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Review

The effect of chromium intake on oxidative stress parameters: A systematic review and meta-analysis

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ABSTRACT

Background: Trivalent chromium is a trace element thought to have a beneficial effect on oxidative stress (OS) parameters and inflammation. This review aimed to investigate the dose-response of chromium and summarize the effects of chromium supplementation on OS parameters in the literature.

Methods: MEDLINE, Scopus, Web of Science and Cochrane CENTRAL databases were searched for RCTs published from inception to January 2021 evaluating the effect of chromium supplementation on OS parameters, namely MDA, TBARS, SOD, TAS, CAT, GPx, and GSH. A random-effects model was used to pool data and calculated standard mean difference and 95 % confidence intervals. Quantified heterogeneity among studies was assessed through Cochrane's I^2 values.

Results: Nine studies enrolling 550 participants met the inclusion criteria. The obtained results indicate that chromium supplementation significantly increases TAC (SMD: 0.46; 95 % CI: 0.08, 0.84; $I^2 = 00.0$ % n = 2) and significantly decreases MDA levels (SMD: −0.46; 95 % CI: −0.86, -0.07; $I^2 = 52.4$ % n = 5). Supplementation did not significantly change CAT, GPx, GSH, SOD, TAS, and TBARS.

Conclusion: Chromium supplementation may improve OS parameters, however, due to high heterogeneity observed in the included studies, these findings should be interpreted with caution. Large RCTs on various patient groups evaluating the impact of chromium supplementation are needed to allow an adequate generalization of the benefits of chromium on human health.

1. Introduction

Oxidative stress (OS) is a phenomenon that emerges when there is an imbalance between the production and accumulation of reactive oxygen species (ROS) and the organism's capacity to neutralize the ROS through enzymatic and non-enzymatic antioxidant defense systems [1]. Low levels of ROS are necessary for activating signaling pathways and regulating various biological and physiological processes, such as

Abbreviations: CAT, Catalase; CI, confidence intervals; GPx, Glutathione peroxidase; GSH, Glutathione; IGT, Impaired Glucose Tolerance; MDA, Malondialdehyde; MetS, Metabolic Syndrome; NAFLD, non-alcoholic fatty liver disease; NO, Nitric Oxide; OS, oxidative stress; PCOS, Polycystic ovary syndrome; RCTs, randomized controlled trials; ROS, Reactive oxygen species; SDs, Standard deviations; SMD, standardized mean difference; SOD, superoxide dismutase; TAC, total antioxidant capacity; TAS, total antioxidant status; TBARS, thiobarbituric acid-reactive substances; T2DM, Type 2 Diabetes Mellitus; UL, upper intake level.

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cellular proliferation and host defense mechanisms [2,3]. Excessive generation of ROS can damage and modify biomolecules, namely proteins, lipids, and DNA, and may consequently play a major role in the pathophysiology of various diseases, such as cancer, cardiovascular diseases, metabolic syndrome, inflammatory diseases, and neurodegenerative diseases [4–8]. Hence, it is evident that the proper functioning of the endogenous antioxidant protection system is crucial for the maintenance of equilibrium [9,10]. In addition, environmental factors, genetics, radiation, toxic exposure, diet, and nutrition may also affect the balance of oxidants/antioxidants [11]. Dietary factors and food elements have been shown to have a massive role in inflammation and oxidative stress control [12–14]. Thus, several dietary factors are considered as exogenous prooxidants or antioxidants [15].

Trivalent chromium [Cr(III)] is a trace element present in many food sources, particularly meat, grain products, nuts, fruit, and brewer's yeast, and is available on the market as a dietary supplement [16–18]. The amount of chromium in food sources varies widely depending on local soil, water conditions, and agricultural and manufacturing processes [19]. The commercial sources of chromium dietary supplements include chromium picolinate, chromium chloride, chromium nicotinate, chromium polynicotinate, chromium citrate, chromium histidinate, and high-chromium yeast [20]. Chromium absorption from food and from dietary supplements is similar and ranges from 0.4 to 2.5 % [18]. The recommended chromium daily intake is 30−35 μg for men and 20−25 μg for women [21]. Overall, chromium is well tolerated, and no serious adverse events have been directly linked to its high intake from food or commercially available supplements. Hence, a tolerable upper intake level (UL) for chromium has not been established although caution should be warranted due to limited scientific data on the latter topic [22]. Chromium (III) and chromium-containing supplements are thought to have a beneficial effect on glucose metabolism and insulin sensitivity, lipid profile, weight loss and body composition, inflammation, and the level of inflammatory mediators. However, current scientific evidence is lacking, and no definitive conclusions can be drawn [23–25].

There is a growing body of literature reporting the effect of chromium supplements on oxidant and antioxidant parameters, but the reported findings are inconclusive. To the best of our knowledge, no quantitative synthesis providing and clarifying the net effects of chromium has been published. Thus, the aim of the present systematic review and meta-analysis of randomized controlled trials was to investigate the dose-response of chromium and summarize the effect of supplement administration on OS parameters.

2. Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist [26] and followed a pre-specified protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42021230594).

2.1. Search strategy

The electronic databases of PubMed/MEDLINE, Scopus, Web of Science and Cochrane Central Register of Controlled Trials were searched from inception up to January 2021 for relevant articles. Search strategies included key terms Chromium OR chromium picolinate OR chromium nicotinate AND Oxidative Stress OR Total Antioxidant Capacity OR antioxidant OR reactive oxygen species OR Catalase OR Oxygen Radical Absorbance OR reactive nitrogen species OR protein carbonyl. No language and publication restriction were applied. The complete search strategy and key words for each database are presented in Appendix A.

2.2. Selection criteria

All titles were screened by two authors against eligibility criteria. Randomized controlled trials (RCTs) including studies with parallel or crossover design that evaluated the effect of chromium supplementation on oxidative stress markers were selected. The included studies contained sufficient data at the beginning and end of the intervention in both chromium supplemented and control groups to compare the difference in means and SDs. Also, completed reference lists of relevant review articles were checked to find additional pertinent RCTs. Studies that were non original, those done on animals, all non-randomized studies without a control group (case studies, case series, cross-sectional, case-control, cohort), and studies presented only as abstracts, review articles, and letters to the editor were excluded. Table 1 shows the Cochrane PICO search criteria used for this meta-analysis.

