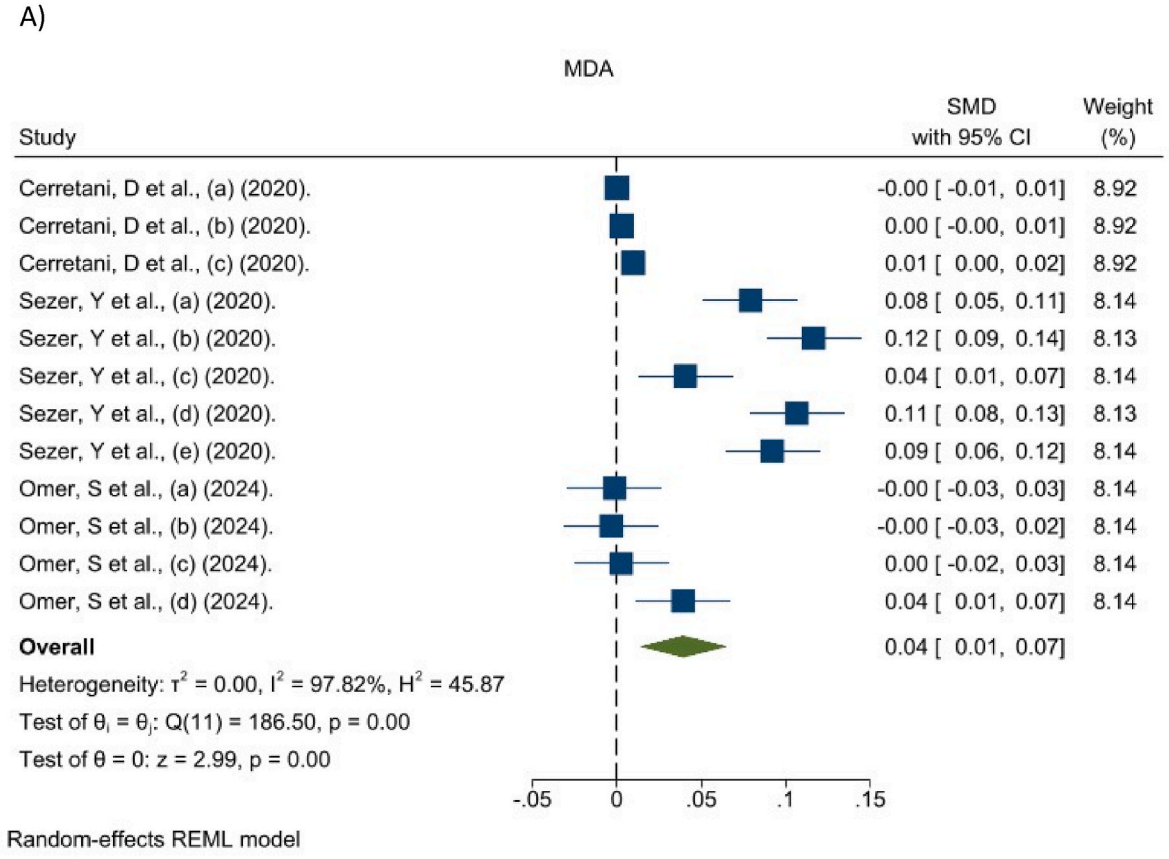


Fig. 3. Forest plot showing the effect size of correlation coefficients between cannabis (natural products and synthetic products) and MDA (lipid peroxidation). A) *In vitro* and B) *In vivo*

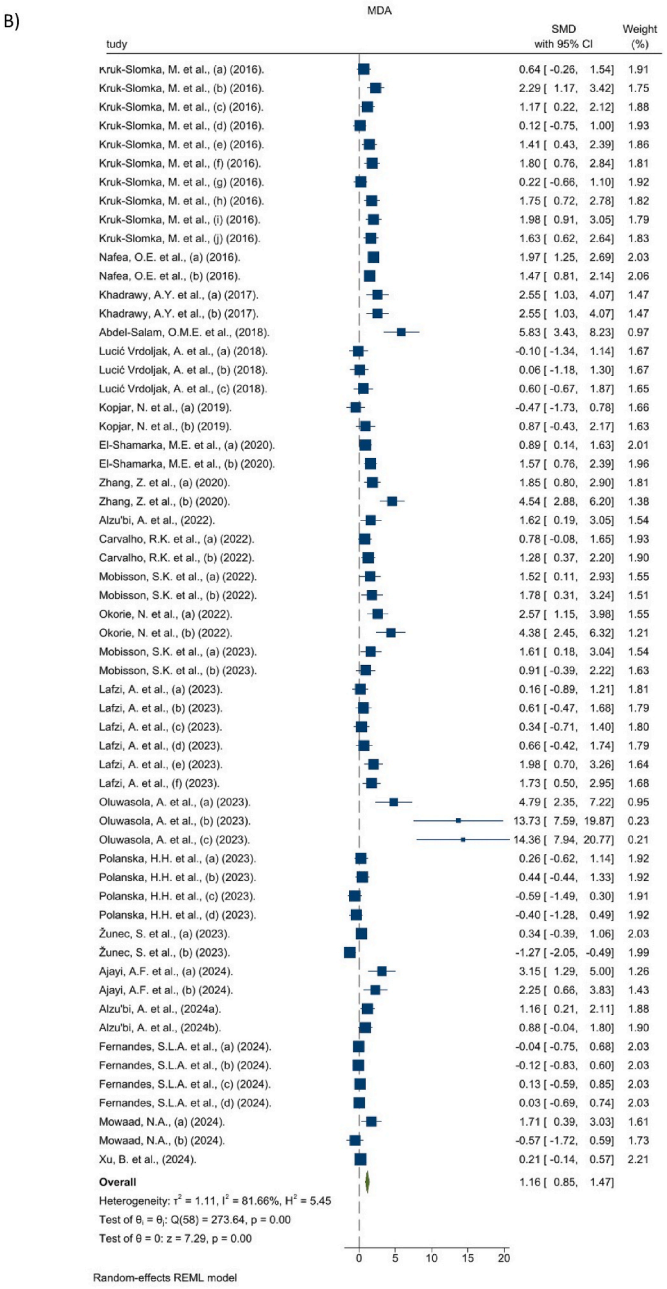


Fig. 3. (*continued*).

peroxidation in cannabis exposed animals relative to controls (SMD = 1.24, 95 % CI [0.84 to 1.65]; $I^2 = 86.29$ %, $p < 0.001$) (Fig. 3).

3.4.3. GSH and GSH/GSSG ratio

As a key indicator of cellular redox status, the GSH/GSSG ratio was examined. A higher GSH/GSSG ratio indicates a more effective redox homeostasis. Due to limited *in vivo* data (only one study available), the analysis was restricted to *in vitro* studies.

Pooled data from 4 *in vitro* studies (8 data points) revealed no statistically significant association between cannabis exposure and changes in the GSH/GSSG ratio (SMD = −0.11, 95 % CI [−0.27 to 0.04]; I^2 = 99.94 %, p = 0.16) (Fig. 4).

However, when GSH activity was examined alone, the meta-analysis revealed a significant reduction following cannabis exposure both *in vitro* (SMD = −0.05, 95 % CI [−0.08 to −0.02]; $I^2 = 99.74$ %, $p < 0.001$) and *in vivo* (SMD = −1.48, 95 % CI [−2.51 to −0.45]; $I^2 = 93.22$ %, $p <$ 0.001).

3.4.4. Total antioxidant and oxidant capacity (TAC and TOC)

Among all included studies, only *in vivo* experiments determined TAC and did not find data or TOC. A meta-analysis of 4 studies (18 data points) indicated that cannabis exposure did not result in a statistically significant change in TAC levels ((SMD = 0.42; 95 % CI [−0.08 to 0.92]; $I^2 = 79.68$ %; p = 0.10) (Fig. 5).

3.4.5. Antioxidant enzymes activity

3.4.5.1. In vitro. Different antioxidant enzymes were studied to assess the impact of cannabis on their activity *in vitro*. The meta-analysis revealed that cannabis could be associated with the reduction of the GR activity (SMD = −0.04, 95 % CI [−0.08 to −0.00]; $I^2 = 98.84$ %, p = 0.03) and CAT activities (SMD = −0.02, 95 % CI [−0.02 to −0.01]; I^2 =

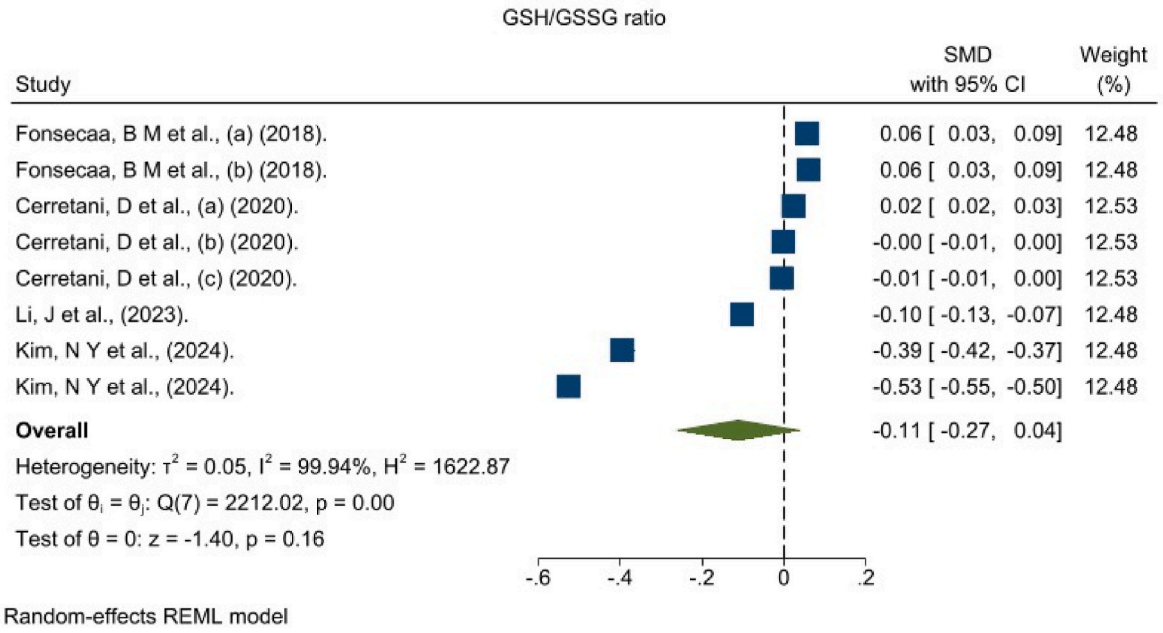


Fig. 4. Forest plot showing the effect size of correlation coefficients between cannabis (natural products and synthetic products) and GSH/GSSG ratio. *In vitro* studies.

