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Oxidative Damage Induced by Nano-titanium Dioxide in Rats and Mice: a Systematic Review and Meta-analysis

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Abstract

Nano-titanium dioxide is a kind of widely used nanomaterial that exhibits various adverse outcomes. However, the role of oxidative stress in this regard remains controversial. This study aimed to evaluate whether oxidative stress is one of the toxicity mechanisms induced by nano-titanium dioxide in rats and mice model. In this meta-analysis, 64 relevant publications were included through detailed database search. The pooled results showed that nano-titanium dioxide exposure could promote the expression of oxidants, such as malonaldehyde (MDA), 8-hydroxy-2-deoxyguanosine (8-OHdG), superoxide anion (O_2^-), and hydrogen peroxide (H_2O_2). Meanwhile, the levels of antioxidant-related enzymes and molecules, such as superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GPx), and catalase (CAT), were reduced. Subgroup analysis revealed that different intervention routes, exposure periods, exposure dosages, and sample sources could affect the oxidative stress when exposed to nano-titanium dioxide. It was worth noting that the levels of MDA, 8-OHdG, and GSH significantly increased ($P < 0.05$) when the particle size of nano-titanium dioxide was < 10 nm, whereas H_2O_2, SOD, and GPx showed the highest effect at 10–40 nm. This study indicated that nano-titanium dioxide could cause oxidative damage by affecting the levels of enzymes and molecules involved in oxidative stress in rats and mice. And these results could provide a reference for studies of the toxicity mechanism induced by nano-titanium dioxide in the future.

Keywords Nano-titanium dioxide · Oxidative stress · Toxicity mechanism · Meta-analysis · Systematic review

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Introduction

With the development of nanotechnology, nanomaterials have been widely used in various fields [1]. Nano-titanium dioxide was widely used in industrial products, medicines, food, and cosmetics [2, 3], due to its small particle size, large surface area per unit mass, and unique optical and electronic properties [4, 5]. Accordingly, nano-titanium dioxide could enter the environment and contact with people through the respiratory tract, digestive tract, and even injection [6–8].

Traditionally, titanium dioxide fine particles were considered to possess poor solubility and low toxicity particles [9]. However, Pelclova et al. observed nucleic acid and protein oxidation markers increased significantly in exhaled breath condensates of workers exposed to nano-titanium dioxide [10]; another prospective cohort study also suggested that inflammatory markers of workers changed [11]. These researches showed that nano-titanium dioxide could cause damage to human health in occupational environment. Moreover, a large number of

animal studies and cell experiments have proven that the exposure of nano-titanium dioxide at different intervention routes, periods, dosages, sample sources, and particle sizes could cause different degrees of damage to organs in rats and mice, such as the liver, kidney, heart, lung, spleen, testis, and ovary [12–14]. The International Agency for Research on Cancer (IARC) classified the nano-titanium dioxide as possibly carcinogenic to humans (Category 2B) [15]. Therefore, the toxicological mechanism of nano-titanium dioxide should be investigated.

Several studies suggested that high level of inflammatory factors and apoptosis-related genes played an important role in the toxicity of nano-titanium dioxide [16]. Other studies confirmed that oxidative stress plays a major role in this respect [17]. In addition, certain experiments have shown that oxidative stress promoted the expression of inflammatory and apoptotic proteins, thus immensely increased the toxic effects of nano-titanium dioxide [18, 19]. The role of oxidative stress in the toxicity of nano-titanium dioxide should be determined.

There have been a large number of articles exploring the relationship between the toxic effects of nano-titanium dioxide and oxidative stress. Previous studies showed that after exposure to nano-titanium dioxide, the oxidative-antioxidant system experienced an imbalance; the levels of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) were decreased, and the level of malonaldehyde (MDA) was increased in a dose-dependent manner in the liver and brain of rats and mice [20, 21]. However, various studies which used different intervention routes, exposure periods, exposure dosages, sample sources, and particle sizes of nano-titanium dioxide obtained different conclusion, even some studies reached the opposite. Geyu et al. observed that the levels of SOD and GPx in the liver of rats increased after exposure to nano-titanium dioxide [22].

The absence of relevant evidence-based evidence is due to the lack of systematic analysis of the relationship between the toxic effects of nano-titanium dioxide and oxidative stress. Thus, systematic evaluation of these studies about oxidative damage caused by nano-titanium dioxide is necessary. This study conducted a meta-analysis of experimental studies on oxidative damage induced by nano-titanium dioxide to describe the role of oxidative stress in the damage induced by nano-titanium dioxide.

Materials and Methods

Search Strategy

A comprehensive literature about toxicity of nano-titanium dioxide has been performed between January 1, 1980, and November 3, 2018. The studies were searched on Pubmed, Web of science, Embase, CNKI, VIP, WanFang, SinoMed databases, restricting to English and Chinese, with keywords included (nano-titanium dioxide OR nano-TiO_2) AND (rats OR mice) AND (oxygenation OR oxidant). The full texts were reviewed and articles that met the research requirements were included in this meta-analysis.

Eligibility Criteria

Eligibility criteria for the meta-analysis were as follows: (1) randomized controlled adult rats or mice experiments and studies published in English and Chinese; (2) no restriction on strain and gender; (3) the experimental group was considered to be exposed to nano-titanium dioxide, the control group was the blank control group, and both of them used the oxidative damage index as the outcome; (4) the highest dosage and the longest experimental period were selected for the

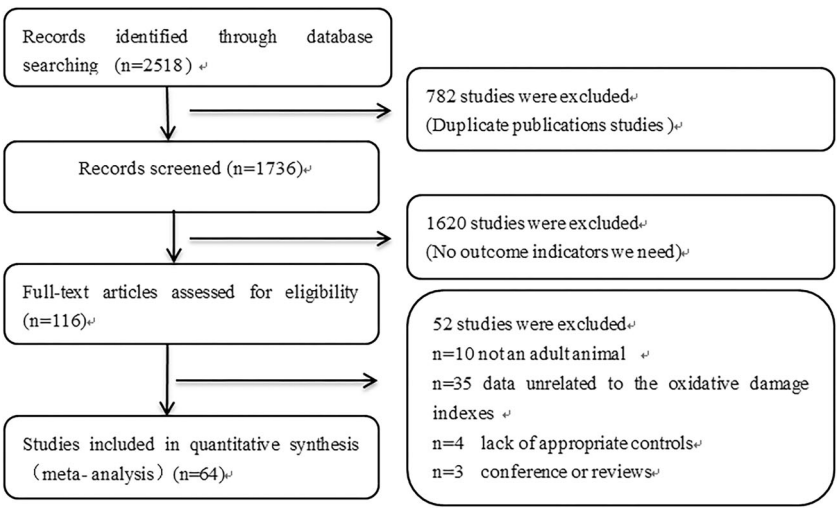

Fig. 1 Flowchart of the search strategy. The meta-analysis included rats and mice studies investigating the oxidative effect of nano-titanium dioxide

Table 1 Characteristics of the studies included in the meta-analysis

Study	Year	Language	Route	Period (days)	Dosage (mg)	Sample source	Size (nm)	Indexes
Abdou, K H [23]	2018	English	gavage	≤ 90	> 100	kidney	> 40	1,7,8,9
Alidadi, H [24]	2018	English	gavage	≤ 7	> 100	liver	unknown	2,7,10
Al-Rasheed [25]	2013	English	gavage	≤ 7	> 100	kidney	> 40	8
Elnagar A [26]	2018	English	gavage	≤ 90	> 100	testis	10-40	2,8
Attia, H F [27]	2013	English	gavage	> 90	> 100	liver	> 40	2,8
Canli [28]	2017	English	gavage	≤ 30	≤100	serum	10-40	7,8,9,10
Chen aijie [29]	2016	Chinese	gavage	≤ 30	≤100	others	> 40	2,7,8,9
Chen he [30]	2012a	Chinese	skin	≤ 7	≤10	serum	10-40	2,4,7,10
Chen he [30]	2012b	Chinese	skin	≤ 7	≤10	serum	> 40	2,4,7,10
Cui yaling [17]	2012	Chinese	gavage	≤ 90	≤100	liver	≤10	2,5,6
Duan yanmei [31]	2011	Chinese	gavage	≤ 90	> 100	others	≤10	2,5,6
El-Shenawy [32]	2016	English	injection	≤ 30	≤100	liver	> 40	1,8
Fan zhiyi [33]	2007	Chinese	R tract	≤ 90	> 100	testis	10-40	2,7
Fadda [34]	2018	English	gavage	≤ 30	> 100	kidney	unknown	8
Grissa [35]	2017	English	gavage	≤ 90	≤100	serum	≤10	2,7,10
Gui suxin [36]	2014	Chinese	gavage	≤ 90	≤10	kidney	≤10	2,4,5,6
Gaoguo dong [37]	2013	Chinese	gavage	≤ 90	≤10	testis	≤10	4,5,6,10
Hassanein [38]	2017	English	gavage	≤ 90	> 100	serum	10-40	1,2,8
Hassanein [39]	2018	English	gavage	≤ 30	> 100	serum	unknown	2,7
Hu renping [40]	2013	Chinese	gavage	≤ 90	≤100	others	≤10	5,6
Jafar [41]	2018	English	gavage	≤ 90	> 100	liver	10-40	2,7,8,9,10
Jia [20]	2017	English	gavage	≤ 90	≤100	liver	≤10	2,5,6
Jin yali [42]	2014	Chinese	gavage	≤ 7	≤100	serum	10-40	2,7
Khorsandi [43]	2015	English	gavage	≤ 30	> 100	liver	> 40	2,7,9
Khorsandi [44]	2017	English	gavage	≤ 90	> 100	testis	10-40	2,7,10
Li yawei [45]	2009	Chinese	gavage	≤ 7	≤10	liver	> 40	2,7,9
Caixia Yu [46]	2018	Chinese	R tract	> 90	≤10	others	> 40	4
Linlin [47]	2017	Chinese	gavage	≤ 30	≤100	kidney	≤10	2,7,9
Liu huangl [19]	2011	Chinese	R tract	≤90	≤100	liver	10-40	2,7,8
Liu huiting [48]	2014	Chinese	injection	≤30	> 100	liver	≤10	2,5,6,7,8,9,10
Liu longlong [49]	2018	Chinese	gavage	≤30	≤100	kidney	≤10	2,7,9
Liu zhiming [50]	2016	Chinese	skin	≤90	> 100	serum	10-40	3
Martins [51]	2017	English	gavage	≤90	≤10	serum	> 40	8,9,10
Meena, R [21]	2015	English	injection	≤30	≤100	testis	10-40	2,7,9,10
Meena [52]	2015	English	injection	≤30	≤100	others	10-40	2,6,7,9,10
Morgan, A [53]	2017	English	gavage	≤90	≤100	kidney	≤10	2,7,8,9
Morgan, A [54]	2018	English	gavage	≤90	> 100	liver	≤10	2,7,8,9
Morgan, AM [55]	2017	English	gavage	≤90	≤100	testis	unknown	2,8,10
Niu linhong [56]	2015	Chinese	gavage	≤7	> 100	liver	> 40	2,7,9
Rizk [57]	2017	English	injection	≤90	> 100	liver	10-40	6,8
Shahin [16]	2017	English	gavage	≤30	≤100	testis	10-40	2,8
Shakeel [6]	2016	English	injection	≤30	> 100	liver	10-40	1,7,8, 10
Sheng, L [58]	2013	English	gavage	≤90	≤10	others	≤10	2,4,5,6,7,10
Shrivastava [7]	2014	English	gavage	≤30	> 100	liver	> 40	3,7,9,10
Shukla [59]	2014	English	gavage	≤30	≤100	liver	10-40	2,8
Song gunglin [60]	2017	English	gavage	≤30	≤100	testis	≤10	2,7
Song mingfen [61]	2015	Chinese	injection	≤7	> 100	liver	≤10	4
Sun qingqing [62]	2014	Chinese	R tract	≤90	≤10	others	≤10	2,5,6,8
Sun, Q [63]	2012	English	R tract	≤90	≤10	others	≤10	2,5,6,8