2.3. Data analysis

All primary studies were checked by two authors (MM and SF) using a standardized data extraction form to evaluate the quality of eligible studies. Data were double checked by a third author (JH) and any discrepancies were discussed with other author (MDE). Author, year of publication, design, country, subjects (n, age, sex), chromium dosage, type of diet, and period of treatment were extracted.

For continuous and binary data, the standardized mean difference (SMD) was calculated. Standard errors of each variable related to oxidative stress in both groups were converted to Standard deviations [27]. A random-effect model based on Inverse-Variance method in STATA (version 13) was used to pool the data. Quantified heterogeneity was completed via heterogeneity chi-squared test with a p-value less than 0.1 and an I^2 statistic over 50 % considered as significant heterogeneity among studies. data was considered statistically significant when $p < 0.05$. Possible publication bias of the results was evaluated using Egger's regression test.

3. Results

3.1. Study selection

Fig. 1 presents a flow diagram of the study selection process and reasons for exclusion. The primary search of major databases yielded 242 records. After removing duplicates, 193 unique articles remained. Two investigators (JH and SF) evaluated titles and abstracts and included 27 trials for full-text evaluation. At the full text evaluation stage, eighteen articles were excluded because they reported no relevant variables (n = 10), did not provide enough information to extract (n = 2), had irrelevant control groups (n = 2), a proprietary compound was used (n = 1) and was non-RCTs (n = 1). In addition, two were removed due to ethical issues. Finally, nine articles met the inclusion criteria for this systematic review and meta-analysis [16,23–25,28–32].

3.2. Study characteristics

The main characteristics of the 9 identified trials are presented in

Table 1
Description of PICO strategy.

Condition	Description
Participant	Unhealthy Adults
Intervention	Chromium supplementation
Comparison	Placebo group
Outcome	MDA, NO, TBARS, SOD, TAS, CAT, GPx, GSH
Study designs	Randomized controlled trials

MDA: Malondialdehyde, NO: Nitric Oxide, TBARS: Thiobarbituric acid reactive substances, SOD: Superoxide dismutase, TAS: Total Antioxidant Status, CAT: Catalase, GPx: Glutathione Peroxidase, GSH: Glutathione.

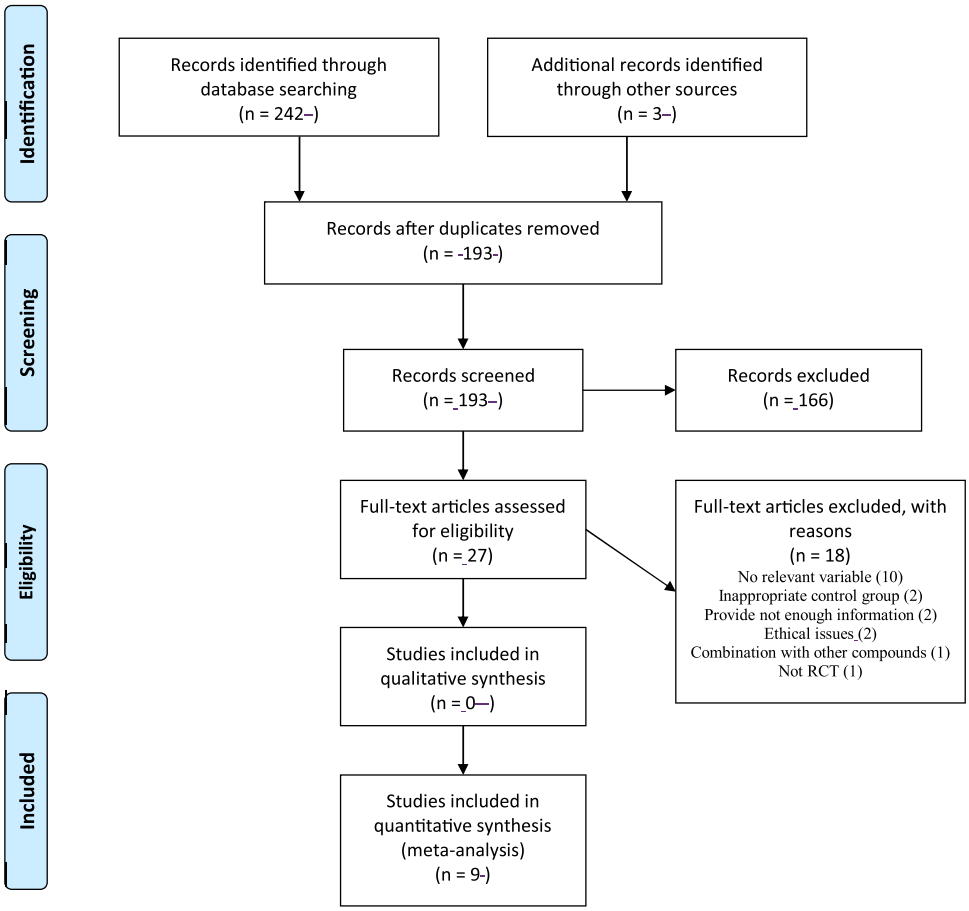

Fig. 1. PRISMA Flow diagram of study selection.

Table 2. In total, 550 subjects were included in these trials. Included studies were published between 2001 and 2020. Four studies were performed in Iran [24,25,28,30], two in the Czech Republic [16,32], two in Taiwan [23,31], and one in Tunisia [29]. Six trials were conducted in patients with type 2 diabetes (T2DM) [23,24,29–32], one in patients with polycystic ovary syndrome [28], one in patients with metabolic syndrome [16], and one patients with non-alcoholic fatty liver disease [25]. The duration of the interventions ranged from 8 to 24 weeks. Four studies used Chromium enriched yeast [16,23,31,32] and the rest of the included trials used Chromium picolinate. Chromium dose used in included trials varied from 200 to 1000 μg/d. The mean age of participants across studies ranged from 33.3 to 61 years, however two studies did not report the participants' age.