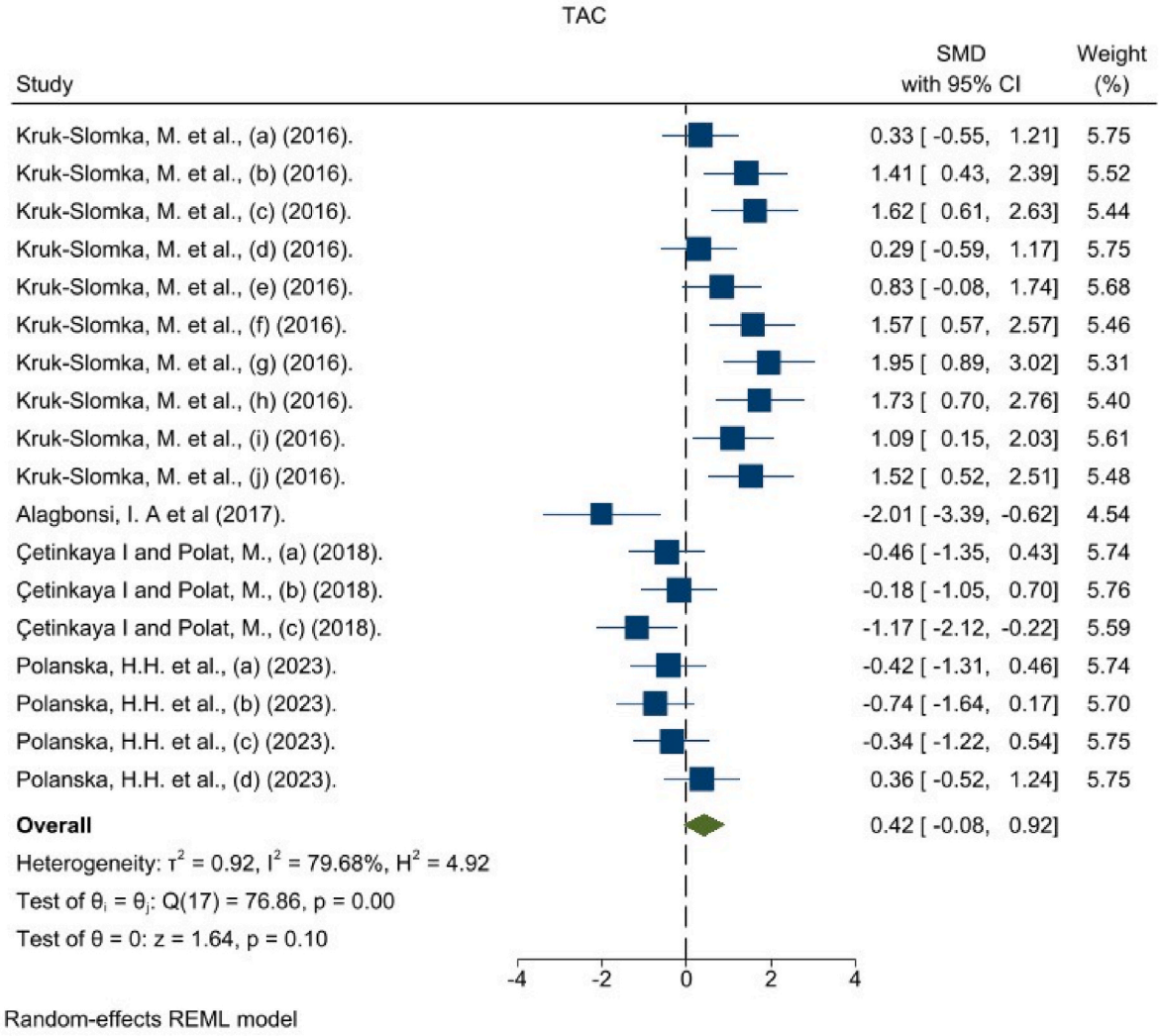


Fig. 5. Forest plot showing the effect size of correlation coefficients between cannabis (natural products and synthetic products) and TAC. *In vivo* studies.

64.24 %, $p < 0.001$) (Figures A, B, C). In contrast, cannabis exposure did not produce a statistically significant effect on GPx activity (SMD = 0, 95 % CI [−0.02 to 0.01]; $I^2 = 84.23$ %, $p = 0.39$) (Fig. 6).

3.4.5.2. In vivo. Several antioxidant enzymes were assessed to determine the effects of cannabis exposure on their activity *in vivo*. The meta-analysis showed that cannabis statistically reduced the activity of SOD (SMD = −0.69, 95 % CI [−1.05 to −0.34]; $I^2 = 81.25$ %, $p < 0.001$), and GPx (SMD = −1.86, 95 % CI [−3.17 to −0.55]; $I^2 = 95.36$ %, $p = 0.01$) (Figures A, B, C). However, no statistically significant difference was observed in CAT activity following cannabis exposure (SMD = −0.58, 95 % CI [−1.40 to 0.24]; $I^2 = 95.74$ %, $p = 0.17$) (Fig. 7).

3.4.6. Phytocannabinoids and synthetic cannabinoids

Phytocannabinoids and synthetic cannabinoids differ in their pharmacodynamics and dose-response relationships, resulting in divergent effects. Therefore, separate meta-analyses were performed for each type.

In *In vitro studies*, both groups significantly increased MDA production (phytocannabinoids: (SMD = 1.09, 95 % CI [0.60 to 1.58]; $I^2 = 83.10$ %, $p = 0.001$); synthetic cannabinoids: (SMD = 0.90, 95 % CI [0.58 to 1.21]; $I^2 = 66.90$ %, $p = 0.001$)). In contrast, no significant effect on CAT activity was found in either case (phytocannabinoids: (SMD = 0.37, 95 % CI [−0.67 to 1.42]; $I^2 = 94.40$ %; $p = 0.48$); synthetic cannabinoids: (SMD = −0.33, 95 % CI [−0.90 to 0.24]; $I^2 = 80.86$ %, $p = 0.25$)). Regarding SOD, phytocannabinoids decreased activity (SMD = −0.99, 95 % CI [−1.38 to −0.60]; $I^2 = 47.03$ %, $p = 0.001$), while synthetic cannabinoids had no effect (SMD = −0.03, 95 % CI [−0.34 to 0.29]; $I^2 = 64.98$ %, $p = 0.87$).

In *In vivo studies*, phytocannabinoids were associated with increased ROS production (SMD = 0.08, 95 % CI [0.03 to 0.12]; $I^2 = 99.65$ %, $p = 0.001$), an effect that was not observed with synthetic cannabinoids (SMD = 0.01, 95 % CI [−0.01 to 0.02]; $I^2 = 99.15$ %, $p = 0.38$). In

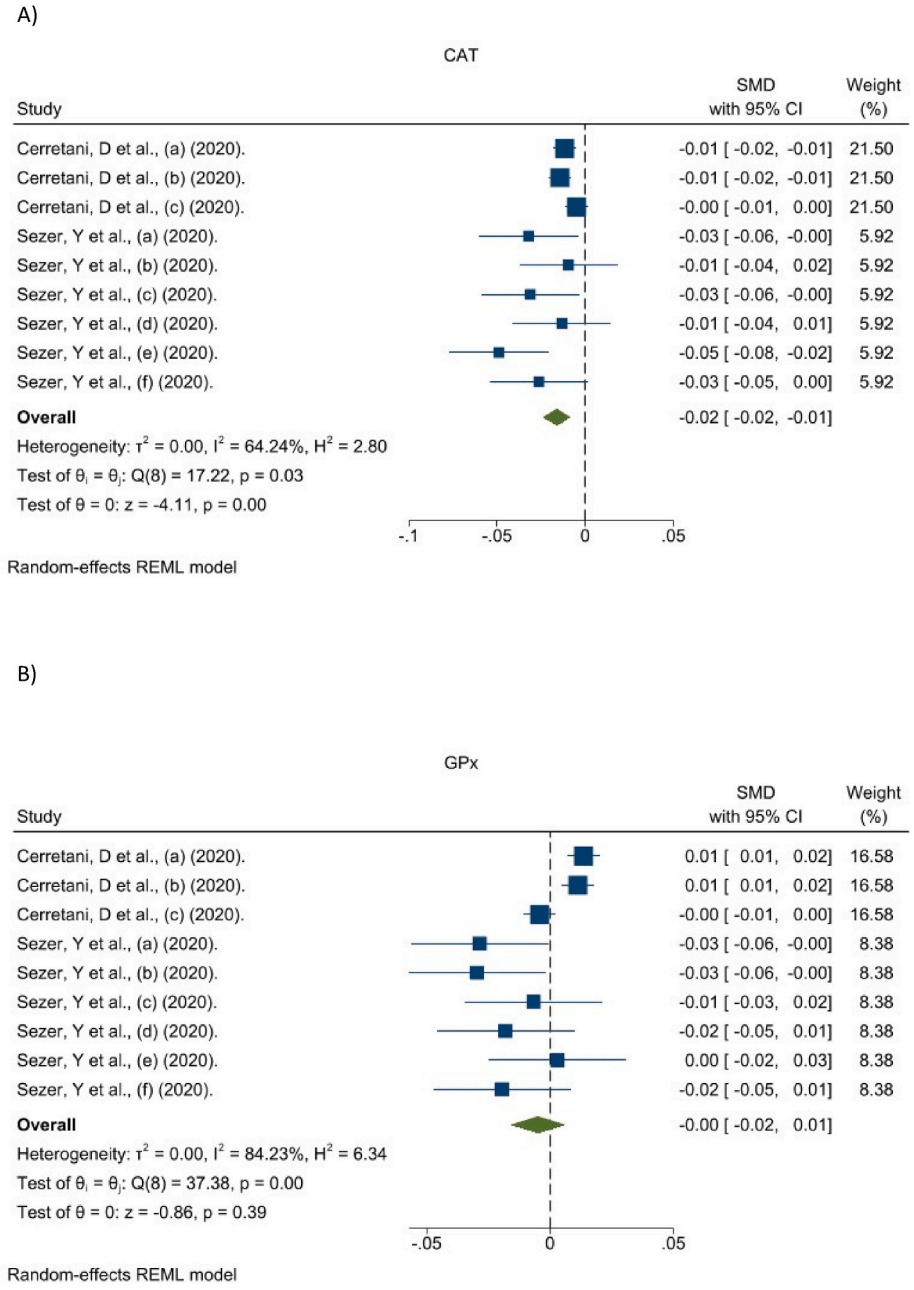


Fig. 6. Forest plot showing the effect size of correlation coefficients between cannabis (natural products and synthetic products) and antioxidant enzymatic activity. *In vitro* studies. A) CAT, B) GPx, C) GR.