Table 1 (continued)

Study	Year	Language	Route	Period (days)	Dosage (mg)	Sample source	Size (nm)	Indexes
Sun Q [64]	2012	English	gavage	≤90	≤10	others	≤10	2,5,6
Tian junzhi [65]	2014	Chinese	injection	≤7	>100	serum	>40	7,9
Wang shu [66]	2009	Chinese	R tract	≤7	≤100	liver	≤10	2,7,9
Wang wenb [67]	2014	Chinese	gavage	≤30	>100	serum	10-40	2,7,9
Wa wenb [68]	2014	Chinese	gavage	≤90	≤100	serum	10-40	2,7,9
Wang, J [69]	2008	English	gavage	≤30	>100	others	>40	2,3,6,7,8,9,10
Wang, Y [70]	2013	English	gavage	≤30	>100	serum	>40	8,9
Wangyun [71]	2014	Chinese	gavage	≤30	>100	liver	>40	2,7,8,9
Chang XH [72]	2014	Chinese	R tract	≤30	≤100	others	10-40	2,7,9,10
YS, L [8]	2018	English	R tract	≤90	≤10	others	10-40	3,6
Yu, X [73]	2014	English	R tract	>90	≤100	serum	≤10	3
Zhang ting [74]	2008	Chinese	R tract	≤7	≤100	liver	≤10	2,7,9
Zhang wenjia [75]	2009a	Chinese	injection	≤30	≤10	serum	≤10	2,7,8
Zhang wenjia [75]	2009b	Chinese	injection	≤30	≤10	serum	10-40	2,7,8
Zhang wenjia [75]	2009c	Chinese	injection	≤30	≤10	serum	>40	2,7,8
Zhao xiaoyu [76]	2013	Chinese	R tract	≤7	>100	liver	>40	2,7,9
Zhaoy, J [77]	2010	English	injection	≤30	>100	kidney	≤10	2,5,6
Zhu yue [78]	2015	Chinese	R tract	≤7	≤10	liver	10-40	2,7,9

R tract:Respiratory tract. 1 LPO, 2 MDA, 3 ROS, 4 8-OHdG, 5 O_2^-, 6 H_2O_2, 7 SOD, 8 GSH, 9 GPx,10 CAT

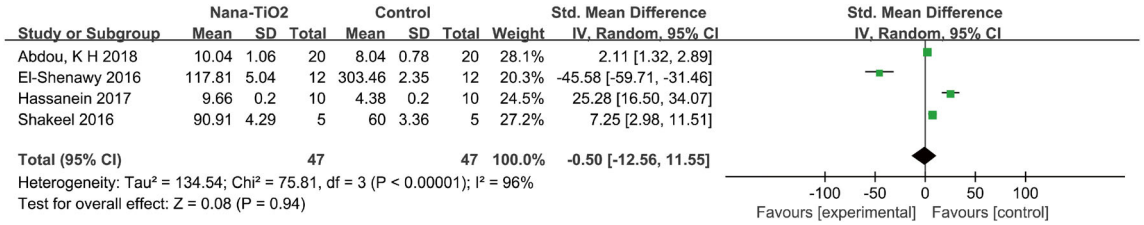

Fig. 2 Effect of nano-titanium dioxide on LPO level. Forest plot showed the effect of nano-titanium dioxide treatment on LPO in the treated and control groups. Nano-titanium dioxide treatment could not change the value of LPO (95% CI, − 12.56–11.55, Z = 0.080, P = 0.94). SMD, standardized mean difference; IV, independent variable; 95% CI, 95% confidence interval; SD, standard deviation

analysis from a range of nano-titanium dioxide dosages and periods. These oxidative damage indexes included lipid peroxidation (LPO), MDA, reactive oxygen species (ROS), 8-hydroxy-2-deoxyguanosine (8-OHdG), superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), SOD, glutathione (GSH), GPx, and CAT. When response was not received from the authors, the numerical values were measured from the graphs by a digital ruler.

The required instructions for the qualified literature comprised the following: (1) biological model: animal species and genders; (2) study design: intervention route, exposure period, exposure dosage, sample source, and particle size of nano-titanium dioxide (less than or equal to 100 nm); (3) main results (oxidative damage indexes): LPO, MDA, ROS, 8-OHdG, O_2^-, H_2O_2, SOD, GSH, GPx, and CAT. A total of 64 published papers were included in this study.

Table 2 Pooled SMDs of oxidants and antioxidants

Indicators	SMD	95% CI		Z	P Value
LPO	−0.50	−12.56	11.55	0.08	0.94
MDA	5.52	4.53	6.52	10.86	<0.01
ROS	1.61	−0.33	3.55	1.62	0.10
8-OHdG	6.04	2.95	9.13	3.83	<0.01
O_2^-	12.28	9.19	15.37	7.79	<0.01
H_2O_2	7.33	4.09	10.57	4.43	<0.01
SOD	−3.31	−4.05	−2.56	8.71	<0.01
GSH	−3.63	−5.20	−2.05	4.52	<0.01
GPx	−3.27	−4.27	−2.28	6.46	<0.01
CAT	−3.03	−4.48	−1.58	4.09	<0.01

SMD, standardized mean difference; 95% CI, 95% confidence interval; Z, test for overall effect, the Z-test result of the combined effect amount; P, the Z-test of the combined effect amount is judged whether it is statistically significant

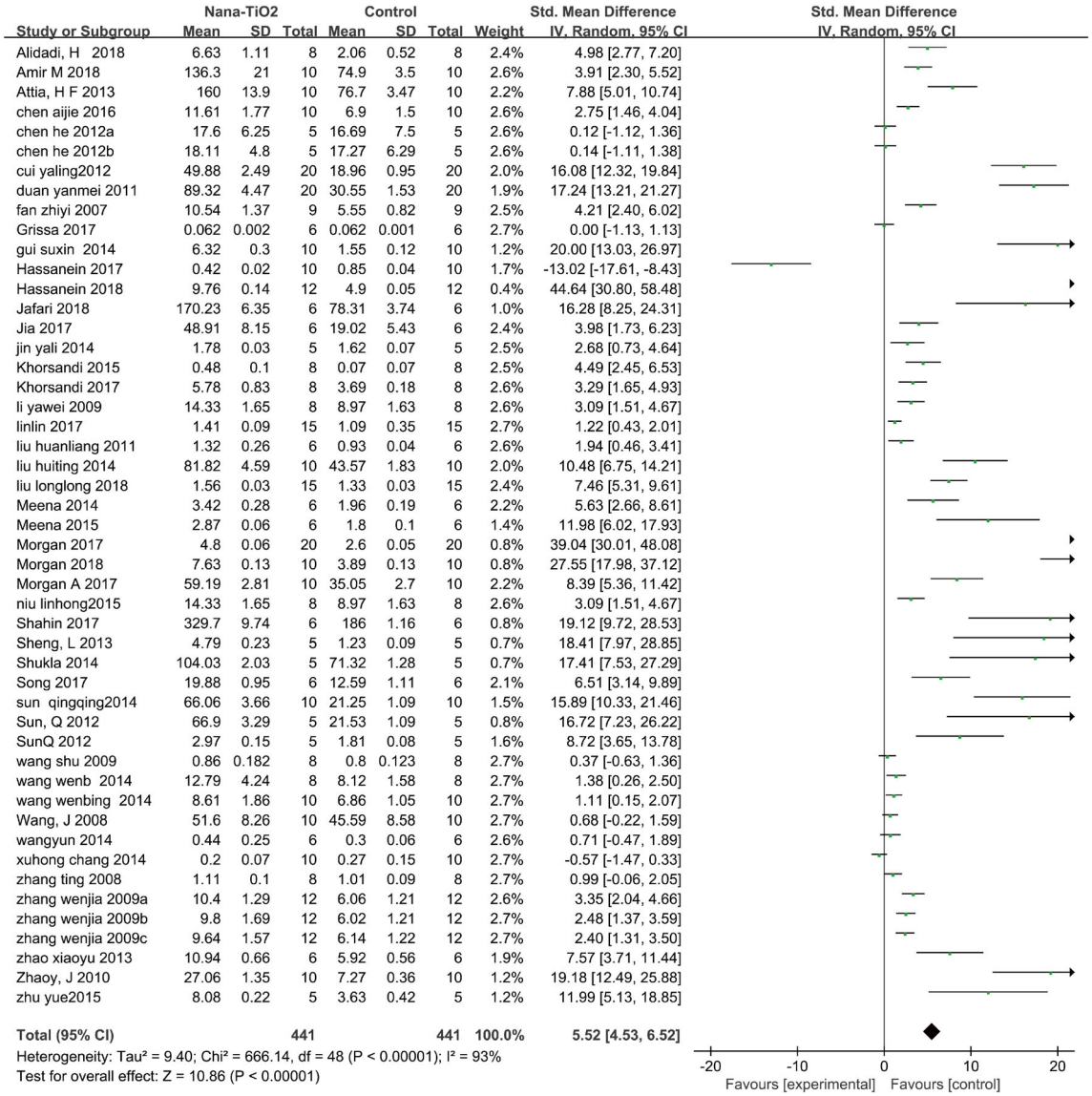

Fig. 3 Effect of nano-titanium dioxide on MDA level. Forest plot showed the effect of nano-titanium dioxide treatment on MDA in the treated and control groups. Nano-titanium dioxide treatment could promote the level of MDA (95% CI, 4.53–6.52, $Z = 10.86$, $P < 0.00001$). SMD, standardized mean difference; IV, independent variable; 95% CI, 95% confidence interval; SD, standard deviation