3.3. Risk of bias of the included trials

The methodological quality of the included trials were assessed through seven domains based on the Cochrane Risk of Bias tool [33]. Only four included trials [23,29–31] did not describe the method used for random sequence generation. Allocation concealment was considered as high risk of bias in three studies [23,29,31]. Blinding was reported in detail in three included studies, but five studies were classified as unclear risk of bias due to not describing the blinding process of participants and personnel, and one study [31] was evaluated as high risk of bias due to not reporting any blinding process. The incomplete outcome criteria had a low risk of bias for six included studies and selective reporting criteria had a low risk of bias for three included studies. One included studies [30] were considered as high risk of bias for the category of other sources of bias due to not reporting age and BMI of participants. The complete risk of bias evaluation is presented in Fig. 2.

3.4. Effect of chromium on oxidative stress parameters

The effect of chromium intake on oxidative stress parameters is presented in Fig. 3. There was a high level of heterogeneity ($I^2 > 50$ %) between studies that evaluated TAC and MDA. However, the obtained results show that chromium supplementation significantly increases TAC (SMD: 0.46; 95 % CI: 0.08, 0.84; $I^2 = 00.0$ % n = 2) and significantly decreases MDA levels (SMD: −0.46; 95 % CI: −0.86, -0.07; $I^2 = 52.4$ % n = 5). In addition, the results obtained in this meta-analysis show that chromium intake did not significantly change CAT (SMD: 0.15; 95 % CI: −0.27, 0.56; $I^2 = 00.0$ %), GPx (SMD: 0.25; 95 % CI: −0.10, 0.60; $I^2 = 56.6$ %), GSH (SMD: 0.11; 95 % CI: −0.16, 0.39; $I^2 = 00.0$ %), SOD (SMD: 0.21; 95 % CI: −0.03, 0.46; $I^2 = 00.0$ %), TAS (SMD: 0.03; 95 % CI: −1.40, 1.47; $I^2 = 89.6$ %) and TBARS (SMD: −0.48; 95 % CI: −1.53, 0.58; $I^2 = 91.0$ %). Studies evaluating these parameters also had high levels of heterogeneity except for CAT, GSH and SOD ($I^2 = 0.00$ %). Subgroup analyses were performed based on disease type, duration, chromium type and dosage and age of participants (Table 3) and no significant differences were observed except in the case of SOD activity which has significantly increased in non-diabetic subjects compared to diabetic patients after chromium intake.

4. Discussion

Reactive species resulting from metabolism have a role in the regulation of intracellular signaling pathways essential for the adequate functioning of cells. The accumulation of these reactive molecules results in oxidative stress and may trigger the activation of the serine and threonine kinase cascades, leading to insulin resistance and inflammatory processes. These processes are well established factors for the

Table 2
Main characteristics of included studies.

Study, (reference)	Country	Disease type	Chromium intervention type	Duration (week)	N (analyzed)	Chromium Dose μg/per day	Female gender n (%)	Age, years		BMI, kg/m^2		Main outcomes*
								Mean ± SD		Mean ± SD		
								Intervention	Control	Intervention	Control	
Amiri Siavashani et al, 2018 [28]	Iran	PCOS	Chromium picolinate	8	40	200	100	33.3 ± 2.7	33.8 ± 1.9	27.7 ± 2.5	27.0 ± 3.9	↔NO
Anderson et al, 2001 [29]	Tunisia	T2DM	Chromium picolinate	24	108	400	–	52.0 ± 1.58	55.5 ± 1.43	29.5 ± 0.16	29.6 ± 0.15	↓TBARS, ↔SOD, ↔GPx
Cheng et al, 2004 [23]	Taiwan	T2DM	chromium-enriched yeast	24	64	1000	57	52.5 ± 2.0	50.8 ± 2.3	27.3 ± 0.7	27.8 ± 0.8	↓TBARS, ↓TAS, ↔SOD, ↔GPx, ↔CAT
Farrokhian et al, 2020 [24]	Iran	T2DM	Chromium picolinate	12	64	200	50	58.0 ± 8.0	60.9 ± 7.7	30.4 ± 4.3	29.9 ± 3.8	↓MDA, ↑TAC
Imanparast et al, 2020 [30]	Iran	T2DM	Chromium picolinate	16	92	500	–	–	–	–	–	↔MDA, ↔TAC
Kooshki et al, 2020 [25]	Iran	NAFLD	Chromium picolinate	12	46	400	39	38.9 ± 7.3	40.3 ± 6.7	30.3 ± 3.0	31.4 ± 4.5	↑TAC, ↑SOD, ↓MDA, ↔GPx
Lai, 2008 [31]	Taiwan	T2DM	chromium-enriched yeast	24	30	1000	53	53.2 ± 2.0	50.5 ± 1.9	30.3 ± 3.0	31.4 ± 4.5	↓TBARS, ↑TAS, ↑GPx
Nussbaumerova et al, 2018 [16]	Czech Republic	MetS and IGT	chromium-enriched yeast	24	70	300	64	57.0 ± 10.0	58.0 ± 9.0	34.9 ± 6.0	31.7 ± 5.1	↔TBARS, ↔GSH, ↑GPx
Racek et al, 2006 [32]	Czech Republic	T2DM	chromium-enriched yeast	12	36	400	75	60.8 ± 8.25	61.8 ± 10.75	33.59 ± 5.6	35.16 ± 6.55	↑GPx, ↔GSH

PCOS: Polycystic ovary syndrome, T2DM: Type 2 Diabetes Mellitus, MDA: Malondialdehyde, NO: Nitric Oxide, TBARS: Thiobarbituric acid reactive substances, SOD: Superoxide dismutase, TAS: Total Antioxidant Status, CAT: Catalase, GPx: Glutathione Peroxidase, GSH: Glutathione, NAFLD: Non-alcoholic Fatty liver disease, MetS: Metabolic Syndrome, IGT: Impaired Glucose Tolerance.
* Main outcomes were expressed in terms of statistical significance ($p < 0.05$) as either increased (↑), decreased (↓), or no difference (↔) between saffron versus placebo group.

occurrence of several diseases, including diabetes, obesity, and metabolic syndrome, due to the activation of stress-sensitive signaling pathways. Additionally, these diseases tend to aggravate oxidative stress, as hyperglycemia and the activation of enzyme NAD(P)H oxidase by inflammatory cytokines result in increased amounts of reactive oxygen species (ROS) [34–38].

