Role of Antioxidant Enzymes in Pathogenesis of Oral Squamous Cell Carcinoma: a Systematic Review and Meta-analysis

Zainab NIAZI[1], Farah FARHAN[2], Sadia MUNEER[3], Hasan MUJTABA[4], Nurul IBRAHIM[5], Norhayati YUSOP[1]

Objective: *To investigate the antioxidant enzyme status in biological samples of patients with oral squamous cell carcinoma (OSCC) and compare them with biological samples of healthy people through a systematic review and meta-analysis.*
Methods: *Antioxidant enzymes of catalase (CAT), sodium dismutase (SOD) and glutathione peroxide (GPx) were included in the analysis. A literature search was conducted of the PubMed, Science Direct, Scopus, Web of Science and Wiley Online Library databases for studies published between January 1999 and December 2022. A total of 831 articles were selected, of which 131 were found to be relevant. Finally, the full texts of 12 studies were screened and included. Studies that evaluated other antioxidant enzymes were excluded. Standardised mean difference (SMD) was derived to conduct a meta-analysis using comprehensive meta-analysis v3 (Biostat, Englewood, NJ, USA). A random effects model with 95% confidence interval (CI) was used to estimate the effect size. P < 0.05 was considered significant.*
Results: *CAT levels were measured in eight studies (n = 567) and the mean values for the OSCC and control groups were 4.81 ± 2.57 and 10.02 ± 1.81, respectively (SMD 3.18, 95% CI 1.01 to 1.42; P = 0.001). SOD level was evaluated in 11 studies (n = 762) and the values for the OSCC and control groups were 3.78 ± 1.45 and 7.34 ± 1.79, respectively (SMD 3.66, 95% CI 1.51 to 1.94; P = 0.001). GPx level was evaluated in 10 studies (n = 697) and the values for the OSCC and control groups were 13.33 ± 1.42 and 16.54 ± 2.9, respectively (SMD 1.91, 95% CI 1.34 to 1.77; P = 0.001). The heterogeneity between the studies was severe ($I^2 \geq 90\%$). The risk of bias between studies was low to moderate.*
Conclusion: *Analysis revealed that the levels of antioxidant enzymes decreased in biological samples of patients with OSSC as compared to healthy controls. Understanding the pathological progress of OSCC by analysing the level of antioxidant enzymes is beneficial in formulating a personalised, targeted pro-oxidant therapy for cancer treatment.*
Keywords: *antioxidant enzymes, oral squamous cell carcinoma, pathogenesis*
Chin J Dent Res 2024;27(3):243–251; doi: 10.3290/j.cjdr.b5698337

1 Universiti Sains Malaysia School of Dental Sciences, Kelantan, Malaysia.
2 Rawal Institute of Health Sciences, Islamabad, Pakistan.
3 National University of Medical Sciences, Islamabad, Pakistan.
4 Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, Pakistan.
5 International Islamic University Malaysia, Pahang, Malaysia.

Corresponding author: Dr Norhayati YUSOP, Basic Sciences and Medical Unit, School of Dental Sciences, Universiti Sains Malaysia, Kelantan, 16150, Malaysia. Tel: 60- 97671185. Email: norhayatiyusop@usm.my

Antioxidant enzymes are proteins that play a critical role in protecting the body from the harmful effects of free radicals.[1,2] Reactive oxygen species (ROS) are chemically reactive molecules that are generated as a byproduct of various cellular processes, including mitochondrial oxidative metabolism.[3] Excessive levels of ROS can cause damage to cells. Hydroxyl radical (OH), hydrogen peroxide (H_2O_2) and superoxide (O^{2-}) are some of the most common ROS generated in cells.[4]

The cellular antioxidant system in mammalian cells is composed of various enzymes that work together to protect cells from the harmful effects of oxidative stress. These enzymes include catalase (CAT), copper/zinc-containing superoxide dismutase (CuZn-SOD), manganese-containing superoxide dismutase (Mn-SOD) and glutathione peroxidase (GPx).[5] Oxidative stress occurs when there is an imbalance between the production of ROS and the ability of cells to detoxify them.[6] There is growing evidence to suggest that oxidative stress and ROS can contribute to the development of cancer.[7]

Cancer is a group of diseases characterised by the abnormal growth and division of cells that can invade and destroy surrounding tissues.[8] Oral cancer is a serious disease that affects a significant number of people worldwide. It is estimated that around 3% of the world's population is affected by oral cancer.[9] It is responsible for a high mortality rate and predominantly occurs in men.[10] Smoking, tobacco use, areca nut chewing and alcohol consumption are among the well-known risk factors for oral cancers. In the context of oral carcinoma, studies have suggested that ROS play a role in the development and progression of the disease. For example, ROS levels have been shown to be higher in oral cancer cells compared to normal oral cells.[11-13]

However, many studies have suggested that the activity levels of SOD, GPx and catalase are associated with the prognosis of cancer, including oral cancer.[14,15] Reactive nitrogen species (RNS) are produced by the body's immune system in response to infection or inflammation. The levels of RNS and nitrosamines are increased in patients with oral squamous cell carcinoma (OSCC), a type of oral cancer.[16] Hence, this analysis is focused on gathering the existing information on the expression status of relevant antioxidant enzymes of CAT, SOD and GPx in the tissues of OSCC. It was hypothesised that antioxidant enzymes play a role in pathogenesis samples of OSCC as compared to healthy tissue. By analysing the gathered data, the present authors aimed to investigate the potential association between antioxidant enzyme expression and OSCC development and progression. This study is expected to be useful in providing key information for future treatment and management of oral cancer.