Exclusion Criteria

Exclusion criteria were as follows: (1) duplicate publications, (2) title and abstract that were irrelevant to nano-titanium dioxide, (3) usage of non-adult animals (less than 2 months or 8 weeks in rats and 6 weeks for mice), (4) data unrelated to the oxidative damage indexes, (5) lack of appropriate controls, (6) conference or reviews.

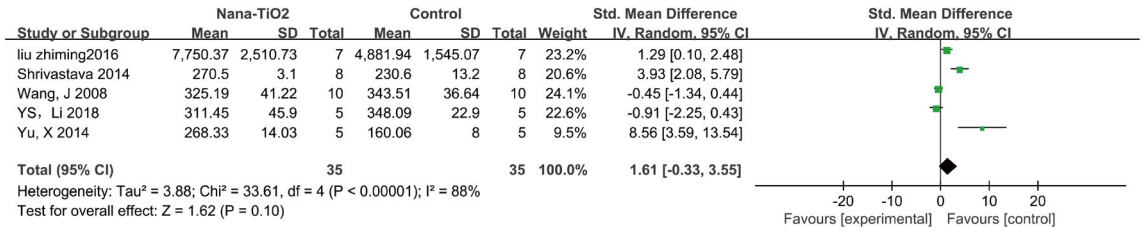

Fig. 4 Effect of nano-titanium dioxide on ROS level. Forest plot showed the effect of nano-titanium dioxide treatment on ROS in the treated and control groups. Nano-titanium dioxide treatment could not change the level of ROS (95% CI, − 0.33–3.55, $Z = 1.62$, $P = 0.10$). SMD, standardized mean difference; IV, independent variable; 95% CI, 95% confidence interval; SD, standard deviation

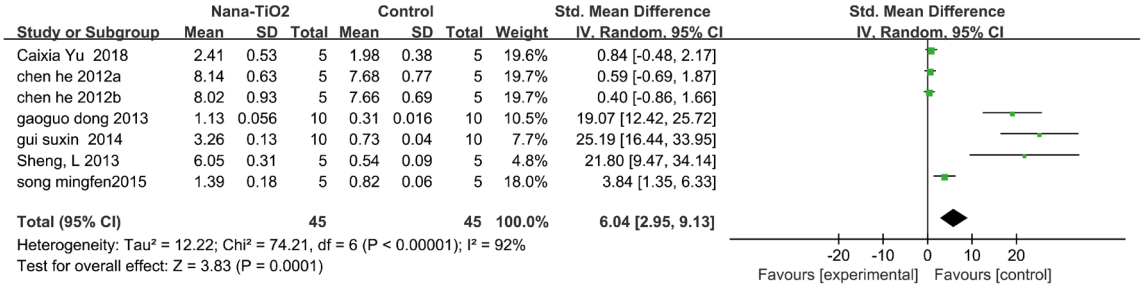

Fig. 5 Effect of nano-titanium dioxide on 8-OHdG level. Forest plot showed the effect of nano-titanium dioxide treatment on 8-OHdG in the treated and control groups. Nano-titanium dioxide treatment could promote the level of 8-OHdG (95% CI, 1.74–5.93, $Z = 3.58$, $P = 0.0003$). SMD, standardized mean difference; IV, independent variable; 95% CI, 95% confidence interval; SD, standard deviation

Data Extraction

The data were extracted independently from each article by two members of the research. The following information were extracted from the complete manuscript of each qualified study: publication characteristics (title of the study, first author, publication date, and journal/magazine), data on the experimental and control groups (n, mean ± SD), subject characteristics (species, gender), intervention route, exposure period, exposure dosage, sample source, and particle size of nano-titanium dioxide. The discrepancies in the information were decided

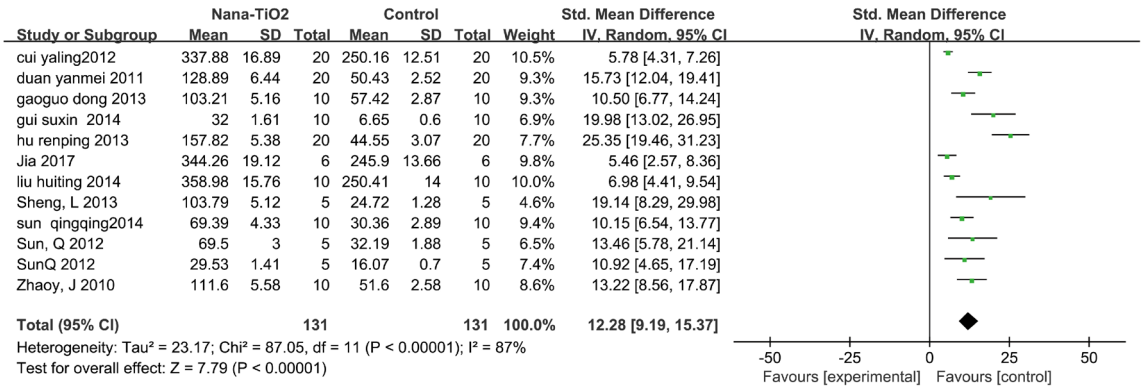

Fig. 6 Effect of nano-titanium dioxide on O_2^- level. Forest plot showed the effect of nano-titanium dioxide treatment on O_2^- in the treated and control groups. Nano-titanium dioxide treatment could promote the level of O_2^- (95% CI, 9.19–15.37, $Z = 7.79$, $P < 0.00001$). SMD, standardized mean difference; IV, independent variable; 95% CI, 95% confidence interval; SD, standard deviation

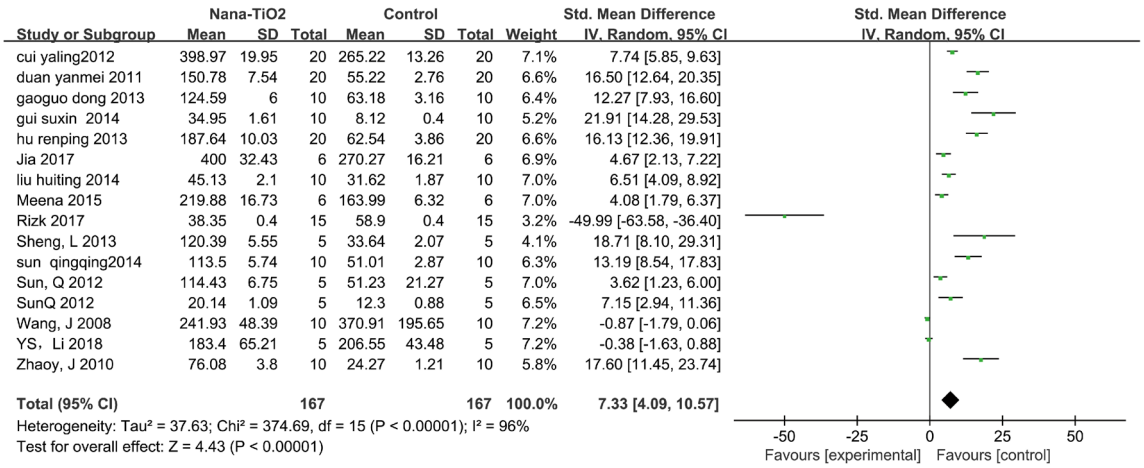

Fig. 7 Effect of nano-titanium dioxide on H_2O_2 level. Forest plot showed the effect of nano-titanium dioxide treatment on H_2O_2 in the treated and control groups. Nano-titanium dioxide treatment could promote the level of H_2O_2 (95% CI, 4.09–10.57, $Z = 4.43$, $P < 0.00001$). SMD, standardized mean difference; IV, independent variable; 95% CI, 95% confidence interval; SD, standard deviation