Oxidative stress may be associated with the onset of diabetes rather than being a later consequence of hyperglycemia, making it a relevant target in the early stages of treatment. The maintenance of the equilibrium between the production of oxygen and nitrogen reactive species and their clearance and inactivation ultimately depends on the action of endogenous antioxidants systems. However, the supplementation of adequate amounts of well-established antioxidants may be needed to reinforce the abilities of cells to protect themselves from the harmful effects of oxidative stress [34,38,39]. In fact, several studies with animal models have shown that treatment with antioxidants may improve insulin sensitivity and other protective processes to reduce or prevent oxidative stress [39–41].

Heavy metals, such as chromium, are usually associated with a toxicity risk for humans and exposure to high concentrations of these elements are known to cause health problems. Despite the potential risk of toxicity, particularly associated to the hexavalent ion, Cr(VI), chromium as the trivalent ion, Cr(III), has long been considered an essential nutrient for humans, required in very low amounts (30 micrograms/day) to aid in several normal physiological processes, including glucose and lipid metabolism [42,43]. However, new evidence based on experiments carried out in a rat model fed with controlled diets of different amounts of chromium has suggested that chromium may have a relevant therapeutic role, rather than just being an essential element. In this study, higher levels of chromium consumption positively impacted glucose metabolism and insulin sensitivity, which reinforces the results of several other studies [44,45]. Further, Dubey et al. (2020) reviewed several studies that reported improvements in lipid profile, insulin action and sensitivity, and lipid and glucose metabolism in both a general patient population and also only in diabetic patients [46]. Recent evidence has suggested that chromium levels are altered in patients with T2DM, increasing the risk of developing diabetic complications and several systematic review and meta-analysis confirmed the beneficial effects of chromium to diabetic patients [47–50]. Moreover, the administration of chromium supplements to diabetic rats resulted in a decrease in oxidative stress and blood levels of proinflammatory cytokines and lipids [51]. In addition, the intake of chromium supplements by diabetic patients has been shown to help restore insulin action and glucose metabolism [46,52–54].

Several studies have reported the effects of chromium on several cellular signaling pathways related to the management of oxidative stress, with different consequences to cells, depending on chromium exposure and the oxidation state of chromium. Although much is still unknown about the specific mechanisms, the interaction between chromium and the intracellular signaling pathways may explain the toxic effects of chromium and its potential beneficial effects [42].

Despite the controversy underlying chromium's role in human health, there is an evident need to understand how chromium supplements may benefit health status, particularly where lipid and glucose metabolism may be impaired or there is an increased risk of oxidative stress. A broad assessment of the effects of chromium on the levels of molecules and enzymes related to oxidative and antioxidant cellular status will help clarify how chromium may influence OS in humans. This systematic review and meta-analysis aimed to fill this gap.

Nine RCTs evaluating the effect on chromium supplementation on oxidative stress parameters were included, enrolling a total of 550 participants with different health conditions, including T2DM, metabolic syndrome, PCOS, and NAFLD. These diseases are all directly or indirectly linked to insulin resistance and/or inflammatory processes, and thus, assessing the effects of chromium supplementation, which is thought to combat OS, may provide valuable information on managing

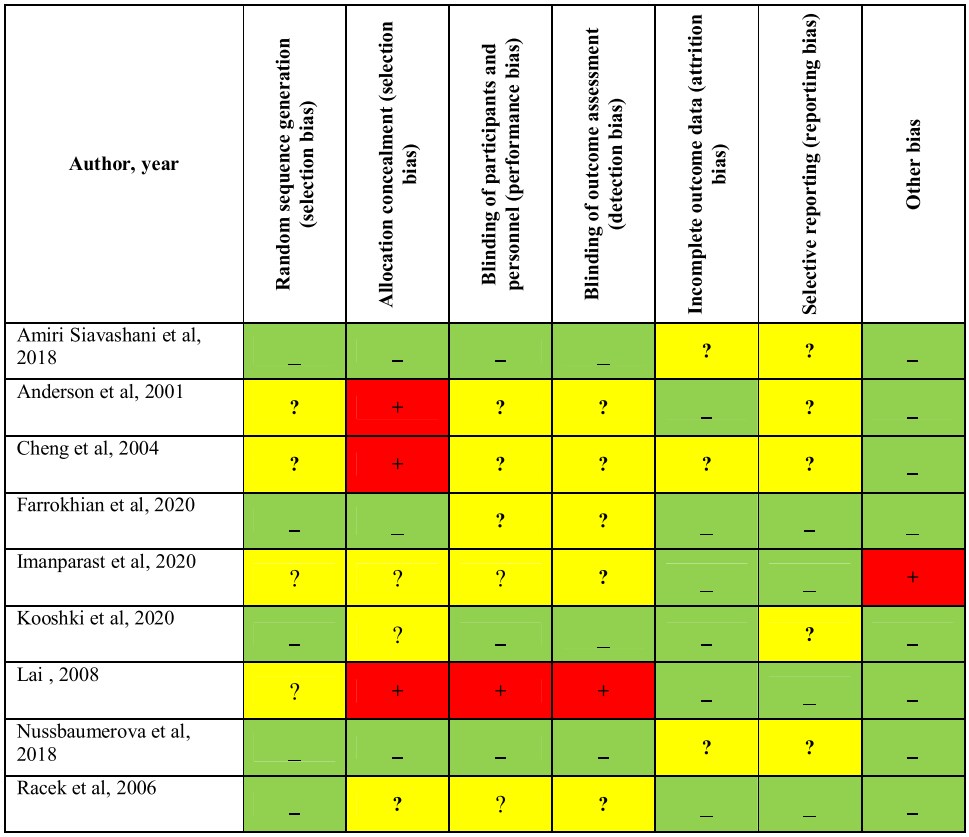

Fig. 2. Assessment of the risk of bias in the included studies.
+: High risk, -: Low risk,? : Unclear.

these health conditions.