C)

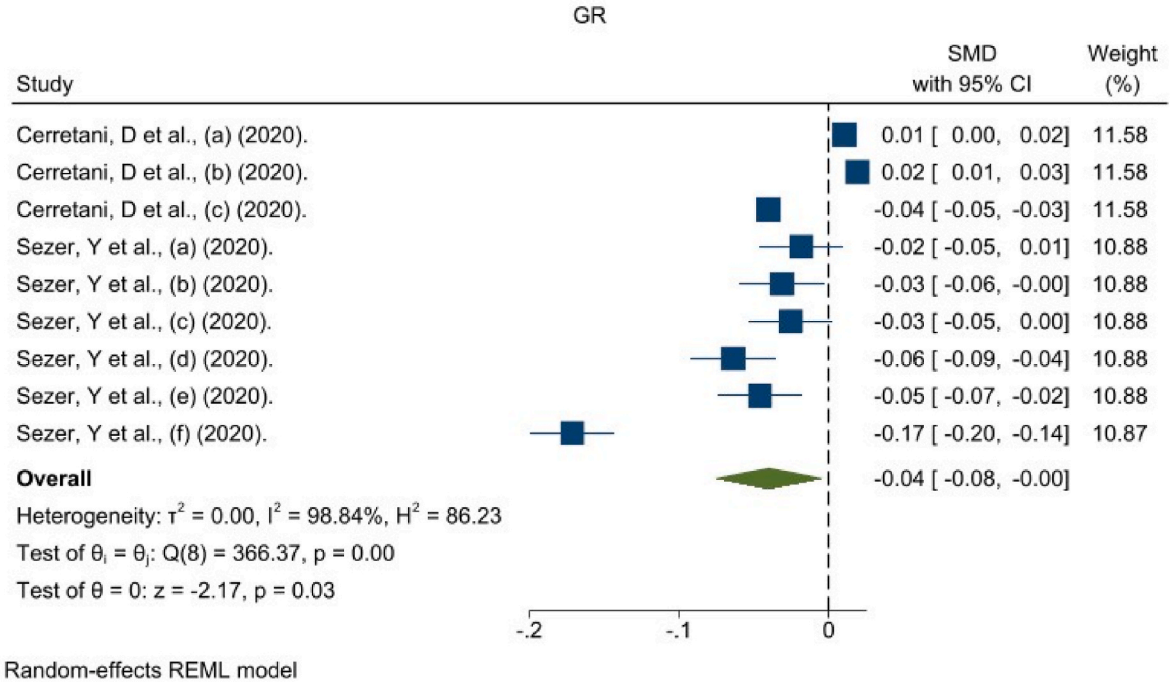


Fig. 6. (*continued*).

contrast, synthetic cannabinoids were associated with reducedGSH activity (SMD = −0.04, 95 % CI [−0.07 to −0.01]; I^2 = 99.71 %; p = 0.001), and also phytocannabinoids (SMD = −0.05, 95 % CI [−0.05 to −0.01]; I^2 = 99.71 %; p = 0.001) (Figs. S1–S5).

3.5. Subgroup analysis

Due to the high level of heterogeneity found among the meta-analysis results, subgroup studies were conducted to explore potential sources of heterogeneity between studies. The covariates examined were: (I) molecule type, (II) concentration/dose and (III) treatment duration, (IV) administration type and (V) animal model (*in vivo*), (VI) system type, and (VII) cancer cell model.

In the *in vitro* subgroup analysis, the type of molecule was identified as a significant source of variability. Specifically, THC was associated with ROS (SMD 0.01, 95 % CI [0.01 to 0.02]; I^2 = 0.00 %, p = 0.79), CBD with MDA (SMD 0.001, 95 % CI [0.00 to 0.02]; I^2 = 0.05 %, p = 0.51) and synthetic analogs with ROS and CAT (SMD -0.02, 95 % CI [−0.03 to −0.01]; I^2 = 42.77 %, p = 0.001) (Table 5).

The *in vivo* subgroup analysis indicated that treatment duration significantly contributed to heterogeneity. Treatments lasting longer than 7 days but not exceeding 28 days were associated with increased malondialdehyde (MDA) levels (SMD 2.25, 95 % CI [1.51 to 2.99]; I^2 = 68.65 %: p = 0.001), and decreased SOD activity (SMD -1.85, 95 % CI [−2.37 to −1.34]; I^2 = 34.64 %, p = 0.001). Treatments longer than 28 days resulted in a significant reduction in glutathione (GSH) activity (SMD -2.3, 95 % CI [−3.12to −1.48]; I^2 = 70.6 %, p = 0.001). The type of molecule also influenced outcomes, with certain compounds being associated with decreased SOD activity: (SMD -1.17, 95 % CI [−2.12 to −0.23]; I^2 = 64.06 %, p = 0.03) and (SMD -0.87, 95 % CI [−1.38 to −0.37]; I^2 = 52.31 %, p = 0.03); combined CBD + THC treatment increased MDA levels (SMD 1.69, 95 % CI [1.25 to 2.13]; I^2 = 0.00 %, p = 0.79) while "other" cannabinoids significantly decreased GPx activity (SMD -4.51, 95 % CI [−6.39 to −2.63]; I^2 = 72.44 %, p = 0.02). Regarding administration methods, oral administration was linked to decreased SOD activity (SMD -1.42, 95 % CI [−2.06to −0.78]; I^2 = 69.59 %, p = 0.001). Finally, the type of biological system influenced outcomes, with MDA levels increasing in reproductive systems. (SMD 1.52, 95 % CI [0.93 to 2.11]; I^2 = 25.16 %, p = 0.24) and SOD decreased (SMD -1.33, 95 % CI [−1.90to −0.75]; I^2 = 39.79 %, p = 0.13). In nervous system models, ROS (SMD 3.24, 95 % CI [1.24 to 5.25]; I^2 = 65.18 %, p = 0.09) and MDA (SMD 1.31, 95 % CI [0.96 to 1.67]; I^2 = 69.32 %, p = 0.001) levels were significantly elevated (Table 6).

Conversely, variations in effect size were observed across different variables. *In vivo*, CAT activity significantly decreased following treatment with "other" cannabinoids and in plasma samples (SMD -5.99, 95 % CI [−9.95 to −2.04]; I^2 = 92.69 %, p = 0.01); (SMD -4.03, 95 % CI [−7.58 to −0.49]; I^2 = 97.79 %, p = 0.001). For GPx, treatment durations of ≤7 days and intraperitoneal injection administration were associated with a reversal of the effect, resulting in increased activity (SMD 0.74, 95 % CI [0.26 to 1.22]; I^2 = 58.59 %, p = 0.03). Additionally, total antioxidant capacity (TAC) in rats showed a significant decrease (SMD -0.52, 95 % CI [−0.91 to −0.13]; I^2 = 27.9 %, p = 0.14), whereas treatments lasting ≤7 days and intraperitoneal administration were linked to an opposite, significant increase in TAC (SMD 0.79, 95 % CI [0.26 to 1.31]; I^2 = 74.96 %, p = 0.001). *In vitro*, treatment with cannabidiol (CBD) significantly decreased the GSH/GSSG ratio (SMD -0.26, 95 % CI [−0.5 to −0.02]; I^2 = 99.81 %, p = 0.001).

3.6. Sensitivity analysis

The outlier analysis involved removing data points that could biased the overall results. In the *in vivo* studies, data from Oluwasola et al., (b) and (c) (2023) were excluded from the ROS analysis, with the association remaining significant (SMD 1.05, 95 % CI [0.76 to 1.34]). For SOD, exclusion of Okorie et al., (b) (2022) and Oluwasola et al., (c) (2023), also preserved the significant effect (SMD -0.57, 95 % CI [−0.76 to −0.25]). Additionally, removal of Kruk-Slomka et al. (2016) from the

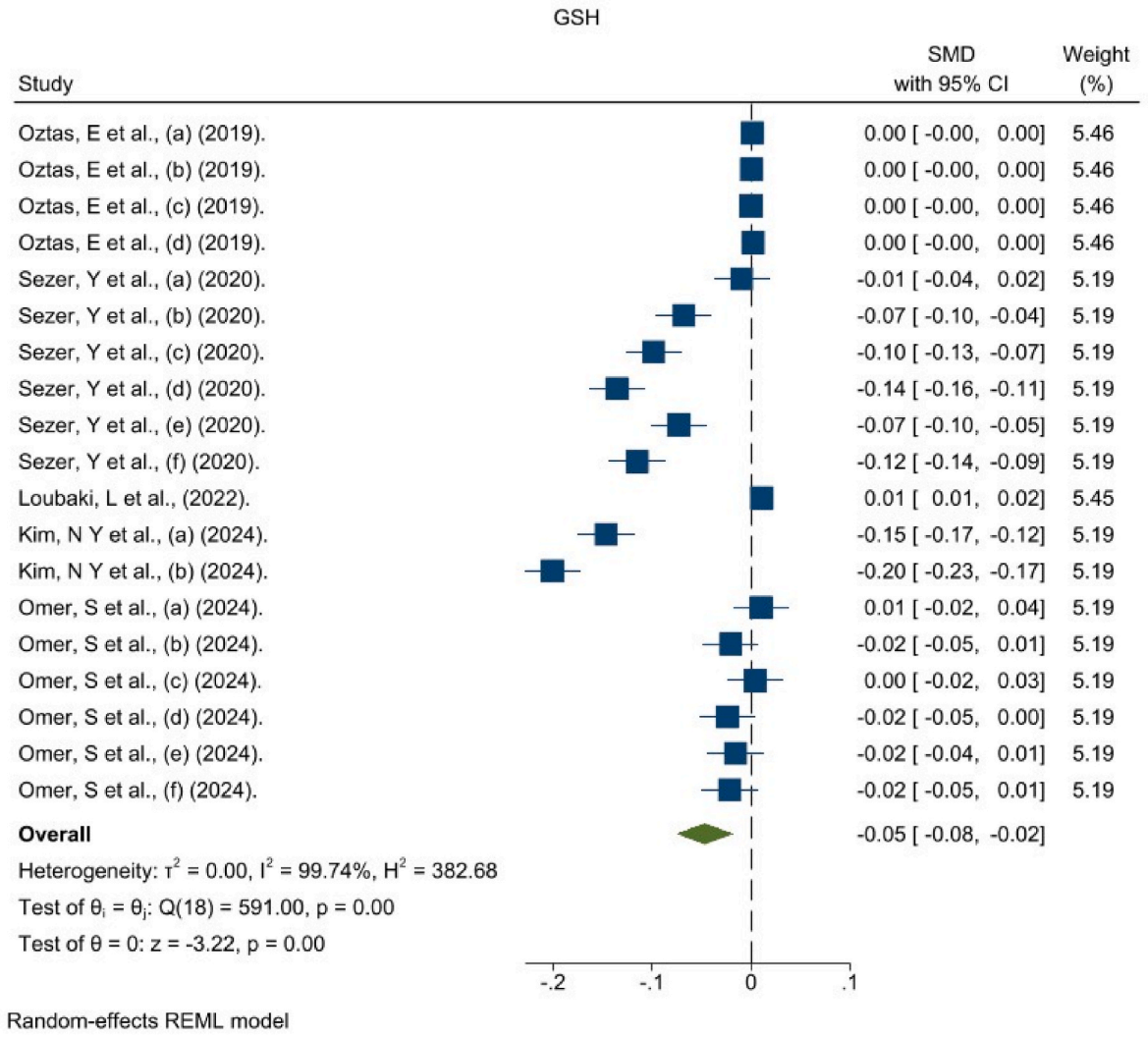


Fig. 6. (*continued*).