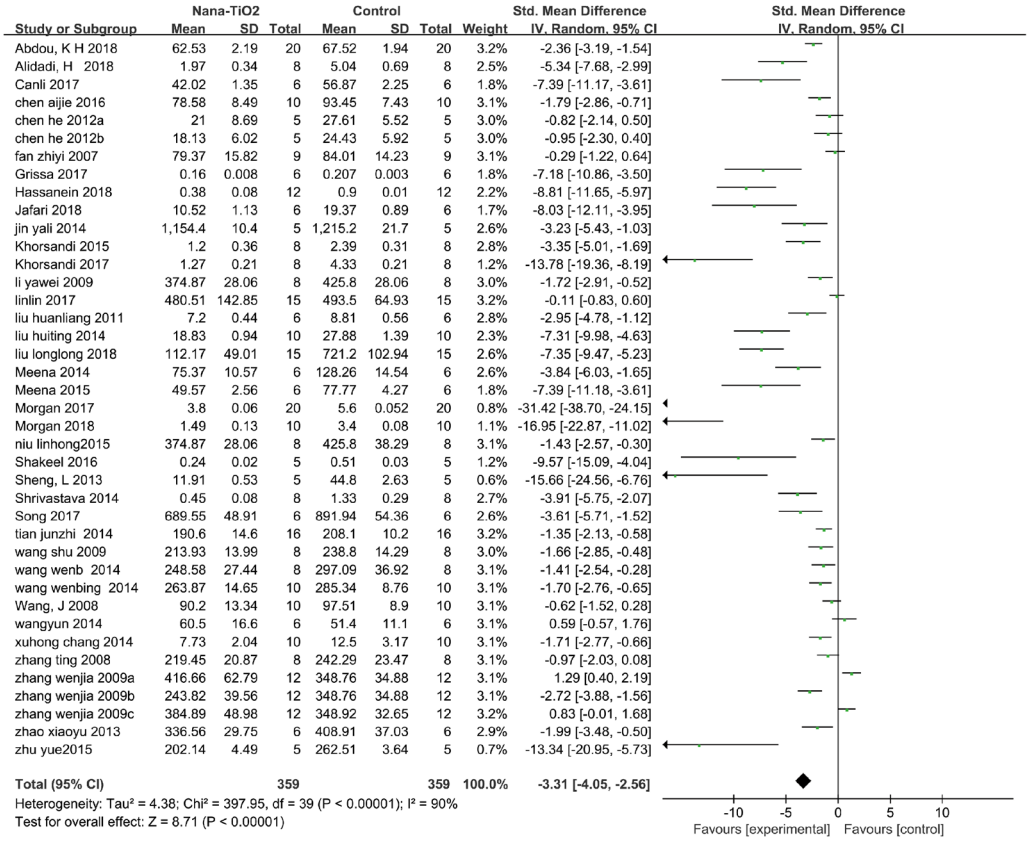

Fig. 8 Effect of nano-titanium dioxide on SOD level. Forest plot showed the effect of nano-titanium dioxide treatment on SOD in the treated and control groups. Nano-titanium dioxide treatment could reduce the level of SOD (95% CI, − 4.05 to − 2.56, $Z = 8.71$, $P < 0.00001$). SMD, standardized mean difference; IV, independent variable; 95% CI, 95% confidence interval; SD, standard deviation

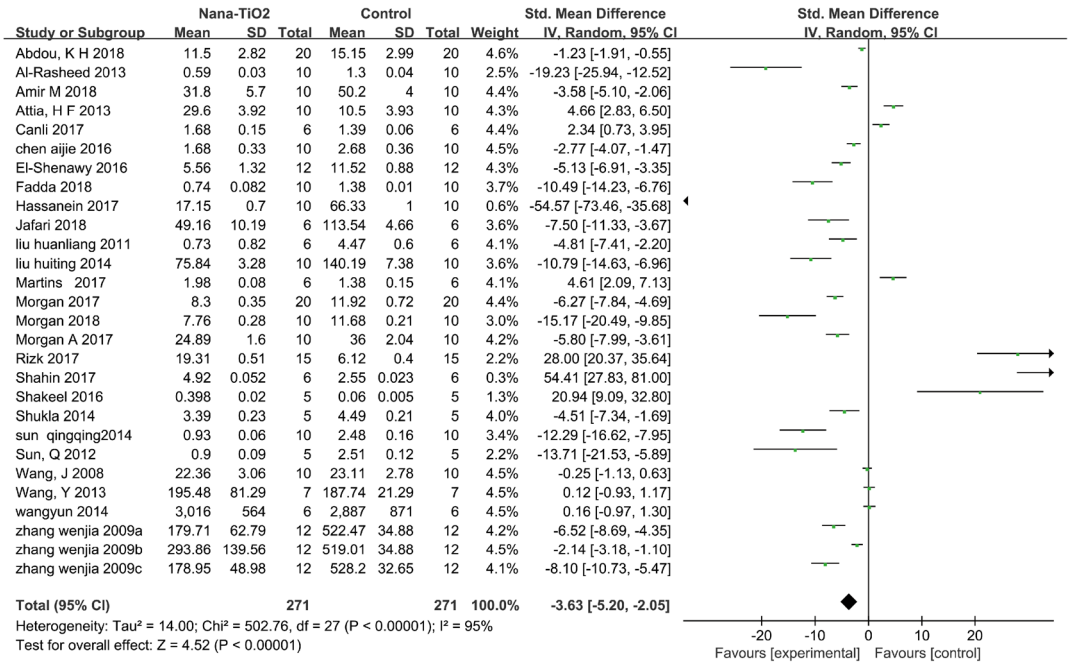

Fig. 9 Effect of nano-titanium dioxide on GSH level. Forest plot showed the effect of nano-titanium dioxide treatment on GSH in the treated and control groups. Nano-titanium dioxide treatment could reduce the level of GSH (95% CI, − 5.20 to − 2.05, $Z = 4.52$, $P < 0.00001$). SMD, standardized mean difference; IV, independent variable; 95% CI, 95% confidence interval; SD, standard deviation

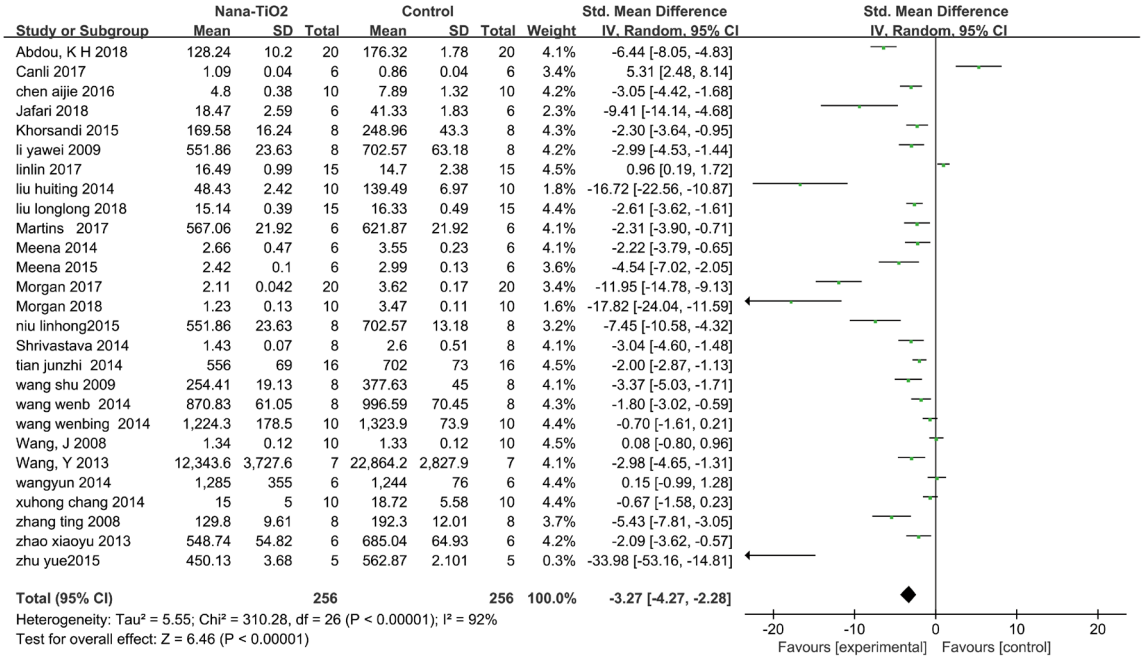

Fig. 10 Effect of nano-titanium dioxide on GPx level. Forest plot showed the effect of nano-titanium dioxide treatment on GPx in the treated and control groups. Nano-titanium dioxide treatment could reduce the level of GPx (95% CI, − 4.27 to − 2.28, $Z = 6.46$, $P < 0.00001$). SMD, standardized mean difference; IV, independent variable; 95% CI, 95% confidence interval; SD, standard deviation

the results by Prof. LJM, when two reviewers held different opinions.

Data Analysis

The mean values for each outcome indicator differed between the experimental and control groups. Significant heterogeneity was detected ($P < 0.05$, $I^2 > 75\%$). Therefore, a random effects model was applied for the meta-analysis. Subgroup analysis was performed to determine the source of heterogeneity. Continuous variables were estimated as standardized mean differences (SMD) with 95% confidence intervals (95% CI) between the nano-titanium dioxide treated and control animals. All reported P values were two-sided and a significance level of 0.05 was used. Subgroup analyses were performed based on the intervention route (respiratory tract, gavage, and injection), exposure period (≤ 7, ≤ 30, and > 30 days), exposure dosage (≤ 10, ≤ 100, > 100 mg), sample source (serum, liver, kidney), and nano-titanium dioxide particle size (< 10, 10–40, > 40 nm), to determine the factors

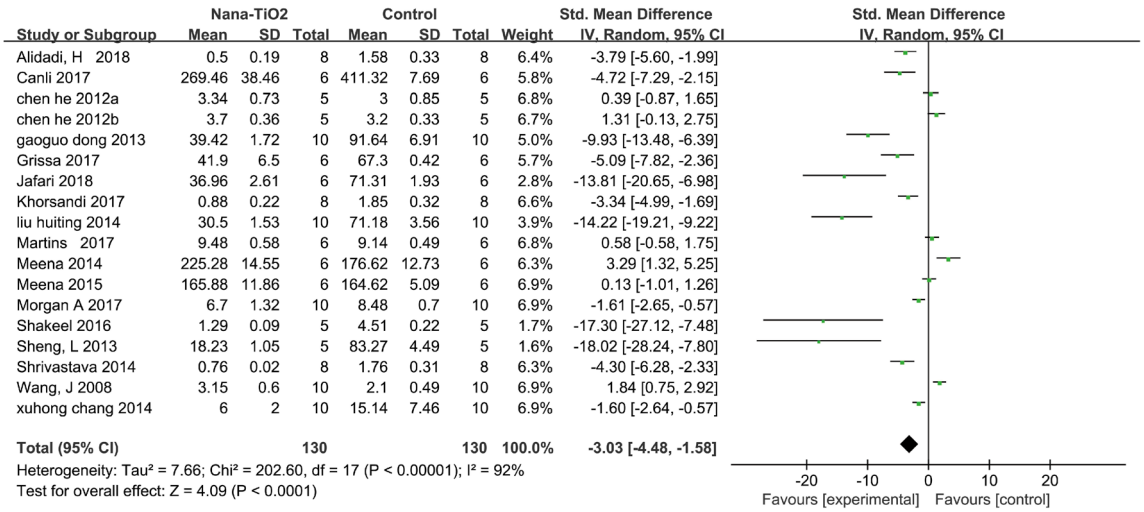

Fig. 11 Effect of nano-titanium dioxide on CAT level. Forest plot showed the effect of nano-titanium dioxide treatment on CAT in the treated and control groups. Nano-titanium dioxide treatment could reduce the level of CAT (95% CI, − 4.48 to − 1.58, $Z = 4.09$, $P < 0.0001$). SMD, standardized mean difference; IV, independent variable; 95% CI, 95% confidence interval; SD, standard deviation