Overall, the obtained results show that chromium supplementation significantly increased total antioxidant capacity (TAC), and significantly decreased malondialdehyde (MDA) levels, which is a known marker for oxidative stress and the main product of lipid peroxidation by free radicals [55]. This suggests that an improvement in antioxidant protection may be achieved through increasing the levels of important cellular antioxidants, such as glutathione, and by reducing lipid degradation of the reactive species. All other considered parameters (TBARS, SOD, TAS, CAT, GPx, and GSH) were not affected by chromium supplementation (Fig. 3). Bearing in mind the high heterogeneity of the included trials, these results should be carefully interpreted considering the various factors that may influence the final outcomes, including age, health status, and duration of the interventions, chromium doses, and type of chromium supplement ingested.

To better evaluate the effects of interventions, sub-group analyses were carried out. The results presented in Table 3 show that the only significant difference observed was between the diabetic and non-diabetic patients. In the sub-group of non-diabetic participants, a significant decrease in SOD levels was observed after Chromium intake which may suggest that although Chromium has been suggested as a putative therapeutic agent to help managing diabetes, its consumption by non-diabetic patients may contribute to reduce protection against oxidative stress.

A possible mechanism that may justify the effect of chromium on controlling the oxidative stress is the effect of this element on gene expression and non-coding RNAs [56,57]. MicroRNAs (miRNAs) are small non-coding RNAs that modulate the expression of several types of messenger RNAs [58,59]. There are a large number of miRNA genes which are related to inflammation, oxidative stress and related parameters [60,61]. It has been shown that chromium has the potential to affect several inflammatory and oxidative stress factors through its effect on related miRNAs [62,63].

The most significant impact of chromium supplements reported in a previous systematic review was an improvement in the glycemic index of T2DM but this study also indicated that the major problem with evaluating the effect of chromium supplementation on parameters related to glucose and lipid metabolism is the great heterogeneity between studies and the lack of statistically significant results. However, this does not mean that there is no beneficial effect [64]. The oxidative stress parameters considered in the present study were not evaluated in the referred systematic review.

Although this systematic review sums up the effects of Chromium intake on several oxidative stress parameters, based on the available trials, some limitations need to be stated: 1) the number of included studies and participants is very small for some variables; 2) serious heterogeneity within and between the included studies should be recognized and so the obtained results must be interpreted with caution; 3) four of the included studies used chromium-enriched yeast, which may have affected the reported outcomes because chromium could be altering the yeast and/or the overall effect may have been influenced by the yeast; 4) some of the included trials suffer from inconsistencies and several risks of biases, for example some of these studies did not evaluate dietary intake for possible dietary intake of chromium which may affect the total amount of chromium intake. For these reasons, the results presented in this study must be carefully interpreted and should constitute an incitive to researchers to further investigate the role of Chromium in human health.

In conclusion, despite this summation of evidence, there is a considerable need for large RCTs evaluating the impact of chromium supplementation to generate sufficient data to allow an adequate generalization of the benefits of chromium on human health. In addition, trials specifically evaluating oxidative stress parameters and including a higher number of participants of various ages, with or