TAC analysis revealed a significant decrease in antioxidant activity (SMD -0.52, IC 95 % [−0.91 to −0.13]; I2 = 27 %, p = 0.001).

For the *in vitro* studies, Kim et al. (2024) was excluded from the analyses of ROS and the GSH/GSSG ratio. After exclusion, the association with increased ROS remained significant (SMD 0.02, 95 % CI [0.01 to 0.03]), whereas no significant association was observed for the GSH/GSSG ratio (SMD 0.01, 95 % CI [−0.04 to −0.05]). Additionally, exclusion of Sezer et al. (2020, dataset f) from the GR analysis maintained the significant decrease in enzyme activity (SMD -0.02, 95 % CI [−0.04 to −0.00]).

3.7. Publication bias

Results of the publication bias assessment are presented in Table 7. (Egger's test) and in Figs. S6 and S7 (funnel plots). Egger's test indicated strong evidence of small-study effects for ROS, MDA, and SOD (*in vivo*), as well as for GSH, and GPx in both *in vitro* and *in vivo* groups. Moderate evidence of bias was detected for CAT and MDA (*in vitro*). No significant evidence of publication bias was found for TAC, GR, and the GSH/GSSG ratio.

Visual inspection of the funnel plots indicated more pronounced asymmetry in the *in vitro* analyses, whereas the *in vivo* funnel plots were generally more widely dispersed. However, Egger's regression test confirmed significant statistical asymmetry for most primary biomarkers, including ROS (p = 0.0007), MDA (p < 0.0001), and SOD (p < 0.0001) in animal studies (Table 7).

This asymmetry suggests the presence of publication bias, likely driven by small-study effects, where smaller experiments with non-significant or null results may remain unpublished. Consequently, while the consistent direction of the effect across different experimental models supports cannabis and OS, results reported for these outcomes should be interpreted with caution, as they may be overestimated due to this bias.

4. Discussion

In recent years, cannabis research has gained significant scientific attention. Although many studies have examined its antioxidant properties across diverse pathological and physiological contexts, significant gaps remain regarding its pro-oxidant effects and potential adverse biological effects suggested by preclinical evidence, whose relevance to humans remains uncertain. This study aims to evaluate the influence of cannabis on redox homeostasis by systematically assessing its pro-oxidant effects through comprehensive *in vivo* and *in vitro* analyses. Notably, this is the first study to focus exclusively on the primary redox biomarkers.

Several pooled estimates, especially from *in vitro* analyses, showed statistically significant but small SMDs. Statistical significance in this setting reflects consistency and precision rather than necessarily large biological effects. In vitro meta-analyses often achieve high statistical

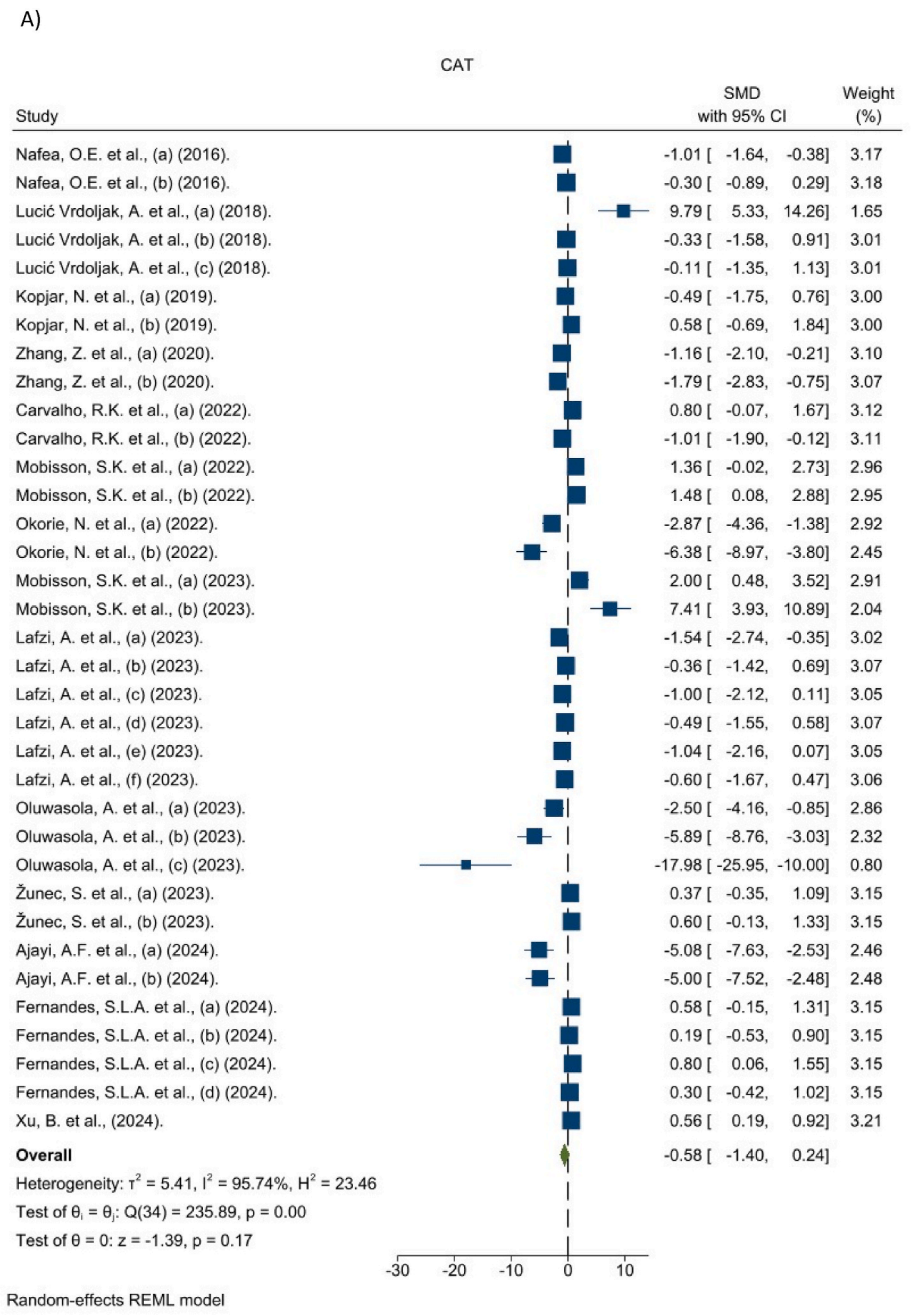
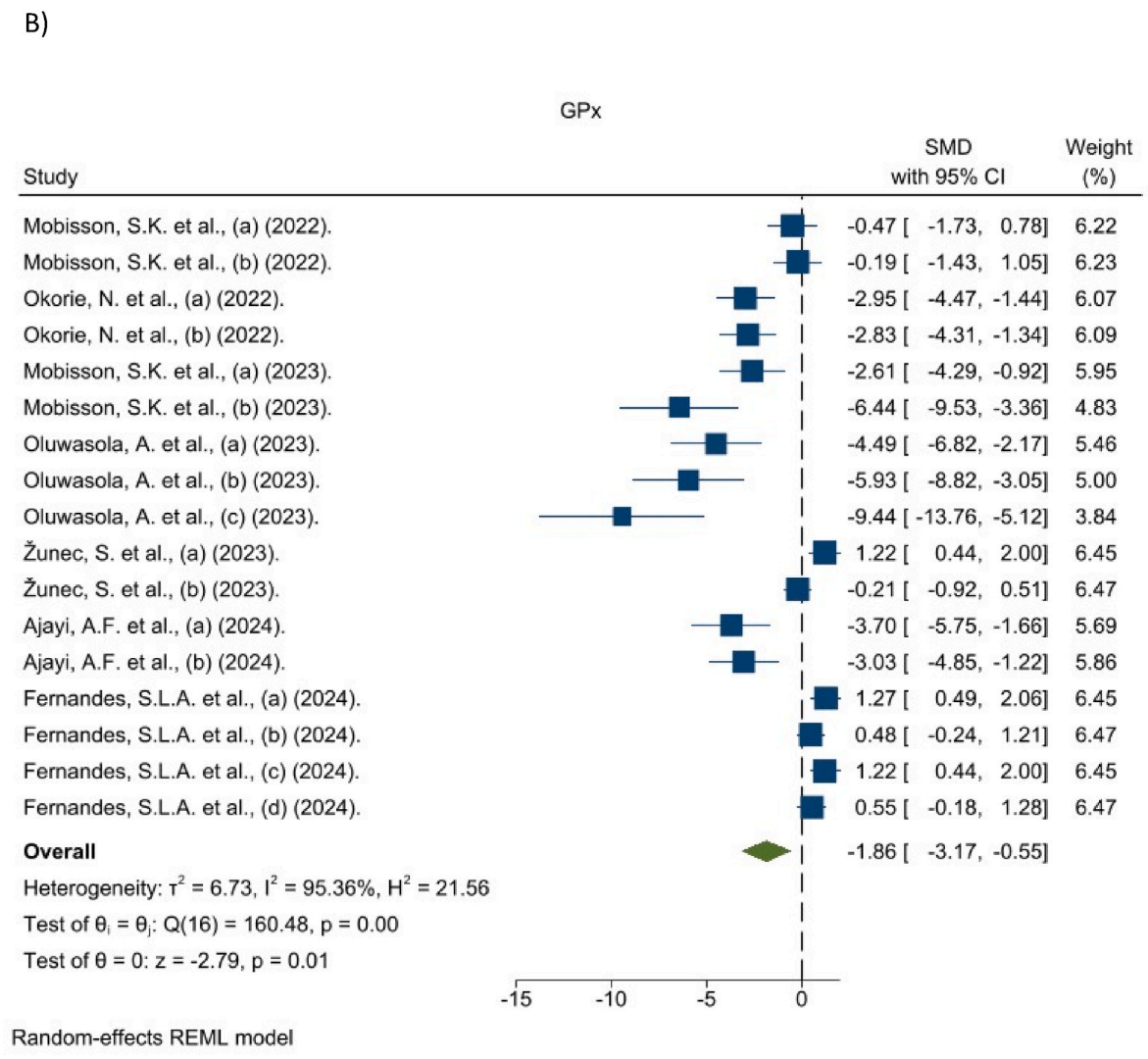


Fig. 7. Forest plot showing the effect size of correlation coefficients between cannabis (natural products and synthetic products) and antioxidant enzymatic activity. *In vivo* studies. A) CAT, B) GPx, C) SOD.

power due to controlled conditions and multiple estimable data points, which can accentuate significance for modest effect sizes. Accordingly, small SMDs should be interpreted as indicating consistent directional changes rather than definitive evidence of substantial biological impact and should be evaluated alongside mechanistic plausibility and *in vivo* findings.