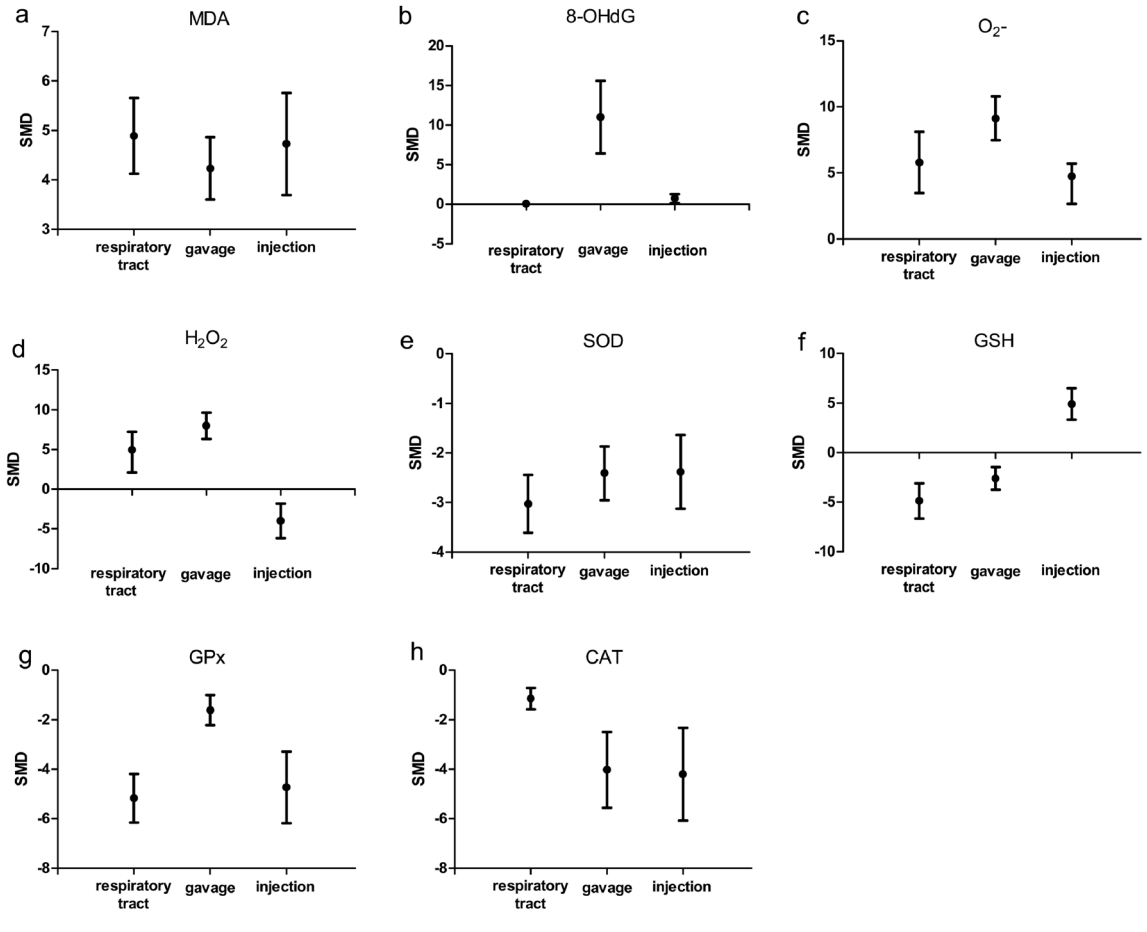

Fig. 12 Subgroup analysis determined the effect of the nano-titanium dioxide intervention route on oxidative damage. SMD, standardized mean difference. Nano-titanium dioxide could promote the expression of 8-OHdG, O_2^-, H_2O_2, and GPx through gavage tract ($P < 0.05$, b, c, d, g). The SMD of GSH and CAT administered through injection and the respiratory tract showed the highest level, respectively ($P < 0.05$, f, h). No statistical difference was detected for other indicators. Data were expressed as SMD and 95% CI

associated with the differences among study results in the outcome indicators. For additional insight, meta-regression was used to analyze the sources of heterogeneity. Publication bias was explored using funnel plots. Sensitivity analysis was performed with one study removed at a time to assess whether the results were remarkably affected by a single study. All analyses were implemented in Review Manager Version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) and Stata 12.0 (StataCorp., College Station, Texas, TX, USA, 2011).

Result

Study Characteristics

Using our search strategy, 2518 references were initially included (Fig. 1), and screened 64 studies (Table 1) were evaluated based on the exclusion criteria for the final meta-analysis. All the subjects were restricted to rats and mice, and the type and extent of oxidative damage caused by nano-titanium dioxide to animal models were investigated (Fig. 2).

Effect of Nano-titanium Dioxide on Oxidants and Antioxidants

In this meta-analysis, 64 papers were identified to measure the changes in 10 indicators and calculate the oxidation and antioxidant levels in rats and mice after exposure to nano-titanium dioxide. Summary analysis showed the levels of oxidants, such as MDA, 8-OHdG, O_2^-, and H_2O_2, which were more highly expressed in the experimental group (nano-titanium dioxide treatment) than the control (Table 2). The results were described in detail in Figs. 3, 4, 5, 6, and 7. In the six evaluations of oxides, the SMD values were showed to be greater than 1, and analysis of MDA, 8-OHdG, O_2^-, and H_2O_2 was associated

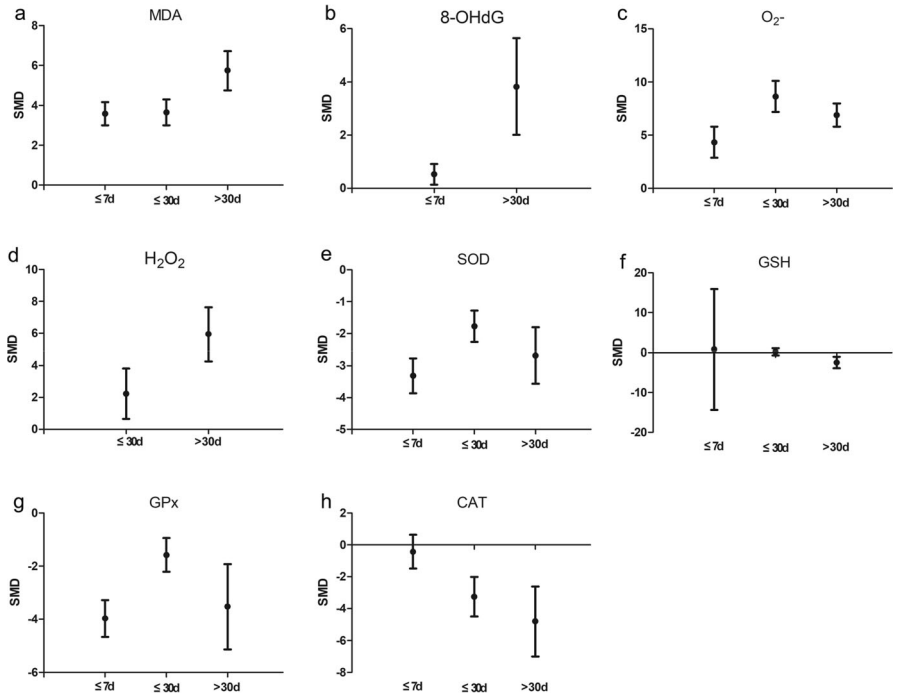

Fig. 13 Subgroup analysis determined the effect of the nano-titanium dioxide period on oxidative damage. SMD, standardized mean difference. The promotive effect of MDA, 8-OHdG, and H_2O_2 in exposure period > 30 days is higher than ≤ 30 days ($P < 0.05$, a, b, d); the O_2^- was showed lowest level which exposure period ≤ 7 days ($P < 0.05$, c), and the SOD and GPx were showed highest level which exposure period ≤ 7 days ($P < 0.05$, e, g). No statistical difference was detected for the other indicators. Data were expressed as SMD and 95% CI