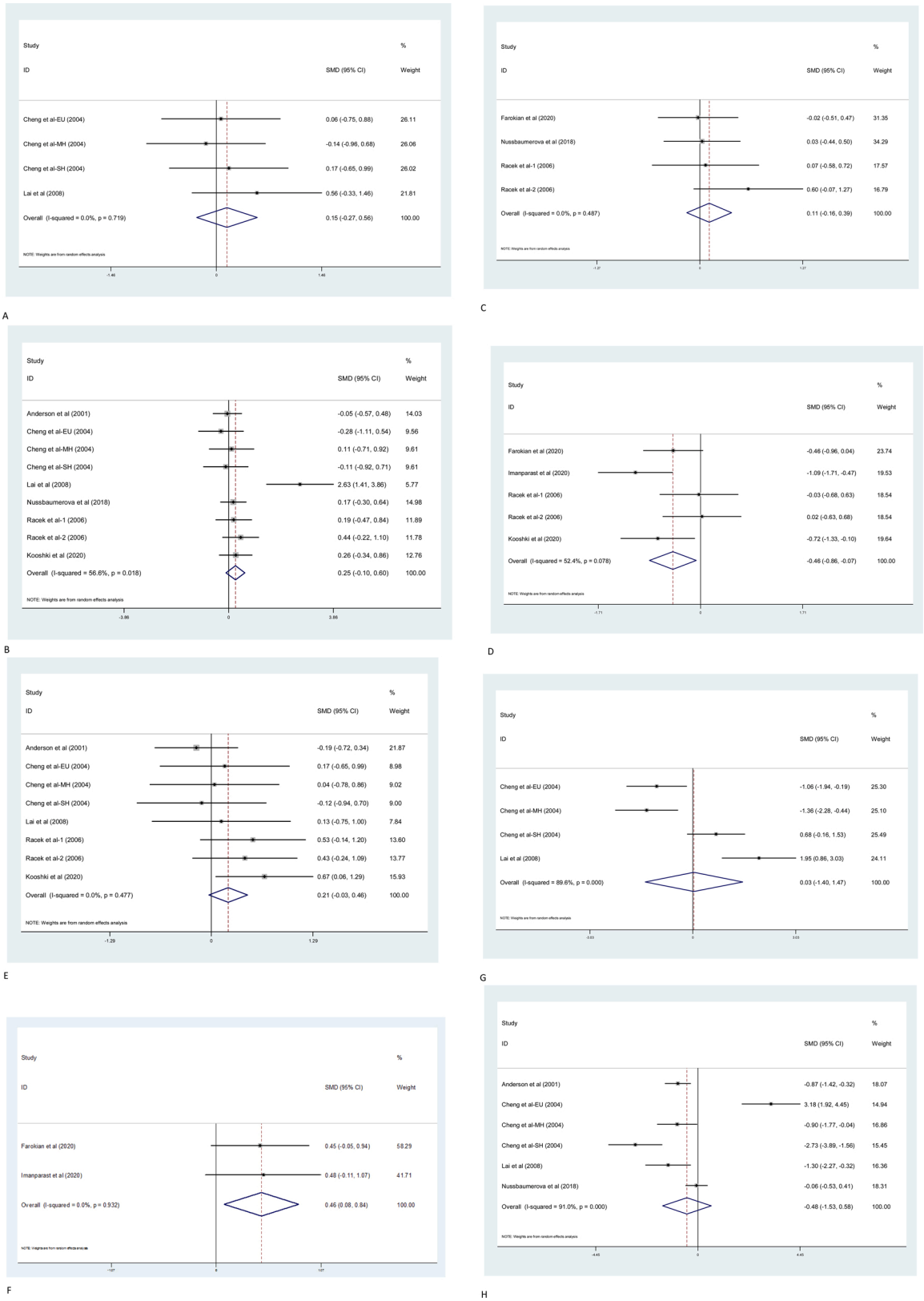

Fig. 3. Forest plots of the effect of Chromium intake on oxidative stress parameters CAT [A], GPx [B], GSH [C], MDA [D], SOD [E], TAC [F], TAS [G] and TBARS [H].

without a specific disease, and with different food habits are of interest. These trials should also be designed to allow a thorough evaluation of different doses and types of chromium supplements. In the meantime, chromium may be considered as a potential therapeutic supplement with the capacity to ameliorate lipid and glucose metabolism, insulin sensitivity, and inflammation through the reduction of oxidative stress, ultimately benefiting patients with diseases that are related with inflammatory processes such as T2DM, metabolic syndrome, obesity, PCOS, NAFLD and others.

Table 3
Subgroup analysis assessing the effect of Chromium on oxidative stress parameters.

Variable	Sub-grouped by		No. of arms	effect size (SMD)	95 % CI	I^2 (%)	P for heterogeneity
GPx	Disease type	Diabetic	7	0.30	−0.20, 0.80	67.3	**0.005**
		Non-Diabetic	2	0.21	−0.16, 0.58	00.0	0.820
	Duration	≥12 weeks	6	0.27	−0.28, 0.83	71.8	**0.003**
		<12 weeks	3	0.29	−0.07, 0.66	00.0	0.859
	Chromium dose	≥400 μg/d	8	0.28	−0.14, 0.70	62.0	**0.010**
		<400 μg/d	1	0.17	−0.30, 0.64	–	–
	Chromium Type	Chromium picolinate	2	0.09	−0.31, 0.48	00.0	0.449
		Chromium-enriched yeast	7	0.33	−0.14, 0.80	66.5	**0.008**
	Age	Senior adults	5	0.49	−0.09, 1.07	75.2	**0.003**
		Middle-age adults	4	0.04	−0.33, 0.41	00.0	0.739
SOD	Disease type	Diabetic	7	0.13	−0.14, 0.40	00.0	0.677
		Non-Diabetic	1	**0.67**	**−0.06, 1.29***	–	–
	Duration	≥12 weeks	7	0.16	−0.10, 0.43	00.0	0.474
		<12 weeks	1	0.53	−0.14, 1.20	–	–
	Chromium Type	Chromium picolinate	2	0.23	−0.62, 1.07	77.2	**0.036**
		Chromium-enriched yeast	6	0.24	−0.07, 0.55	00.0	0.835
	Age	Senior adults	4	0.18	−0.17, 0.54	14.5	0.320
		Middle-age adults	4	0.27	−0.11, 0.64	00.0	0.407
TBARS	Disease type	Diabetic	5	0.56	−1.98, 0.87	92.0	**0.000**
		Non-Diabetic	1	−0.06	−0.53, 0.41	–	–
	Chromium dose	≥400 μg/d	5	0.56	−1.98, 0.87	92.0	**0.000**
		<400 μg/d	1	−0.06	−0.53, 0.41	–	–
	Age	Senior adults	3	−0.66	−1.38, 0.05	74.3	**0.020**
		Middle-age adults	3	−0.16	−3.22, 2.90	95.8	**0.000**

SMD: Standard mean difference, CI: confidence interval. MDA: Malondialdehyde, TBARS: Thiobarbituric acid reactive substances, SOD: Superoxide dismutase, GPx: Glutathione Peroxidase, GSH: Glutathione.
Bold values signifies that they are main outcomes of the analysis.
* Statistically significant.

Author statement

This study did not involve any human or animal subjects.

Acknowledgments

None.

Declaration of Competing Interest

The authors have no competing interests to report.

Appendix A

Groups	Descriptors
Outcome	Glutathione Reductase OR Reductase, Glutathione OR Glutathione Peroxidase OR Peroxidase Glutathione OR Superoxide Dismutase OR Dismutase Superoxide OR Oxidative Stress OR Stress Oxidative OR Stress, Oxidative OR Total Antioxidant Capacity OR Total Antioxidant Status OR antioxidant OR Oxidant OR reactive oxygen species OR Catalase OR Oxygen Radical Absorbance OR reactive nitrogen species OR protein carbonyl OR lipid peroxide OR Total Radical Trapping Antioxidant Parameter OR Malondialdehyde OR Nitric oxide OR 8-hydroxydeoxyguanosine OR thiobarbituric acid reactive substances OR nitrotyrosine OR sulfhydryl group OR oxidized LDL lipoprotein OR xanthine oxidase OR paraoxonase-1
Exposure	Chromium OR chromium picolinate OR chromium nicotinate
Setting	Randomized controlled trial OR controlled clinical trial OR randomized controlled trials OR random allocation OR double blind method OR single blind method OR clinical trial OR clinical trials OR placebos OR placebo OR random

PUBMED
Number of localized studies: 76
Limits: humans
Number of studies after applying limits: 36