A fundamental aspect for interpreting our results is the high statistical heterogeneity observed in the meta-analyses. This variability is a direct reflection of the inherent complexity of the phenomenon under study: preclinical literature that is enormously diverse in terms of compounds, biological models, and experimental designs. Under such conditions, pooled estimates should be interpreted with caution and cannot be assumed to represent a single underlying effect. Instead, this heterogeneity indicates a potential relationship whose presence and intensity are modulated by multiple factors. Therefore, the primary value of our quantitative synthesis lies not solely in the pooled estimates, but in its ability to systematize this variability and, through subgroup analyses, begin to identify the specific conditions that influence the redox outcome. Consequently, our results point toward a contextual association rather than a universal causality. Moreover, although some *in vitro* standardized mean differences (SMDs) are small, they provide a possible directional signal. Their biological relevance is context dependent and becomes more compelling when considered alongside the larger *in vivo* effects reported here.

Both *in vitro* and *in vivo* analyses in this study suggested an association that cannabis-exposure may have induced oxidative stress, characterized by increased ROS production and lipid peroxidation alongside reduced activity of key antioxidant enzymes (except for GPx *in vitro* and



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CAT *in vivo*). *In vitro* studies encompassed various cell types with varying sensitivities to cannabis concentrations and exposure times; however, a common finding is that high concentrations may exert toxic effects (Pagano et al., 2020). Notably, most studies employing cannabidiol (CBD) use high concentrations (>10 μM), while others, such as Goenka (2022) (Goenka, 2022), apply lower doses of CBD and THC over prolonged exposure periods (six days). Under these conditions, an increase in ROS generation was observed in certain models. This pro-oxidant effect has been suggested to be mediated by CBD-induced mitochondrial dysfunction, evidenced by impaired respiratory chain activity, decreased intracellular adenosine triphosphate (ATP) levels, upregulation of stress-responsive chaperones Heat Shock Protein 60 and 70 (HSP60 and HSP70), and ROS production (Podinic et al., 2024; Schultze et al., 2017).

Furthermore, CBD-induced ROS generation has been suggested to be mediated by its promiscuous receptor binding, particularly to Transient Receptor Potential Vanilloid type 1 and 2 (TRPV1/TRPV2) channels (de la Harpe et al., 2022; Misri et al., 2022), which triggers massive Ca^{2+} influx into the cytosol. This cytosolic Ca^{2+} surge causes endoplasmic reticulum (ER) overload, provoking ER stress and subsequent Ca^{2+} release from ER stores. Mitochondria then internalize excess Ca^{2+} via MCU, mPTP opening. The consequent loss of mitochondrial membrane potential (ΔΨm) disrupts electron transport, driving pathological ROS production (Loubaki et al., 2022; Mould et al., 2021; Wu et al., 2018). This oxidative cascade activates autophagic and pro-apoptotic pathways as caspases 3/7 and 9, and ferropoptosis pathways are activated (Hamad and Olsen, 2021; Kim et al., 2024; Li et al., 2023; Omer et al., 2024).

Synthetic cannabinoid analogs, including JWH-018/122, UR-144 (Almada et al., 2020; Fonseca et al., 2019), CB-83 (Cerretani et al., 2020), AKB48 (Oztas et al., 2019)and CP55940 (Soto-Mercado et al., 2020), have been suggested to induce similar pathological pathways involving mitochondrial dysfunction (ROS overproduction, ΔΨm collapse), Ca^{2+} dysregulation (cytosolic overload via TRP/ion channel activation), and cell death activation (caspase-mediated apoptosis, impaired autophagic flux). However, their effects differ mechanistically; for example, JWH-018 exhibits high affinity for CB1 receptors, driving rapid Ca^{2+} influx, whereas JWH-122 acts independently of CB1 and CB2 receptors. These differences highlight the critical need for further research to better understand the pathophysiological consequences associated with synthetic cannabinoid abuse (Almada et al., 2020; Fonseca et al., 2019).

Excessive ROS overwhelm antioxidant defenses, disrupting redox homeostasis and impairing enzymatic function. Elevated ROS inhibit GSH synthesis, shift the GSH/GSSG balance toward oxidation, and inactivate GPX4, promoting lipid peroxidation and cell death via apoptosis and ferroptosis (Kim et al., 2024; Liu et al., 2022). ROS also impair CAT and SOD through downregulation or oxidative modification of their catalytic sites (Nandi et al., 2019). Synthetic cannabinoids,

C)

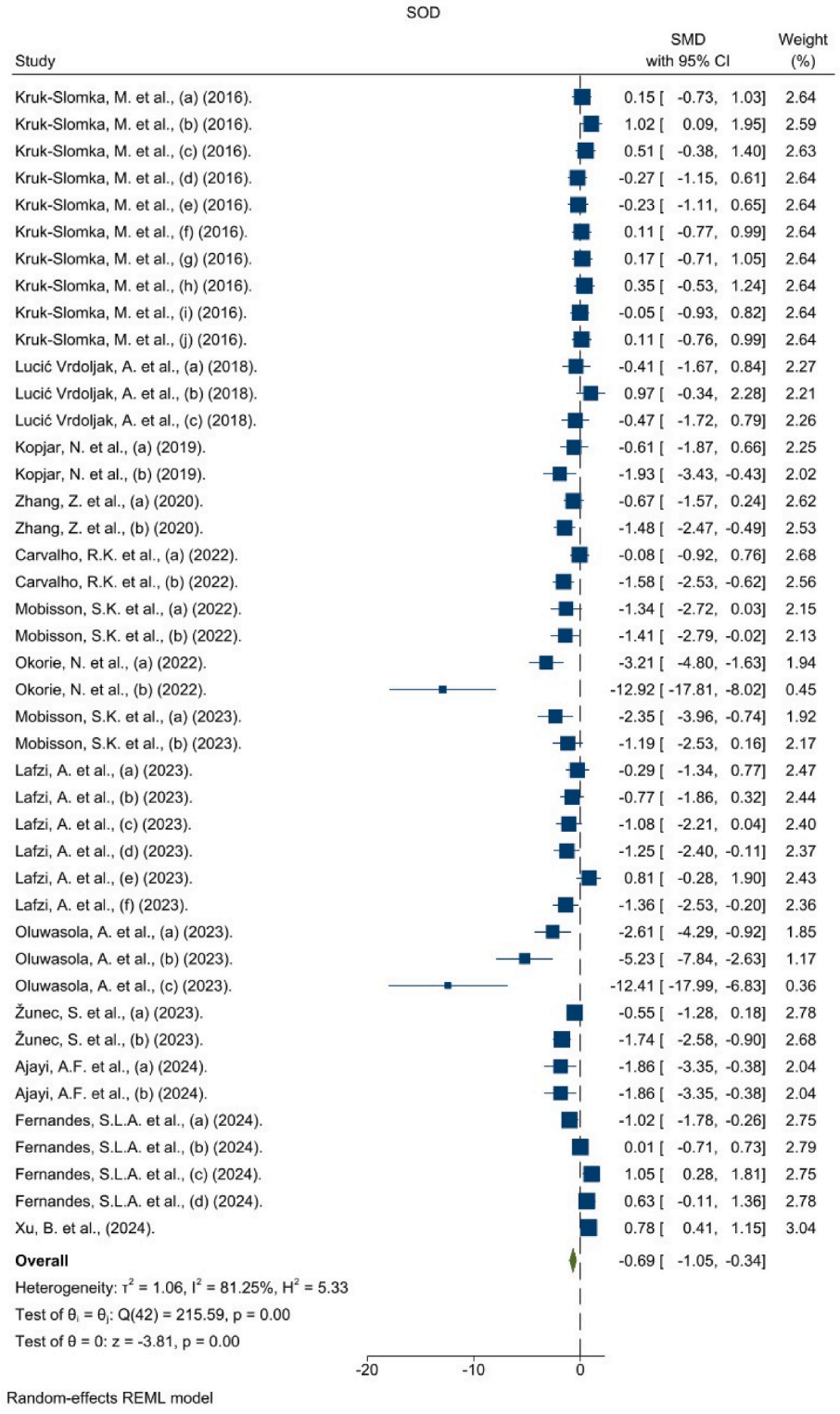

Fig. 7. (*continued*).

including the highly potent JWH-018 (Sezer et al., 2020), exacerbate this oxidative damage by intensifying ROS generation and further suppressing enzymatic activity, thereby contributing to pronounced neurotoxicity in some experimental models.

Conversely, other studies have shown that novel cannabinoids such as cannabidibutol (CBDB) and cannabidiphorol (CBDP), as well as sesquiterpenes from cannabis like β-caryophyllene and humulene and their oxidized forms, also induce dose-dependent cellular damage through oxidative stress generation (Salbini et al., 2021; Tazi et al., 2022). For example, Tazi et al. (2022) (Tazi et al., 2022) demonstrated that exposure to cannabis smoke condensate (CSC) leads to significant ROS overproduction, disrupting redox homeostasis and activating both