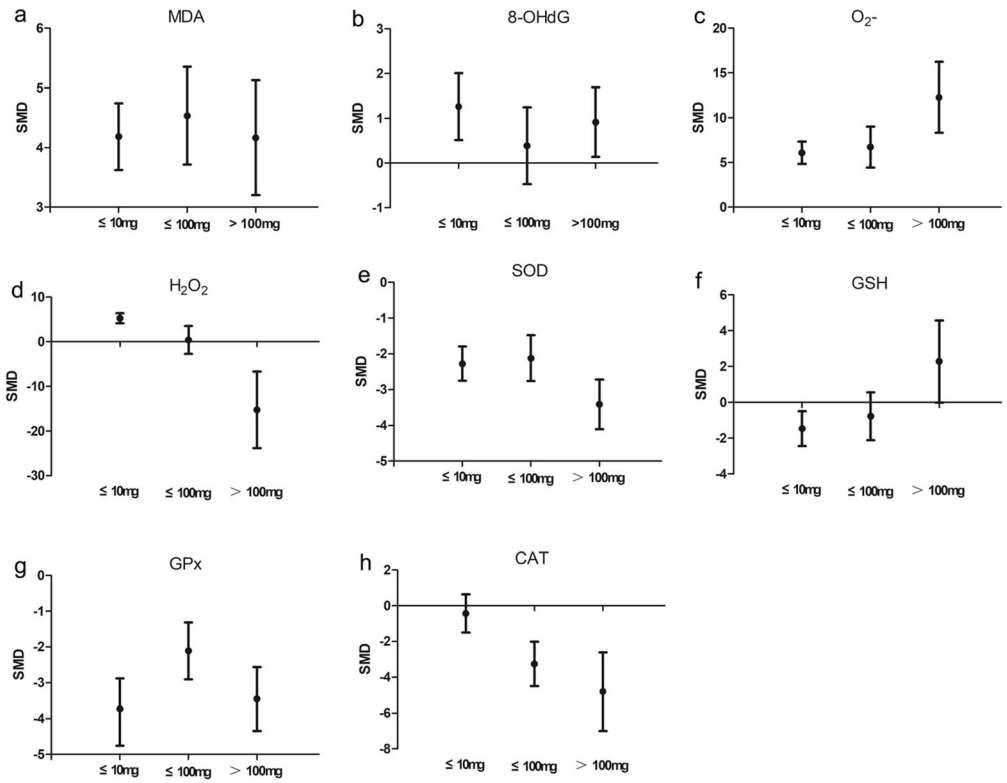

Fig. 14 Subgroup analysis determined the effect of the nano-titanium dioxide dosage on oxidative damage. SMD, standardized mean difference. The absolute SMD of O_2^-, H_2O_2 were showed highest level in exposure dosage > 100 mg ($P < 0.05$, c, d). No statistical difference was detected for the other indicators. Data were expressed as SMD and 95% CI

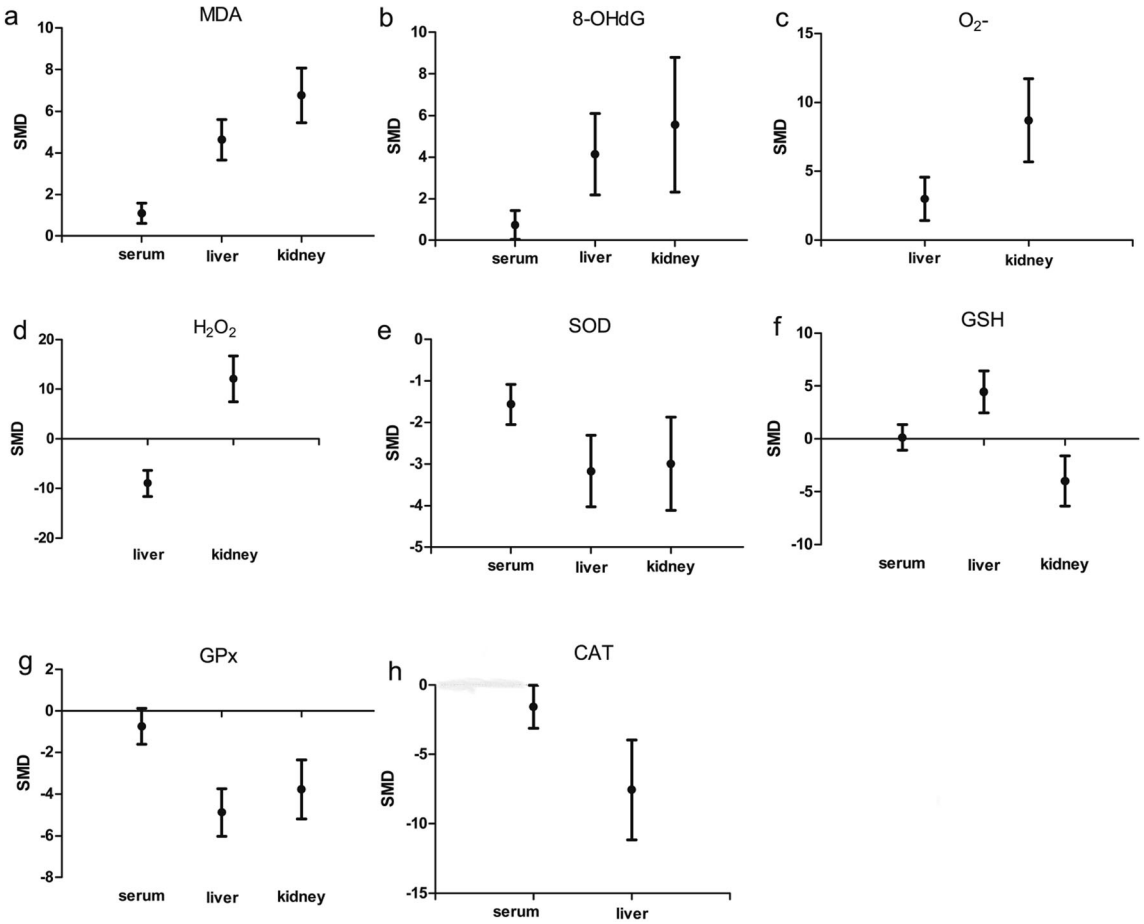

Fig. 15 Subgroup analysis determined the effect of the nano-titanium dioxide sample sources on oxidative damage. SMD, standardized mean difference. The absolute SMD values of MDA, 8-OHdG, SOD, and CAT indicated that tissue samples were higher than serum samples ($P < 0.05$, a, b, e, h); the SMD values of O_2^-, H_2O_2 indicated that kidney samples were higher than liver samples ($P < 0.05$, c, d); the GSH showed the opposite trend ($P < 0.05$, f). No statistical difference was detected for the other indicators. Data were expressed as SMD and 95% CI

with significant heterogeneity ($P < 0.01$). For the antioxidant levels, pooled analysis of the indicators showed that SOD, GSH, GPx, and CAT levels were lower in the experimental group (nano-titanium dioxide treatment) than the control (Table 2). The results were described in detail in Figs. 8, 9, 10, and 11. In the four assessments of antioxidants, the SMD values were showed to be less than − 2, and analysis of each molecule was associated with significant heterogeneity ($P < 0.01$).

Subgroup Analysis

The subgroup analysis explored the source of heterogeneity by intervention route (respiratory tract, gavage, and injection), period of nano-titanium dioxide treatment (≤ 7, ≤ 30, > 30 days), nano-titanium dioxide dosage (≤ 10, ≤ 100, > 100 mg), sample source (serum, liver, kidney), and particle size of nano-titanium dioxide (< 10, 10–40, > 40 nm).

The SMD values of 8-OHdG, O_2^-, H_2O_2, and GPx indicated that gavage tract administration was higher than injection ($P < 0.05$, see Fig. 12b, c, d, g), whereas those of GSH and CAT through injection and respiratory tract administration showed the highest level, respectively ($P < 0.05$, see Fig. 12f, h).

The SMD values of MDA, 8-OHdG, and H_2O_2 indicated that it yielded higher levels at an exposure period > 30 days than ≤ 30 or ≤ 7 days ($P < 0.05$, see Fig. 13a, b, d); the SMD value of O_2^- at an exposure period ≤ 7 days showed the lowest level ($P < 0.05$, see Fig. 13c), and the SMD values of SOD and GPx at an exposure period ≤ 7 days showed the highest level ($P < 0.05$, see Fig. 13e, g).

The absolute SMD values of O_2^-, H_2O_2 at exposure dosage > 100 mg showed the highest level ($P < 0.05$, see Fig. 14c, d).

The absolute SMD values of MDA, 8-OHdG, SOD, and CAT indicated that tissue samples were higher than serum samples ($P < 0.05$, see Fig. 15a, b, e, h). The SMD