	Descriptors	Number of studies reached
#1	"chromium"[MeSH Terms] OR "chromium"[All Fields] OR ("picolinic acid"[Supplementary Concept] OR "picolinic acid"[All Fields] OR "chromium picolinate"[All Fields]) OR (("chromium"[MeSH Terms] OR "chromium"[All Fields]) AND ("niacin"[MeSH Terms] OR "niacin"[All Fields] OR "nicotinate"[All Fields] OR "nicotinates"[All Fields] OR "nicotinic"[All Fields]))	41376
#2	((((((((((((((((((((((((((((("Glutathione Reductase"[Mesh] OR ("glutathione reductase"[MeSH Terms] OR ("glutathione"[All Fields] AND "reductase"[All Fields]) OR "glutathione reductase"[All Fields] OR ("reductase"[All Fields] AND "glutathione"[All Fields]) OR "reductase, glutathione"[All Fields])) OR "Glutathione Peroxidase"[Mesh]) OR (("peroxidases"[MeSH Terms] OR "peroxidases"[All Fields] OR "peroxidase"[All Fields] OR "peroxidase"[MeSH Terms]) AND ("glutathione"[MeSH Terms] OR "glutathione"[All Fields]))) OR ("superoxide dismutase"[MeSH Terms] OR ("superoxide"[All Fields] AND "dismutase"[All Fields]) OR "superoxide dismutase"[All Fields])) OR "Superoxide Dismutase"[Mesh]) OR	716869

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	Descriptors	Number of studies reached
	(Dismutase[All Fields] AND ("superoxides"[MeSH Terms] OR "superoxides"[All Fields] OR "superoxide"[All Fields])) OR "Oxidative Stress"[Mesh]) OR ("oxidative stress"[MeSH Terms] OR ("oxidative"[All Fields] AND "stress"[All Fields]) OR "oxidative stress"[All Fields] OR ("stress"[All Fields] AND "oxidative"[All Fields]) OR "stress oxidative"[All Fields])) OR ("oxidative stress"[MeSH Terms] OR ("oxidative"[All Fields] AND "stress"[All Fields]) OR "oxidative stress"[All Fields] OR ("stress"[All Fields] AND "oxidative"[All Fields]) OR "stress, oxidative"[All Fields])) OR (Total[All Fields] AND ("antioxidants"[Pharmacological Action] OR "antioxidants"[MeSH Terms] OR "antioxidants"[All Fields] OR "antioxidant"[All Fields]) AND Capacity [All Fields])) OR "Antioxidants"[Mesh]) OR "Oxidants"[Mesh]) OR "Reactive Oxygen Species"[Mesh]) OR "Catalase"[Mesh]) OR "Oxygen Radical Absorbance Capacity"[Mesh]) OR "Reactive Nitrogen Species"[Mesh]) OR ((("proteins"[MeSH Terms] OR "proteins"[All Fields] OR "protein"[All Fields]) AND carbonyl[All Fields])) OR "Lipid Peroxides"[Mesh]) OR (Total[All Fields] AND Radical[All Fields] AND Trapping[All Fields] AND ("antioxidants"[Pharmacological Action] OR "antioxidants"[MeSH Terms] OR "antioxidants"[All Fields] OR "antioxidant"[All Fields]) AND Parameter [All Fields])) OR "Malondialdehyde"[Mesh]) OR "Nitric Oxide"[Mesh]) OR "8-oxo-7-hydrodeoxyguanosine"[Supplementary Concept]) OR "Thiobarbituric Acid Reactive Substances"[Mesh]) OR "3-nitrotyrosine"[Supplementary Concept]) OR ("3-nitrotyrosine"[Supplementary Concept] OR "3-nitrotyrosine"[All Fields] OR "nitrotyrosine"[All Fields])) OR "Sulfhydryl Compounds"[Mesh]) OR ("sulfhydryl compounds"[MeSH Terms] OR ("sulfhydryl"[All Fields] AND "compounds"[All Fields]) OR "sulfhydryl compounds"[All Fields] OR ("sulfhydryl"[All Fields] AND "group"[All Fields]) OR "sulfhydryl group"[All Fields])) OR "oxidized low density lipoprotein"[Supplementary Concept]) OR (("oxidized low density lipoprotein"[Supplementary Concept] OR "oxidized low density lipoprotein"[All Fields] OR "oxidized ldl"[All Fields]) AND ("lipoproteins"[MeSH Terms] OR "lipoproteins"[All Fields] OR "lipoprotein"[All Fields]))) OR "Xanthine Oxidase"[Mesh]) OR "Aryldialkylphosphatase"[Mesh]) OR ("aryldialkylphosphatase"[MeSH Terms] OR "aryldialkylphosphatase"[All Fields] OR "paraoxonase 1"[All Fields])	
#3	((((((((("Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type]) OR "Randomized Controlled Trials as Topic"[Mesh]) OR "Random Allocation"[Mesh]) OR "Double-Blind Method"[Mesh]) OR "Single-Blind Method"[Mesh]) OR "Clinical Trial"[Publication Type]) OR ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trials"[All Fields])) OR "Placebos"[Mesh]) OR ("placebos"[MeSH Terms] OR "placebos"[All Fields] OR "placebo"[All Fields])) OR ("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "random"[All Fields])	173013
#4	**#1** AND **#2** AND #3	76

WEB OF SCIENCE
Number of localized studies: 79
Limits: documents types (articles)
Number of studies after applying limits: 50