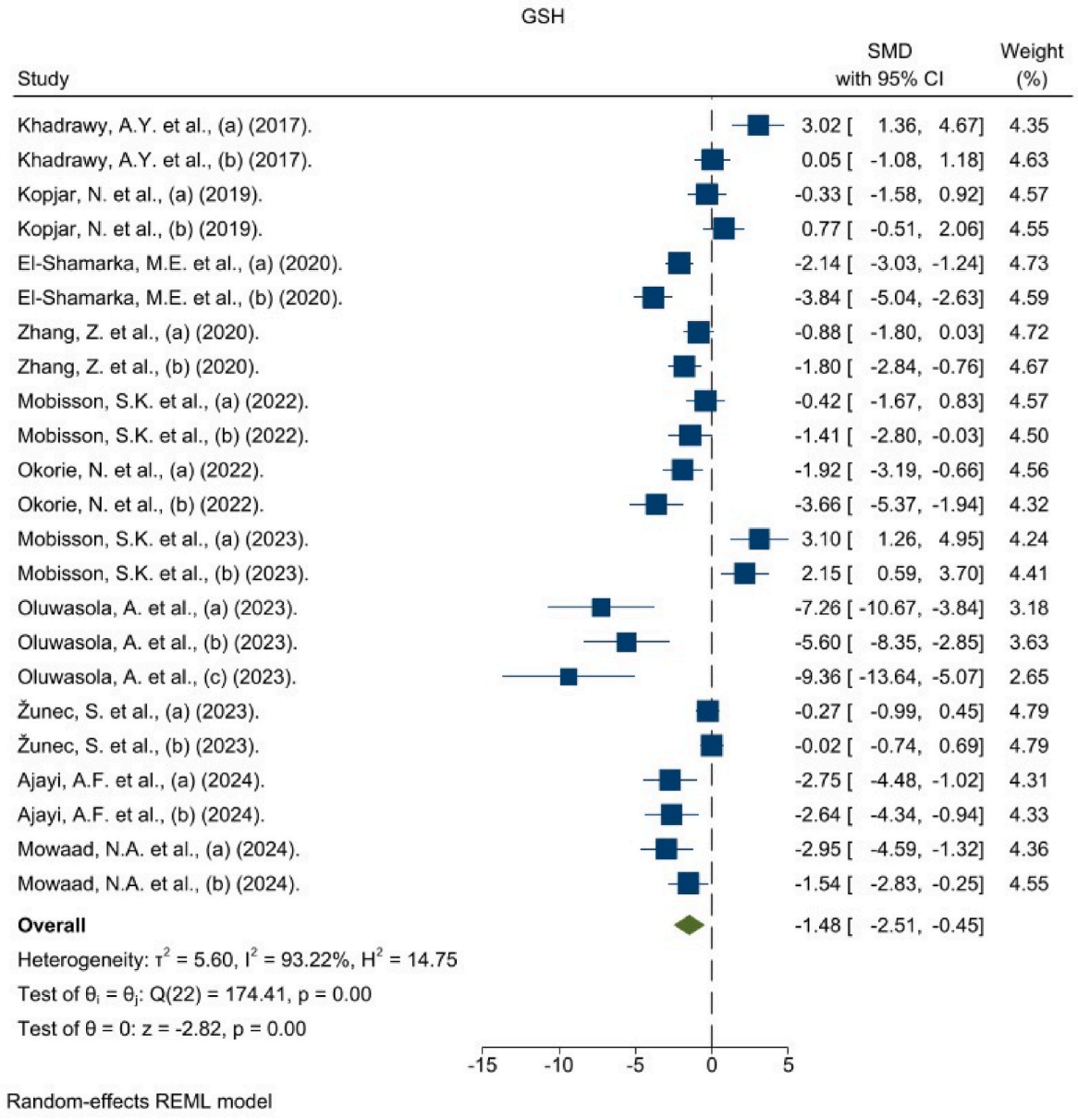

Fig. 7. (*continued*).

apoptotic and autophagic pathways.

In vivo studies on cannabinoids display considerable diversity, varying in target organs, specific compounds, treatment durations, dosages, and administration routes. This diversity is a key source of the statistical heterogeneity highlighted in our meta-analyses. Nevertheless, quantitative analyses indicate that cannabis exposure can disrupt redox homeostasis in animal models, although the effect size and consistency vary greatly. Although fewer studies have directly measured ROS levels, our analysis suggests an association with increased ROS following cannabis exposure in some models. For example, Alagbonsi & Olayaki. (2017) (Alagbonsi & Olayaki. (2017) suggested that administration of cannabis leaf extract (2 mg/kg for 30 days) elevated ROS levels, contributing to sperm toxicity. Additionally, CBD has been found to be a possible suppressor of the nuclear factor erythroid 2–related factor 2 (Nrf2), a key transcription factor regulating oxidative stress responses, leading to heightened ROS production and subsequent proapoptotic signaling via the TRPV2 receptor (Misri et al., 2022). Similarly, in zebrafish models of neurodegeneration, exposure to the synthetic analog MDA-19 (20 mg/L in aqueous solution) induced neurotoxic changesassociated with elevated ROS levels (Xu et al., 2024).

Most studies reviewed in this work examine MDA as a biomarker of oxidative stress due to its chemical stability and ease of detection in post-mortem tissues using accessible instrumental techniques with minimal requirements. MDA is a byproduct of lipid peroxidation, a process initiated when excessive ROS react with membrane lipids, generating electrophilic species (Su et al., 2019). This mechanism is particularly relevant in in experimental neural tissues, which are highly susceptible to oxidative damage because of its elevated mitochondrial lipid content and high oxygen consumption (Muralikrishna Adibhatla and Franklin Hatcher, 2010; Song et al., 2024). In this study, cannabis treatment is associated with increased MDA levels and, consequently, enhanced lipid peroxidation caused by oxidative stress. Several studies highlight the neurotoxic effects linked to this process. Khadrawy et al. (2017) (Khadrawy et al., 2017). found that a 10 mg/kg dose of cannabis extract increased MDA levels could be associated with a higher predisposition to depression-like phenotype in animal models. Similarly, Alzu'bi et al. (2024a) (Alzu'bi et al. (2024a) study showed that administering 3 mg/kg of the synthetic cannabinoid AB-FUBINACA for 5 days

Table 5
Subgroups *in vitro* analysis.

	Outcome	Subgroup		No.studies	No.data points	SMD (95% CI)	I^2	P value
In vitro								
	ROS	Total				0.04 [0.02 to 0.06]	99.86%	0.001
		Molecule						
			B	1	1	-	-	-
			CBD	11	20	0.09 [0.04 to 0.15]	99.63%	0.001
			O	5	20	0.04 [0.00 to 0.07]	99.63%	0.001
			SYN	5	21	0.01 [-0.01 to 0.02]	98.15%	0.001
			THC	3	5	0.01 [0.01 to 0.02]	0.00%	0.79
		Concentration						
			≤10 μM	11	33	0.02 [0.01 to 0.02]	94.93%	0.001
			10–50 μM	12	24	0.05 [0.00 to 0.10]	99.85%	0.001
			>50 μM	2	6	0.06 [0.01 to 0.11]	99.63%	0.001
		Time						
			min-12 h	6	12	0.07 [0.01 to 0.14]	99.95%	0.001
			24 h	11	33	0.04 [0.01 to 0.07]	99.87%	0.001
			>48 h	7	19	0.01 [-0.01 to 0.03]	97.03%	0.001
		Tissue						
			Epithelial	12	37	0.02 [0.01 to 0.02]	95.81%	0.001
			Hematopoietic	4	12	0.02 [0.00 to 0.004]	99.28%	0.001
			Mesenquimal	2	8	−0.01 [-0.04 to 0.02]	98.21%	0.001
			Nervous	3	10	0.12 [0.01 to 0.23]	99.96%	0.001
		Cancerous						
			No	5	15	0.01 [-0.02 to 0.03]	98.75%	0.001
			Yes	16	52	0.05 [0.02 to 0.07]	99.9%	0.001
	MDA	Total				0.04 [0.01 to 0.07]	97.82%	0.001
		Molecule						
			CBD	2	3	0.01 [0.00 to 0.02]	0.05%	0.51
			SYN	2	6	0.07 [0.03 to 0.11]	94.46%	0.001
			THC	2	3	0.01 [-0.01 to 0.03]	70.28%	0.04
		Concentration						
			≤10 μM	3	4	0.02 [-0.02 to 0.06]	92.48%	0.001
			10–50 μM	3	6	0.03 [0.00 to 0.07]	97.81%	0.001
			>50 μM	1	2	0.1 [0-08 to 0.12]	0.18%	0.47
	GSH/GSSG	Total				−0.11 [-0.27 to 0.04]	99.94%	0.001
		Molecule						
			CBD	3	4	−0.26 [-0.5 to −0.02]	99.81%	0.001
			SYN	2	3	0.04 [0.02 to 0.07]	78.96%	0.001
			THC	1	1	-	-	-
		Concentration						
			≤10 μM	2	2	−0.04 [-0.16 to 0.08]	98.65%	0.001
			10–50 μM	3	6	−0.14 [-0.34 to 0.07]	99.94%	0.001
		Time						
			min-12 h	1	1	-	-	-
			24 h	2	4	−0.13 [-0.39 to 0.13]	99.98%	0.001
			>48 h	2	3	0.01 [-0.1 to 0.11]	97.68%	0.001
		Tissue						
			Epithelial	2	4	−0.02 [-0.07 to 0.03]	99.47%	0.001
			Mesenquimal	1	2	0.06 [0.04 to 0.08]	0.00%	0.001
			Nervous	1	2	−0.46 [-0.59 to −0.33]	97.61%	0.001
	GSH	Total				−0.05 [-0.08 to −0.02]	99.74%	0.001
		Molecule						
			B	1	1	-	-	-
			CBD	2	4	−0.09 [-0.19 to 0.01]	98.02%	0.001
			SYN	3	12	−0.04 [-0.07 to −0.01]	99.71%	0.001
			THC	1	2	−0.01 [-0.04 to 0.02]	49.28%	16
		Concentration						
			≤10 μM	3	6	−0.01 [-0.03 to 0.01]	86.62%	0.001
			10–50 μM	4	9	−0.07 [-0.12 to −0.02]	99.74%	0.001
			>50 μM	2	4	−0.05 [-0.1 to 0.01]	99.82%	0.001
		Tissue						

(*continued on next page*)

Table 5 (*continued*)

Outcome	Subgroup		No.studies	No.data points	SMD (95% CI)	I^2	P value
		Epithelial	1	1	-	-	-
		Hematopoietic	1	6	−0.01 [-0.02 to 0.00]	7.4%	0.37
		Nervous	3	12	−0.07 [-0.11 to −0.03]	99.85%	0.001
CAT	Total				−0.02 [-0.02 to −0.01]	64.24%	0.001
	Molecule						
		CBD	1	1	-	-	-
		SYN	2	7	−0.02 [-0.03 to −0.01]	42.77%	0.11
		THC	1	1	-	-	-
	Concentration						
		≤10 μM	2	3	−0.01 [-0.02 to −0.01]	0.08%	0.36
		10–50 μM	2	4	−0.01 [-0.02 to −0.00]	55.52%	0.08
		>50 μM	1	2	−0.04 [-0.06 to −0.02]	22.84%	0.25
	Tissue						
		Epithelial	1	3	−0.01 [-0.02 to −0.00]	56.28%	0.1
		Nervous	1	6	−0.03 [-0.04 to −0.02]	2.84%	0.4
GPx	Total				0.00 [-0.02 to 0.01]	84.23%	0.39
	Molecule						
		CBD	1	1	-	-	-
		SYN	2	7	−0.01 [-0.02 to 0.00]	66.40%	0.001
		THC	1	1	-	-	-
	Concentration						
		≤10 μM	2	3	−0.01 [-0.04 to 0.02]	84.54%	0.001
		10–50 μM	2	4	0.00 [-0.01 to 0.01]	78.03%	0.001
		>50 μM	1	2	−0.01 [-0.03 to 0.01]	21.46%	0.26
	Tissue						
		Epithelial	1	3	0.01 [0.00 to 0.02]	89.08%	0.001
		Nervous	1	6	−0.02 [-0.03 to −0.01]	0.06%	0.54
GR	Total				−0.04 [-0.08 to −0.00]	98.94%	0.001
	Molecule						
		CBD	1	1	-	-	-
		SYN	2	7	−0.05 [-0.09 to −0.01]	96.58%	0.001
		THC	1	1	-	-	-
	Concentration						
		≤10 μM	2	3	−0.01 [-0.04 to 0.02]	79.58%	0.001
		10–50 μM	2	4	0.03 [-0.06 to 0.01]	97.45%	0.001
		>50 μM	1	2	−0.11 [-0.23 to 0.01]	97.45%	0.001
	Tissue						
		Epithelial	1	3	0.00 [-0.04 to 0.03]	99.00%	0.001
		Nervous	1	6	−0.06 [-0.11 to −0.01]	93.91%	0.001

significantly increased MDA levels, triggering oxidative stress and damaging the hippocampus, alongside reductions in brain-derived neurotrophic factor (BDNF) and N-methyl-D-aspartate (NMDA) glutamate receptors. This synthetic analog has also been linked to hepatotoxicity and nephrotoxicity (Alzu'bi et al., 2024b; Alzu'bi et al., 2022). Furthermore, cannabis not only raises MDA levels independently but also may exacerbate lipid peroxidation-inducing effects of other substances, including steroids, neurostimulants, and various drugs (Abdel-Salam et al., 2018; El-Shamarka et al., 2020; Mowaad et al., 2024; Nafea et al., 2016).