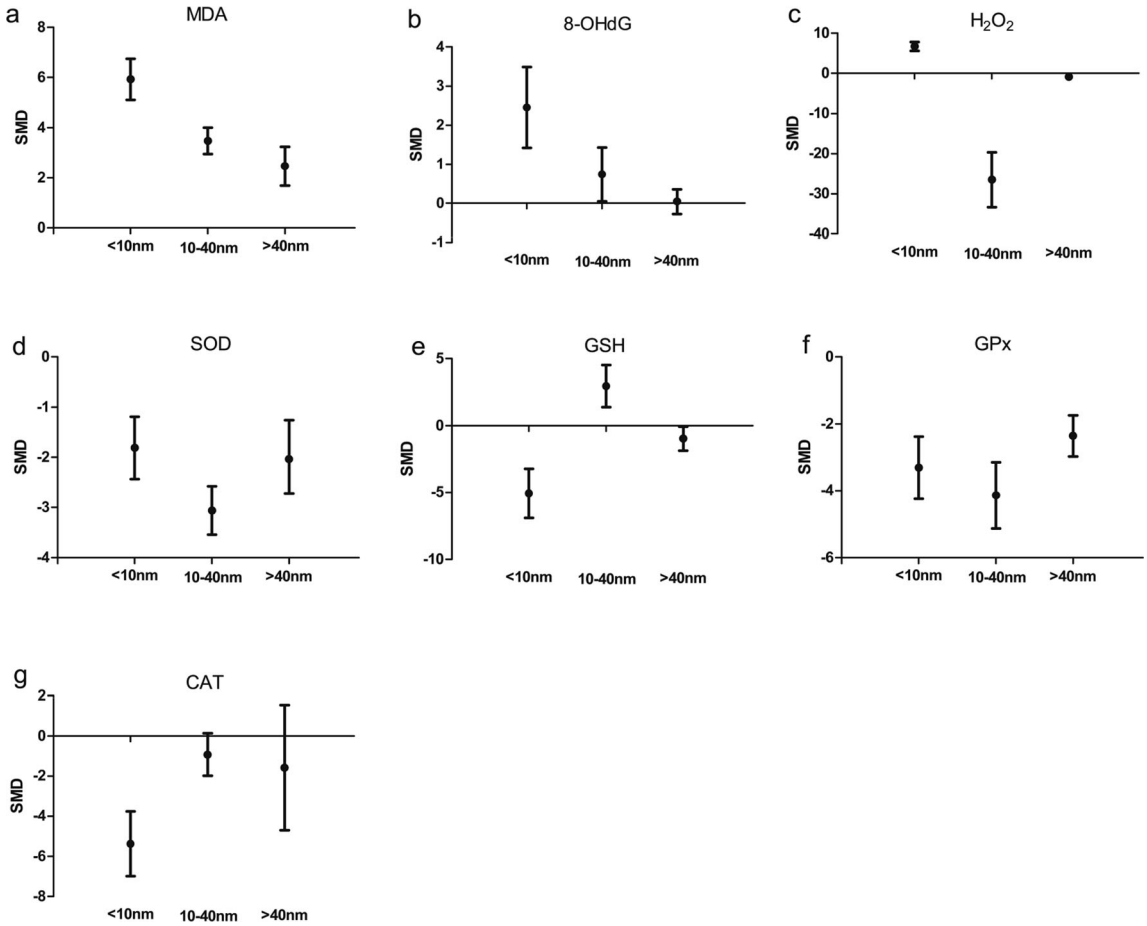

Fig. 16 Subgroup analysis determined the effect of the nano-titanium dioxide particle size on oxidative damage. SMD, standardized mean difference. The absolute SMD values of MDA, 8-OHdG, and GSH particle size < 10 nm were higher than < 40 nm or 10–40 nm ($P < 0.05$, a, b, e), and the absolute SMD value of H_2O_2, SOD, and GPx showed the highest effect at 10–40 nm ($P < 0.05$, c, d, f). No statistical difference was detected for the other indicators. Data were expressed as SMD and 95% CI

values of O_2^- and H_2O_2 indicated that their levels were higher in kidney samples than liver samples ($P < 0.05$, see Fig. 15c, d), and the GSH showed the opposite trend ($P < 0.05$, see Fig. 15f).

The absolute SMD values of MDA, 8-OHdG, and GSH indicated that particle size < 10 nm were higher than < 40 or 10–40 nm ($P < 0.05$, see Fig. 16a, b, e), whereas those of H_2O_2, SOD, and GPx showed the highest effect at 10–40 nm ($P < 0.05$, see Fig. 16c, d, f).

Meta-regression

The meta-regression analysis showed that intervention route was significantly associated with the differences in H_2O_2, GSH, and GPx. The experiment period was significantly associated with the differences in O_2^-, H_2O_2, and GPx. The dosage was significantly associated with the differences in GPx and CAT. Meanwhile, MDA, O_2^-, H_2O_2, GSH, and GPx significantly varied in different sample sources. Nano-titanium dioxide particle size was significantly associated with the differences in MDA, H_2O_2, and CAT (Table 3).

Sensitivity Analysis

Sensitivity analysis was implemented to evaluate the robustness of our results. All results were located on the two sides of the midline with no notable deviation (Fig. 17). These results indicate that no individual study influenced the combined results.

Publication Bias

The funnel plot for the studies revealed that all indicators except GSH exhibited publication bias (Egger's test, $P < 0.05$). Thus, a trim-and-fill method was used to identify and correct the asymmetry of funnel plot caused by publication bias (Fig. 18).

Table 3 Results of the univariate meta-regression analysis

Indicators	Coefficient	SE	*t*	*P*	95% CI	
					Lower limits	Upper limits
MDA						
Route	− 0.68	0.61	− 1.12	0.264	− 1.89	0.52
Period	0.74	0.6	1.23	0.221	− 0.45	1.94
Dosage	0.24	0.63	0.38	0.703	− 1	1.49
Samples	1.06	0.3	3.44	0.001	0.45	1.67
Size	− 1.95	0.67	− 2.89	0.004	− 3.29	− 0.61
O_2^-						
Route	− 1.97	1.3	− 1.52	0.137	− 1.6	0.65
Period	4.38	1.66	2.64	0.011	1.03	7.74
Dosage	2.02	1.28	1.58	0.122	− 0.56	4.61
Samples	1.55	0.62	2.49	0.016	0.298	2.81
H_2O_2						
Route	− 10.6	3.2	− 3.3	0.002	− 17.01	− 4.18
Period	11.04	3.76	2.93	0.005	3.5	18.57
Dosage	2.38	2.26	1.05	0.298	− 2.16	6.92
Samples	6.36	1.49	4.24	0.000	3.36	9.35
Size	− 25.93	3.68	− 7.03	0.000	− 33.31	− 18.55
SOD						
Route	0.63	0.43	1.46	0.145	− 0.22	1.49
Period	0.52	0.49	1.06	0.289	− 0.44	1.49
Dosage	− 0.34	0.42	− 0.8	0.425	− 1.18	0.5
Samples	− 0.29	0.22	− 1.34	0.182	− 0.73	0.13
Size	0	0.5	0	0.998	− 0.99	1
GSH						
Route	5.51	1.68	3.27	0.002	2.16	8.87
Period	− 2.24	2.32	− 0.97	0.336	− 6.86	2.37
Dosage	2.35	1.83	1.28	0.204	− 1.3	6.01
Samples	− 2.12	0.83	− 2.28	0.025	− 3.97	− 0.26
Size	1.35	2.14	0.63	0.528	− 2.91	5.63
GPx						
Route	6.4	1.17	5.48	0.000	4.09	8.72
Period	4.25	1.32	3.21	0.002	1.63	6.87
Dosage	4.02	1.11	3.61	0.000	1.81	6.22
Samples	− 1.74	0.63	− 2.75	0.007	− 3	− 0.49
Size	1.52	1.29	1.18	0.241	− 1.03	4.09
CAT						
Route	0.12	1.03	0.12	0.907	− 1.96	2.20
Period	− 2.58	1.32	− 1.95	0.058	− 5.26	0.09
Dosage	− 2.84	0.99	− 2.85	0.007	− 4.85	− 0.82
Samples	0.24	0.51	0.47	0.640	− 0.79	1.28
Size	2.89	1.32	2.17	0.035	0.2	5.57

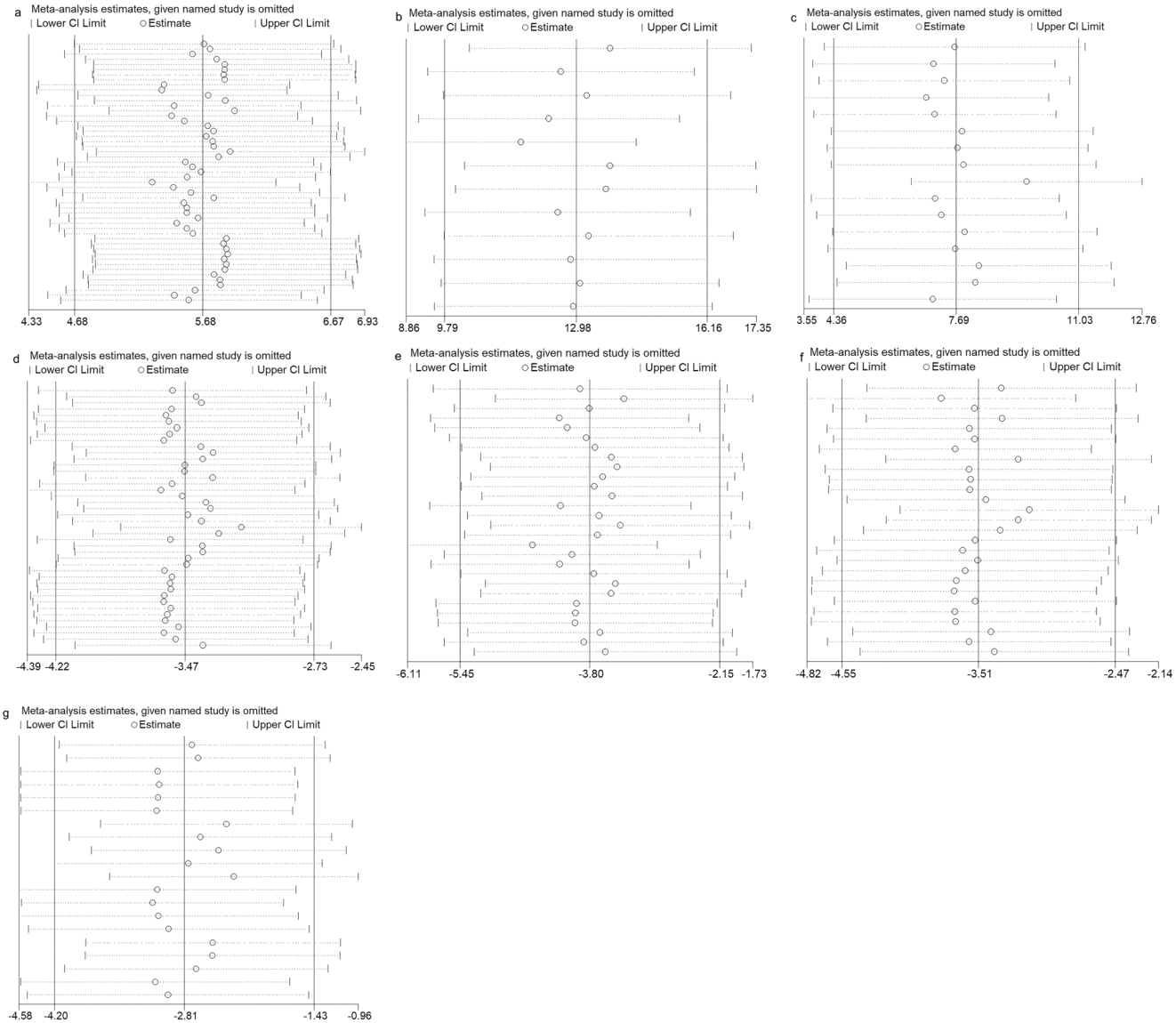

Fig. 17 Sensitivity analysis. Stable results were observed for all studies, indicating that no individual study influenced the combined results. SMD, standard mean difference; SE, standard error. a, MDA. b, O_2^-. c, H_2O_2. d, SOD. e, GSH. f, GPx. g, CAT

Discussion

Animal experiments in rats and mice showed that nano-titanium dioxide particles could produce ROS accumulated in organs, cause imbalance of the oxidation-antioxidant system, and lead to oxidative damage in animal tissues [6, 38]. The results indicated that nano-titanium dioxide significantly increased the levels of oxidants, such as MDA, O_2^-, and H_2O_2, and reduced the levels of anti-oxidative enzymes, such as SOD, GSH, GPx, and CAT. Meanwhile, nano-titanium dioxide induced breakage of DNA strands resulting in production of 8-OHdG. In addition, the results indicated that oxidative damage caused by nano-titanium dioxide was related to intervention route, period of nano-titanium dioxide treatment, nano-titanium dioxide dosage, sample source, and particle size of nano-titanium dioxide.