	Descriptors	Number of studies reached
#1	TS=("Chromium") OR TS=("chromium picolinate") OR TS=("chromium nicotinate")	117895
#2	TS=("Glutathione Reductase") OR TS=("Reductase, Glutathione") OR TS=("Glutathione Peroxidase") OR TS=("Peroxidase Glutathione") OR TS=(Superoxide Dismutase) OR TS=("Dismutase Superoxide") OR TS=("Oxidative Stress") OR TS=("Stress Oxidative") OR TS=("Stress, Oxidative") OR TS=("Total Antioxidant Capacity") OR TS=("Total Antioxidant Status") OR TS=("antioxidant") OR TS=("Oxidant") OR TS=("reactive oxygen species") OR TS=("Catalase") OR TS=("Oxygen Radical Absorbance") OR TS=("reactive nitrogen species") OR TS=("protein carbonyl") OR TS=("lipid peroxide") OR TS=("Total Radical Trapping Antioxidant Parameter") OR TS=("Malondialdehyde") OR TS=("Nitric oxide") OR TS=("8-hydroxydeoxyguanosine") OR TS=("thiobarbituric acid reactive substances") OR TS=("nitrotyrosine") OR TS=("sulfhydryl group") OR TS=("oxidized LDL lipoprotein") OR TS=("xanthine oxidase") OR TS=("paraoxonase-1")	1030754
#3	TS=(Randomized controlled trial) OR TS=(controlled clinical trial) OR TS=(randomized controlled trials) OR TS=(random allocation) OR TS=(double blind method) OR TS=(single blind method) OR TS=(clinical trial) OR TS=(clinical trials) OR TS=(placebos) OR TS=(placebo) OR TS=(random)	1825087
#4	**#1** AND **#2** AND **#3**	79

SCOPUS
Number of localized studies: 216
Limits: *document type* (article and article in press)
Number of studies after applying limits: 142

	Descriptors	Number of studies reached
#1	(TITLE-ABS-KEY (chromium)) OR (TITLE-ABS-KEY (chromium AND picolinate)) OR (TITLE-ABS-KEY (chromium AND nicotinate))	230648
#2	((TITLE-ABS-KEY (glutathione AND reductase)) OR (TITLE-ABS-KEY (reductase, AND glutathione)) OR (TITLE-ABS-KEY (glutathione AND peroxidase)) OR (TITLE-ABS-KEY (peroxidase AND glutathione)) OR (TITLE-ABS-KEY (superoxide AND dismutase)) (TITLE-ABS-KEY (dismutase AND superoxide)) OR (TITLE-ABS-KEY (oxidative AND stress)) OR (TITLE-ABS-KEY (stress AND oxidative)) OR (TITLE-ABS-KEY (stress, AND oxidative))) OR ((TITLE-ABS-KEY (stress, AND oxidative)) OR (TITLE-ABS-KEY (total AND antioxidant AND capacity)) OR (TITLE-ABS-KEY (total AND antioxidant AND status)) OR (TITLE-ABS-KEY (antioxidant)) OR (TITLE-ABS-KEY (oxidant)) OR (TITLE-ABS-KEY (reactive AND oxygen AND species)) OR (TITLE-ABS-KEY (catalase))) OR ((TITLE-ABS-KEY (oxygen AND radical AND absorbance)) OR (TITLE-ABS-KEY (reactive AND nitrogen AND species)) OR (TITLE-ABS-KEY (protein AND carbonyl)) OR (TITLE-ABS-KEY (lipid AND peroxide)) OR (TITLE-ABS-KEY (total AND radical AND trapping AND antioxidant AND parameter)) OR (TITLE-ABS-KEY (malondialdehyde)) OR (TITLE-ABS-KEY (nitric AND oxide))) OR ((TITLE-ABS-KEY (8-hydroxydeoxyguanosine)) OR (TITLE-ABS-KEY (thiobarbituric AND acid AND reactive AND substances)) OR (TITLE-ABS-KEY (nitrotyrosine)) OR (TITLE-ABS-KEY (sulfhydryl AND group)) OR (TITLE-ABS-KEY (oxidized AND ldl AND lipoprotein)) OR (TITLE-ABS-KEY (xanthine AND oxidase)) OR (TITLE-ABS-KEY (paraoxonase-1)))	1142335
#3	(TITLE-ABS-KEY (randomized AND controlled AND trial) OR TITLE-ABS-KEY (controlled AND clinical AND trial) OR TITLE-ABS-KEY (randomized AND controlled AND trials) OR TITLE-ABS-KEY (random AND allocation) OR TITLE-ABS-KEY (double AND blind AND method) OR TITLE-ABS-KEY	3228187

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	Descriptors	Number of studies reached
	(single AND blind AND method) OR TITLE-ABS-KEY (clinical AND trial) OR TITLE-ABS-KEY (clinical AND trials) OR TITLE-ABS-KEY (placebos) OR TITLE-ABS-KEY (placebo) OR TITLE-ABS-KEY (random))	
#4	**#1** AND **#2** AND **#3**	216

COCHRANE
Number of localized studies: 14
Limits: -
Number of studies after applying limits: 14

	Descriptors	Number of studies reached
#1	Me ("chromium") or ("chromium picolinate"):ti,ab,kw or ("chromium nicotinate"):ti,ab,kw	159
#2	Me ("Glutathione Reductase") or ("Reductase, Glutathione"):ti,ab,kw or ("Glutathione Peroxidase"):ti,ab,kw or ("Peroxidase Glutathione"):ti,ab,kw or ("Superoxide Dismutase"):ti,ab,kw or ("Dismutase Superoxide"):ti,ab,kw or ("Oxidative Stress"):ti,ab,kw or ("Stress Oxidative"):ti,ab,kw or ("Stress, Oxidative"):ti,ab,kw or ("Total Antioxidant Capacity"):ti,ab,kw or ("Total Antioxidant Status"):ti,ab,kw or ("antioxidant"):ti,ab,kw or ("Oxidant"):ti, ab,kw or ("reactive oxygen species"):ti,ab,kw or ("Catalase"):ti,ab,kw or ("Oxygen Radical Absorbance"):ti,ab,kw or ("reactive nitrogen species"):ti,ab, kw or ("protein carbonyl"):ti,ab,kw or ("lipid peroxide"):ti,ab,kw or ("Total Radical Trapping Antioxidant Parameter"):ti,ab,kw or ("Malondialdehyde"):ti,ab,kw or ("Nitric oxide"):ti,ab,kw or ("8-hydroxydeoxyguanosine"):ti,ab,kw or ("thiobarbituric acid reactive substances"):ti, ab,kw or ("nitrotyrosine"):ti,ab,kw or ("sulfhydryl group"):ti,ab,kw or ("oxidized LDL lipoprotein"):ti,ab,kw or ("xanthine oxidase"):ti,ab,kw or ("paraoxonase-1"):ti,ab,kw	26522
#3	**#1** AND **#2**	14

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