MDA is highly cytotoxic and reacts with amino acid residues in proteins, disrupting enzymatic active sites, including those of antioxidant enzymes such as CAT, SOD, GSH, and GPx (Ayala et al., 2014; Del Rio et al., 2005; Jové et al., 2020). Elevated MDA levels have been linked to reduced SOD activity (Arya et al., 2021), consistent with meta-analytic findings showing decreased antioxidant enzyme activity *in vitro*. In contrast, CAT activity shows variable responses, suggesting that dose and duration of cannabis exposure critically influence its regulation.

For instance, studies such as Mobisson et al. (2022) (Mobisson et al., 2022) which used CBD oil at doses of 0.1 and 0.2 mg/kg for 14 days, and Kopjar et al. (2019) and Žunec et al. (2023) (Kopjar et al., 2019; Žunec et al., 2023), which administered THC at 7 mg/kg for 7 days, reported decreases in the activity of enzymes such as SOD, GSH, and GPx, but observed no significant changes in CAT activity. In contrast, longer or higher-dose exposures, such as Carvalho et al. (2022)and Zhang et al. (2020) (Carvalho et al., 2022; Zhang et al., 2020), who administered 2 mg/kg of THC for 28 days and 2 months, respectively, as well as Okorie et al. (2022) (Okorie et al., 2022), who used 4 mg/kg of marijuana extract for 42 days, and Carvalho et al. (2022) with 15 and 30 mg/kg of CBD oil, suggested reductions in CAT activity. One possible explanation is the critical role of CAT as a key ROS-scavenging enzyme, which may enable it to maintain functional activity longer than other antioxidant enzymes, acting as a final line of defense under conditions of oxidative stress (Jomova et al., 2024). Nevertheless, prolonged or high dose exposure to cannabis appears to surpass this protective capacity. Additionally, the overall decline in antioxidant enzyme activity observed in some studies may be linked to the overproduction of ROS, which in turn can alter the expression of miRNAs that regulate these enzymes. For example, miR-17-3p, miR-23a, and miR-212 are known to modulate SOD expression; miR-30 b and miR-551 b regulate CAT; and miR-181a and miR-17-3p affect GPx. Cannabis-induced oxidative stress may upregulate these miRNAs, thereby downregulating the expression and activity of their antioxidant enzymes (Ciesielska et al., 2021). Another

Table 6
Subgroups *in vivo* analysis.

	Outcome	Sugroup		No.studies	No.data points	SMD (95% CI)	I^2	P value
In vivo	**ROS**	Total				0.93 [0.1 to 1.75]	92.17%	0.001
		Animal						
			Fish	1	1	-	-	-
			Mice	2	4	0.04 [0.01 to 0.07]	0.00%	0.32
			Rats	2	3	1.85 [-0.37 to 4.08]	92.17%	0.001
		Molecule						
			CBD	1	1	-	-	-
			CBG	1	2	0.8 [0.15 to 1.45]	0.00%	0.38
			O	1	1	-	-	-
			SYN	1	1	-	-	-
			THC	1	2	0.23 [-0.25 to 0.71]	24.38%	0.26
		Concentration						
			≤2 mg-Kg	2	3	1.85 [-0.37 to 4.08]	90.66%	0.001
			>2 mg-Kg y ≤ 7 mg-Kg	1	3	0.23 [-0.25 to 0.71]	24.38%	0.26
			>7 mg-Kg y ≤ 30 mg-Kg	2	2	1.14 [-1.16 to 3.45]	93.83%	0.001
		Time						
			≤7 days	3	5	0.53 [-0.25 to 1.32]	89.14%	0.001
			>28 days	2	3	1.85 [-0.37 to 4.08]	90.66%	0.001
		Tissue						
			Nervous	2	2	3.24 [1.24 to 5.25]	65.18%	0.09
			Plasma	2	5	0.42 [0.00 to 0.83]	27.22%	0.24
		Administration						
			Aqueous solution	1	1	-	-	-
			Injected intraperitoneally	1	3	0.23 [-0.25 to 0.71]	24.38%	0.26
			Oral	2	3	1.85 [-0.37 to 4.08]	90.66%	0.001
	MDA	Total				1.16 [0.85 to 1.47]	81.66%	0.001
		Animal						
			Fish	2	5	0.11 [-0.15 to 0.36]	0.00%	0.92
			Mice	5	19	1.18 [0.71 to 1.66]	77.91%	0.001
			Rats	14	35	1.4 [0.92 to 1.88]	81.96%	0.001
		Molecule						
			B	2	4	1.69 [1.25 to 2.13]	0.00%	0.79
			CBD	3	6	0.53 [-0.2 to 1.25]	67.5%	0.01
			CBG	1	2	0.35 [-0.27 to 0.98]	0.00%	0.78
			O	3	7	5.12 [1.29 to 8.95]	96.44%	0.001
			SYN	7	25	0.9 [0.58 to 1.21]	66.9%	0.001
			THC	8	15	1.33 [0.47 to 2.19]	88.64%	0.001
		Concentration						
			≤2 mg-Kg	11	34	1.2 [0.8 to 1.6]	78.84%	0.001
			>2 mg-Kg y ≤ 7 mg-Kg	6	13	0.67 [-0.02 to 1.37]	76.92%	0.001
			>7 mg-Kg y ≤ 30 mg-Kg	6	10	1.45 [0.6 to 2.4]	88.09%	0.001
			>100 mg-Kg	1	2	1.7 [1.21 to 2.19]	0.00%	0.32
		Time						
			≤7 days	11	30	0.74 [0.4 to 1.09]	75.36%	0.001
			>7 days y ≤ 28 days	7	13	2.25 [1.51 to 2.99]	68.65%	0.001
			>28 days	7	17	1.2 [0.52 to 1.88]	87.31%	0.001
		Tissue						
			Cardiac	2	4	0.24 [-0.5 to 0.97]	60.12%	0.07
			Hepatic	5	10	0.15 [-0.16 to 0.45]	0.00%	0.52
			Nervous	9	23	1.31 [0.96 to 167]	69.32%	0.001
			Ocular	1	2	3.12 [0.48 to 5.75]	86.19%	0.01
			Plasma	4	9	3.57 [0.28 to 6.87]	98.44%	0.001
			Renal	2	3	065 [0.07 to 1.23]	0.00%	0.75
			Reproductive	3	6	1.52 [0.93 to 2.11]	25.16%	0.24
			Respiratory	1	2	1.85 [0.96 to 2.73]	0.00%	0.78
		Administration						
			Aqueous solution	1	1	-	-	-
			Injected intraperitoneally	12	34	1.09 [0.71 to 1.47]	80.03%	0.001
			Oral	9	22	1.15 [0.61 to 1.69]	77.9%	0.001
			Inhaled	1	2	3.35 [1.59 to 5.11]	54.81%	0.14
	GSH	Total				−1.48 [-2.51 to −0.45]	93.22%	0.001
		Animal						
			Mice	2	4	−0.67 [-1.41 to 0.06]	67.7%	0.03
			Rats	9	19	−1.70 [-2.98 to −0.41]	92.95%	0.001
		Molecule						
			B	1	2	−0.87 [-1.84 to 0.1]	7.85%	0.3
			CBD	1	2	2.55 [1.36 to 3.73]	0.00%	0.44
			O	3	7	−4.09 [-5.96 to −2.22]	84.63%	0.001
			SYN	1	1	-	-	-
			THC	6	11	−0.75 [-1.79 to 0.28]	90.77%	0.001
		Concentration						
			≤2 mg-Kg	6	11	−1.44 [-2.89 to 0.01]	91.13%	0.001
			>2 mg-Kg y ≤ 7 mg-Kg	3	6	−2.07 [-4,94 to 0.81]	97.14%	0.001
			>7 mg-Kg y ≤ 30 mg-Kg	3	6	−1.26 [-3.19 to 0.66]	93.01%	0.001

(*continued on next page*)

Table 6 (*continued*)