The oxidation process of nano-titanium dioxide is complex [58]. Nano-titanium dioxide penetrated the cell membrane and produced ROS [77, 79]. These ROS (O_2^- and H_2O_2) could bind to LPO to destroy the cell membrane permeability. The reaction of ROS and unsaturated fatty acids in the membrane could enhance LPO and decompose numerous free radicals [80]. Meanwhile, MDA as an intermediate causes the free radical chain reaction by catalyzing O_2 to form O_2^-, and produces a number of ROS [27]. In addition, ROS could cause DNA oxidative damage and produce a large amount of

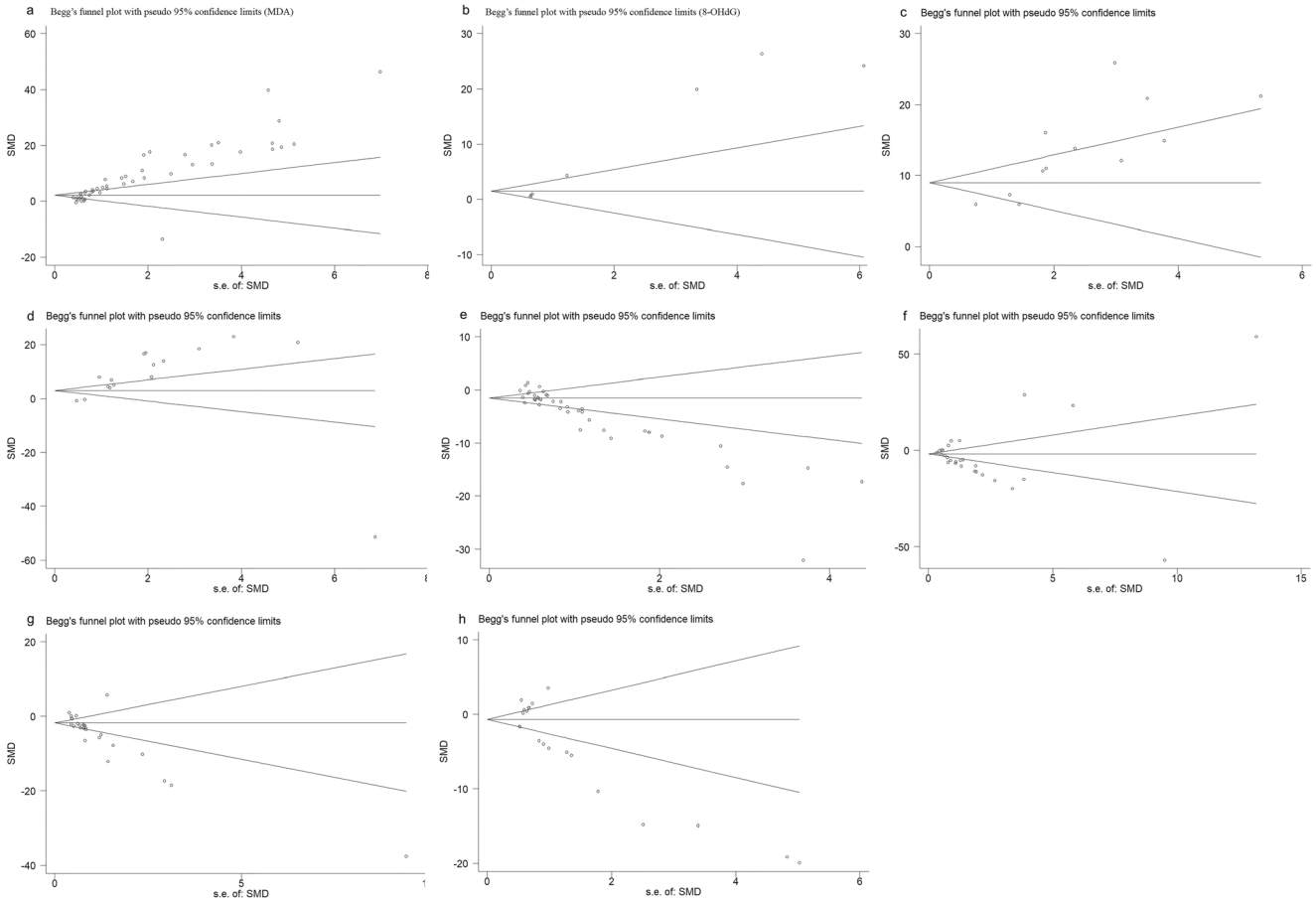

Fig. 18 Funnel plot for the studies. The middle line showed overall estimated standard mean difference. SMD, standard mean difference; SE, standard error. a, MDA. b, 8-OHdG. c, O_2^-. d, H_2O_2. e, SOD. f, GSH. g, GPx. h, CAT

8-OHdG by acting on mitochondria [58]. The antioxidant system is activated when the level of oxides is overexpressed. First, SOD catalyzes O_2^- to form H_2O_2. Then, GSH, GPx, and CAT work collectively to generate H_2O from H_2O_2 in order to remove excess free radicals and peroxides [41, 53, 69]. The oxidative

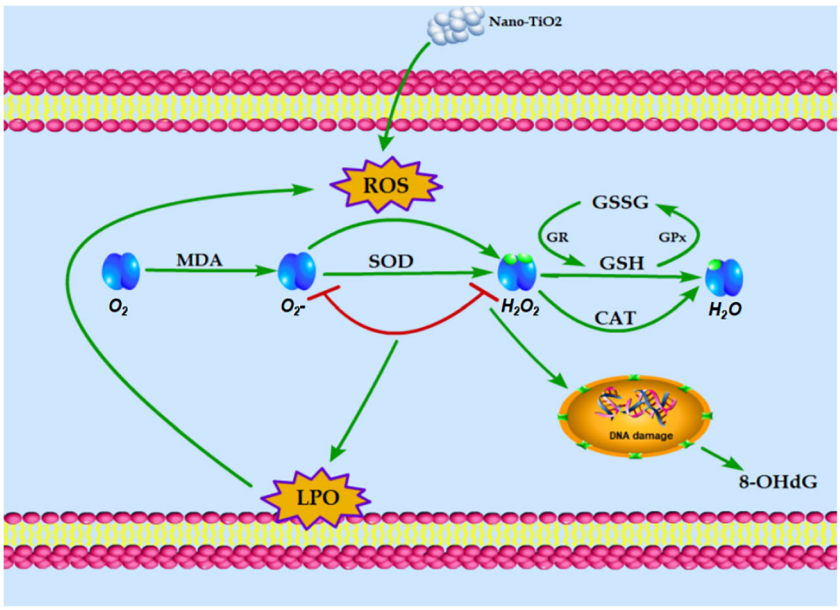

Fig. 19 Oxidative mechanism of nano-titanium dioxide. Nano-titanium dioxide could cause oxidative injury by reducing the activity of anti-oxidative enzymes and increasing the oxidative production, and leading to nucleic acid damage in the body

mechanism of nano-titanium dioxide is shown in Fig. 19. Numerous factors affect the role of enzymes and related molecules involved in oxidative stress caused by nano-titanium dioxide, and these might explain the heterogeneity among studies.

The subgroup analysis of this study indicated that the levels of 8-OHdG, O_2^-, H_2O_2, and GPx significantly increased through gavage administration rather than injection. This condition might be attributed to the longer period exposure in gavage; the continuous activation of oxidation system leads to serious oxidative damage to the body, so that the recovery might be slower [20]. Compared with serum, nano-titanium dioxide could significantly alter the levels of oxidative- and antioxidant-related molecules in the liver and kidney. The reason might be owed to nano-titanium dioxide which mainly acts on the liver and kidney [81, 82].

In this meta-analysis, long exposure period and high dosage could increase the levels of MDA, 8-OHdG, O_2^-, and H_2O_2. Some studies support the time-dependent and dose-dependent effects of toxicity induced by nano-titanium dioxide [27, 58]. With the decreased of nano-titanium dioxide particle size, the surface activity increased and clearance capacity of organisms gradually decreased [83, 84]. When the particle size of nano-titanium dioxide was small, high levels of MDA, 8-OHdG were observed; GSH activity of antioxidant enzymes was inhibited. Besides, the levels of H_2O_2, SOD, and GPx were higher at a particle size of 10–40 nm, suggesting the possible non-linear relationship between the toxicity effect of nano-titanium dioxide and particle size. The meta-analysis of Chang et al. showed that the proportion of positive studies on nano-titanium dioxide–induced cytotoxicity at a particle size of 10–40 nm for 24 h was higher than that with a particle size greater than other groups [85].

Conclusion

The results of this meta-analysis indicated that nano-titanium dioxide could cause oxidative damage in organs of rats and mice. Nano-titanium dioxide elevated the levels of oxidative enzymes and decreased the levels of antioxidants. Further studies showed that higher dosage, longer period, and smaller particle size of nano-titanium dioxide promote the formation of oxides when exposed to the liver and kidney, resulting in the imbalance of oxidation-antioxidant system and body damage. This paper might supplement the regulatory toxicity mechanism of nano-titanium dioxide, and future research whether nano-titanium dioxide could result oxidative damage to human body should be confirmed.

Limitation

The limitation of this study is the significant heterogeneity of combined effects. Crystal and surface conditions should be the focus of future research due to their significant influence on nano-titanium dioxide–induced toxicity. However, these factors were excluded in this study, as they were rarely mentioned in the articles. Instead, this study included animal manuscripts, and cell publications were disregarded.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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