	Outcome	Sugroup		No.studies	No.data points	SMD (95% CI)	I^2	P value
		Time						
			≤7 days	2	4	−0.06 [-0.5 to 0.38]	0.00%	0.55
			>7 days y ≤ 28 days	6	12	−1.66 [-3.71 to 0.39]	94.47%	0.001
			>28 days	4	7	−2.3 [-3.12 to −1.48]	70.6%	0.001
		Tissue	Cardiac	1	2	−2.15 [-3.52 to −0.78]	43.32%	0.18
			Nervous	3	6	−0.46 [-2.32 to 1.41]	93.13%	0.001
			Ocular	1	2	−1.31 [-2.20 to −0.41]	40.21%	0.2
			Plasma	3	7	−3.59 [-6.07 to −1.11]	95.7%	0.001
			Reproductive	3	6	−0.34 [-2.27 to 1.59]	89.26%	0.001
		Administration						
			Injected intraperitoneally	5	10	−1.05 [-2.16 to 0.07]	91.53%	0.001
			Oral	5	11	−1.87 [-3.98 to 0.24]	94.07%	0.001
			Inhaled	1	2	−2.69 [-4.38 to −1]	60.7%	0.11
CAT	Total				0.58 [-1.4 to 0.24]	95.74%	0.001	
	Animal							
		Fish	2	5	0.51 [0.25 to 0.77]	0.00%	0.77	
		Mice	3	6	−0.33 [-1.18 to 0.53]	83.51%	0.001	
		Rats	9	24	−0.97 [-2.4 to 0.46]	96.56%	0.001	
	Molecule							
		B	2	4	0.24 [-0.95 to 1.44]	86.47%	0.001	
		CBD	2	4	1.99 [-1.22 to 5.2]	96.11%	0.001	
		O	2	5	−5.99 [-9.95 to −2.04]	92.69%	0.01	
		SYN	5	12	−0.33 [-0.9 to 0.24]	80.86%	0.001	
		THC	5	10	0.1 [-1.69 to 1.49]	94.84%	0.001	
	Concentration							
		≤2 mg-Kg	8	16	−0.74 [-1.76 to 0.29]	94.04%	0.001	
		>2 mg-Kg y ≤ 7 mg-Kg	4	9	−1 [-4.85 to 2.86]	98.78%	0.001	
		>7 mg-Kg y ≤ 30 mg-Kg	2	3	0.15 [-0.91 to 1.21]	85.62%	0.001	
		>100 mg-Kg	1	2	−0.65 [-1.34 to 0.05]	61.51%	0.11	
	Time							
		≤7 days	6	15	0.14 [-0.22 to 0.51]	60.59%	0.001	
		>7 days y ≤ 28 days	6	13	−1.65 [-4.1 to 0.81]	96.66%	0.001	
		>28 days	4	7	−1.3 [-2.61 to 0.02]	93.64%	0.001	
	Tissue	Cardiac	1	2	0.54 [0.03 to 1.06]	0.00%	0.34	
		Hepatic	3	7	0.54 [-1.22 to 2.3]	94.46%	0.001	
		Nervous	3	5	−0.14 [-0.79 to 0.51]	76.98%	0.001	
		Ocular	1	2	−1.45 [-2.15 to −0.75]	0.00%	0.38	
		Plasma	3	7	−4.03 [-7.58 to −0.49]	97.79%	0.001	
		Renal	1	2	−0.73 [-1.5 to 0.03]	0.00%	0.51	
		Reproductive	4	8	0.2 [-2.39 to 2.79]	96.18%	0.001	
		Respiratory	1	2	−0.81 [-1.58 to −0.04]	0.00%	0.57	
	Administration							
		Aqueous solution						
		Injected intraperitoneally	4	14	−0.28 [-0.73 to 0.16]	71.58%	0.001	
		Oral	8	18	−0.56 [-2.53 to 1.4]	97.71%	0.001	
		Inhaled	1	2	−4.46 [-7.89 to −1.03]	81.22%	0.02	
SOD	Total				−0.69 [-1.05 to −0.34]	81.25%	0.001	
	Animal							
		Fish	2	5	0.31 [-0.4 to 1.01]	83.35%	0.001	
		Mice	3	16	−0.26 [-0.63 to 0.11]	64.86%	0.001	
		Rats	8	22	−159 [-2.28 to −0.89]	81.01%	0.001	
	Molecule							
		B	1	2	−1.37 [-2.35 to −0.4]	0.00%	0.001	
		CBD	2	4	−1.17 [-2.12 to −0.23]	64.06%	0.03	
		O	2	5	−6.72 [-10.9 to −2.54]	92.5%	0.001	
		SYN	5	22	−0.03 [-0.34 to 0.29]	64.98%	0.001	
		THC	5	10	−0.87 [-1.38 to −0.37]	52.31%	0.03	
	Concentration							
		≤2 mg-Kg	9	28	−0.67 [-1.09 to −0.25]	78.37%	0.001	
		>2 mg-Kg y ≤ 7 mg-Kg	5	11	−1.18 [-2.3 to −0.05]	89.95%	0.001	
		>7 mg-Kg y ≤ 30 mg-Kg	1	2	−0.24 [-1.58 to 1.11]	90.79%	0.001	
	Time							
		≤7 days	7	25	−0.03 [-0.33 to 0.27]	0,66	0.001	
		>7 days y ≤ 28 days	6	13	−1.85 [-2.37 to −1.34]	34.64%	0.001	
		>28 days	3	5	−2.88 [-6.88 to 1.13]	98.5%	0.001	
	Tissue							
		Cardiac	1	2	0.83 [0.3 to 1.36]	0.00%	0.44	
		Hepatic	3	7	−0.35 [-0.8 to 0.11]	29.53%	0.21	
		Nervous	3	13	0.16 [-0.15 to 0.47]	41.41%	0.02	
		Ocular	1	2	−1.05 [-1.84 to −0.25]	29.97%	0.23	
		Plasma	3	7	−4.94 [-8.32 to −1.56]	97.18%	0.001	
		Renal	1	2	−1.17 [-1.97 to −0.37]	0.00%	0.84	
		Reproductive	4	8	−1.33 [-1.90 to −0.75]	39.79%	0.13	
		Respiratory	1	2	−0.27 [-2.40 to 1.86]	86.01%	0.01	
	Administration							
		Injected intraperitoneally	5	24	−0.22 [-0.53 to 0.1]	66.26%	0.001	

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Table 6 (*continued*)

	Outcome	Sugroup		No.studies	No.data points	SMD (95% CI)	I^2	P value
		Oral	7	16	−1.42 [-2.06 to −0.78]	69.59%	0.001	
		Inhaled	1	2	−7.78 [-17.27 to 1.72]	92.68%	0.001	
GPx	Total				−1.86 [-3.17 to −0.55]	95.36%	0.01	
	Animal							
		Fish	1	4	0.86 [0.45 to 1.27]	17.27%	0.3	
		Mice	1	2	0.5 [-0.9 to 1.9]	85.64%	0.01	
		Rats	5	11	−3.39 [-4.74 to −2.04]	82.68%	0.001	
	Molecule							
		B	1	2	−0.33 [-1.22 to 0.55]	0.00%	0.75	
		CBD	1	2	−4.3 [-8.03 to −0.57]	78.14%	0.03	
		O	2	5	−4.51 [-6.39 to −2.63]	72.44%	0.02	
		SYN	2	5	0.15 [-1.4 to 1.69]	93.75%	0.001	
		THC	2	3	−0.55 [-2.89 to 1.79]	94.3%	0.001	
	Concentration							
		≤2 mg-Kg	6	13	−1.56 [-2.8 to −0.31]	93.07%	0.001	
		>2 mg-Kg y ≤ 7 mg-Kg	2	4	−3.26 [-8 to 1.48]	98.27%	0.001	
	Time							
		≤7 days	2	6	0.74 [0.26 to 1.22]	58.59%	0.03	
		>7 days y ≤ 28 days	5	10	−3.5 [-5.03 to −1.97]	84.42%	0.001	
		>28 days	1	1	-	-	-	
	Tissue							
		Cardiac	1	2	0.87 [0.21 to 1.53]	34.41%	0.22	
		Hepatic	1	2	0.86 [0.09 to 1.64]	52.51%	0.15	
		Plasma	3	7	−3.14 [-5.58 to −0.7]	95.45%	0.001	
		Reproductive	3	6	−2.47 [−4.15 to −0.79]	82.88%	0.001	
	Administration							
		Injected intraperitoneally	2	6	0.74 [0.26 to 1.22]	58.59%	0.03	
		Oral	4	9	−3.63 [-5.39 to −1.87]	85.99%	0.001	
		Inhaled	1	2	−2.89 [-3.95 to −1.83]	0.00%	0.9	
TAC	Total				0.42 [-0.08 to 0.92]	79.68%		
	Animal							
		Mice	1	10	1.19 [0.82 to 1.56]	33.15%	0.15	
		Rats	3	8	−0.52 [-0.91 to −0.13]	27.9%	0.14	
	Molecule							
		CBG	1	3	0.5 [-1.01 to 0.02]	0.00%	0.81	
		CBD	1	1	-	-	-	
		O	1	1	-	-	-	
		SYN	2	13	0.79 [0.26 to 1.31]	74.96%	0.001	
	Concentration							
		≤2 mg-Kg	4	16	0.26 [-0.24 to 0.76]	77.99%	0.001	
		>2 mg-Kg y ≤ 7 mg-Kg	1	2	1.72 [0.99 to 2.45]	0.00%	0.56	
	Time							
		≤7 days	2	13	0.79 [0.26 to 1.31]	74.96%	0.001	
		>28 days	2	5	−0.51 [-1.13 to 0.11]	51.6%	0.07	
	Tissue							
		Cardiac	1	1	-	-	-	
		Hepatic	2	3	−0.27 [-0.92 to 0.37]	36.56%	0.21	
		Nervous	3	12	0.79 [0.14 to 1.44]	80.83%	0.001	
		Plasma	1	2	−0.38 [-1.01 to 0.24]	0.00%	0.9	
	Administration							
		Injected intraperitoneally	2	13	0.79 [0.26 to 1.31]	74.96%	0.001	
		Oral	2	5	−0.51 [-1.13 to 0.1]	51.6%	0.07	

Table 7
Publication bias Egger's test.

Parameter	Animal Studies p-value	Cellular Studies p-value
ROS	0.0007	0.0014
MDA	<0.0001	0.0698
CAT	0.0413	0.0116
SOD	<0.0001	-
GSH	0.0005	0.0168
GPx	<0.0001	0.0046
TAC	0.7897	-
GR	-	0.1098
GSH/GSSG	-	0.2222

contributing factor may be the suppression of transcription factors such as Nrf2 and nuclear factor kappa B (NF-κB), both of which are central regulators of antioxidant defense mechanisms. Various polyphenols and peptides have been shown to influence these signaling pathways, regulating the antioxidant response. Notably, cannabidiol has been shown to modulate Nrf2 activity and its interaction with NF-κB, especially under high ROS conditions. This modulation may alter the expression of antioxidant enzymes and contribute to the observed reduction in their activity in specific experimental contexts (Atalay Ekiner et al., 2022; Obeme-Nmom et al., 2024).

Recent studies provide further support for the mechanisms proposed in this work. Cannabinoids have been shown to modulate cancer cell metabolism by acting on redox- and stress-related signaling pathways, including ROS-dependent mechanisms, thereby affecting tumor bioenergetics and survival (Sun et al., 2023). Additionally, emerging evidence indicates that cannabinoids can modulate redox-sensitive immune pathways in a dose- and context-dependent manner, with potential beneficial or adverse effects depending on exposure conditions (Hassan et al., 2023).

5. Limitations and considerations

Preclinical animal studies play a pivotal role in elucidating the therapeutic and toxic effects of compounds. However, variations in

animal models, experimental methodologies, and outcome measurements across studies can introduce significant bias. Additionally, our analysis included *in vitro* data, which, while valuable for mechanistic value, often employ divergent cellular models and experimental conditions, thereby limiting their translational relevance to the physiological complexity of a whole organism. The use of a standardized data extraction tool may have inadvertently introduced measurement bias, particularly when integrating heterogeneous datasets. Furthermore, the stringent inclusion criteria required by the scope of this study may have led to the exclusion of potentially relevant research, thereby influencing the overall findings. To comprehensively elucidate cannabinoid-induced redox imbalance, future research should expand its scope to include additional biomarkers, as nitric oxide synthase (NOS) activity and pro-inflammatory interleukins, to better assess the interplay between oxidative stress and inflammatory responses, as well as the broader toxicological effects.

6. Conclusion

This study highlights the complex and variable relationship between cannabis exposure and oxidative stress in preclinical models. Our *in vitro* and *in vivo* findings suggest that various cannabinoids have the potential toincrease ROS production, promote the formation of lipid peroxidation products such as MDA and may impair the activity of key antioxidant enzymes involved in counteracting oxidative stress. However, the high levels of heterogeneity and the marginal effect size observed in certain parameters indicate that these pro-oxidant effects are highly context-dependent rather than a uniform biological response. These results underscore the need for further research to better understand the diverse effects of cannabinoids. While these findings provide mechanistic insights, they should be interpreted as potential biological signals in preclinical settings, and caution is required when extrapolating these results to definitive human health risks.

CRediT authorship contribution statement

A. Sanz-Pérez: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **T. Pérez:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **E. González-Burgos:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yrtph.2026.106067.

Data availability

Data will be made available on request.

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