Materials and methods

This systematic review and meta-analysis was conducted according to the population (samples with OSSC positive patients), intervention/exposure (enzymes CAT, SOD and GPx), controls (samples from normal tissue from the same patients) and outcomes (levels of antioxidant enzymes (PIECO) strategy. It was conducted through the assessment of the relevant literature.

Databases and search engine

The study protocol was performed strictly adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.[17] The PubMed, Science Direct, Scopus, Web of Science and Wiley Online Library databases were searched for literature published between January 1999 and December 2022. A total of 12 case-controlled and cohort studies were included to investigate the status of antioxidant enzyme levels in patients with OSCC. Including studies that compare OSCC patients with healthy controls is also important to establish potential differences in antioxidant enzyme levels that may be associated with the development or progression of OSCC. The MeSH terms used in the literature search included "carcinoma, squamous cell", "mouth neoplasms", "squamous cell carcinoma of head and neck", "antioxidants enzymes and "pathology, oral". All studies discussing the role of antioxidant enzymes in OSCC and the control group were shortlisted and identified based on abstract and title screening. The relevant studies and abstracts were saved in Mendeley Web to have a proper reference.

Eligibility criteria

The inclusion criteria were case-control and cohort studies that evaluate the association between antioxidants and OSCC. Additionally, the criterion for including studies with sufficient data for calculating 95% confidence interval (CI) is important to ensure that the analysis was based on robust and reliable data. The following characteristics were extracted from each study: main author, publication year, sample size, level of antioxidant enzymes (catalase, sodium dismutase, glutathione peroxidase) and measurements in biological samples of OSCC patients and the control group. Articles not published in English or on unrelated topics, cadaveric studies and reviews, studies that did not include the three antioxidant enzymes CAT, SOD or GPx and measurement standards that were not the same were all excluded.

Antioxidant enzyme levels were assessed by polymerase chain reaction (PCR), DNA analysis and immunohistochemistry. These tests are extremely reliable.[9,11] All the studies were analysed fully, including the methodology and variables to be measured. After evaluating all the features, the authors reviewed them against the search criteria. All the shortcomings of studies were

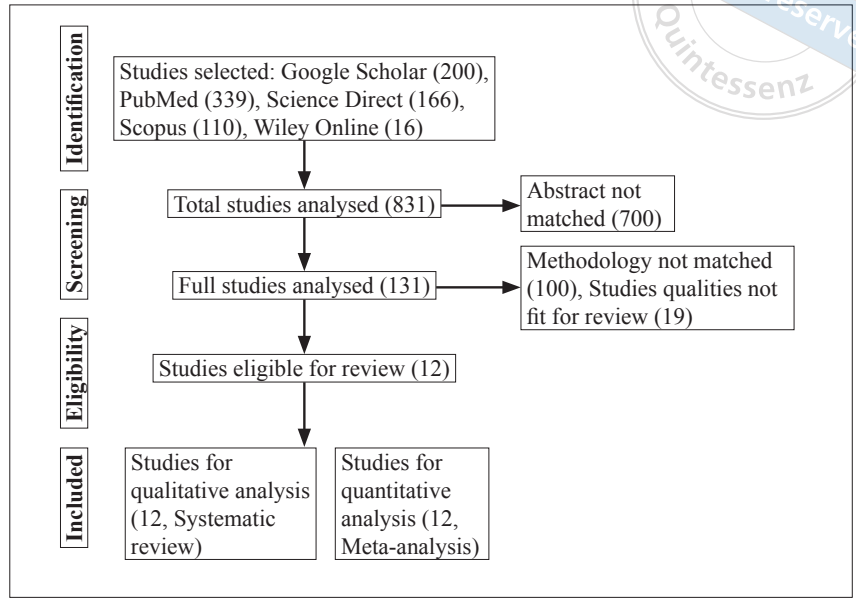

Fig 1 Study selection: PRISMA flowchart.

evaluated by entering values in the Newcastle-Ottawa quality assessment scale (NOS). The data were collected and tabulated separately in the specified format.

Data extraction and outcomes

Levels of antioxidant enzymes and their mean analysis were the outcomes, whereas study design, age range, sex, sampling technique, sample size and their *P* values were extracted from articles and tabulated in a separate table for detailed analysis.

Data collection and assessment

Two independent reviewers (ZN and FF) were involved in the literature review process. They independently reviewed the full texts of studies that passed the initial screening process, extracting relevant data from each one. Any disagreement between these two investigators was resolved through discussion with a third author. Duplicate references were eliminated using manual reference management software Mendeley to save time and reduce the risk of errors. The NOS was used to assess the quality of the studies.[18] The NOS is divided into three sections, which assess the quality of a study's selection, comparability and outcome investigation. It assigns points or stars for each question in each section of the scale. For cohort studies, a score of up to 3 is categorised as high risk of bias, a score between 4 and 6 is classed as moderate risk of bias, and a score between 7 and 9 is categorised as low risk of bias. For cross-sectional studies, a score of up to 4 is categorised as high risk of bias, a score between 5 and 6 is classed as moderate risk of bias, a score between 7 and 8 is deemed low risk of bias, and a score between 9 and 10 is categorised as very low risk of bias.

Data synthesis

The standardised mean difference (SMD) was used in the meta-analysis to pool the results of studies that had reported outcomes using different measurement scales or units. It was calculated by dividing the difference in means of the two groups by the pooled standard deviation. For SMD, statistical software Comprehensive Meta-Analysis v 3.0 (Biostat, Englewood, NJ, USA) was used.[19] SMD was employed to compare the levels of CAT, SOD and GPx biomarkers between patients with OSCC and a control group with an effect size of 95% CI. A random-effects model was used to account for significant heterogeneity with I^2, Q test and T-squared values among the studies in this analysis. Prediction intervals with forest plots and publication bias with funnel plots was used. Studies with the same values of CAT, SOD and GPx in similar units were included.

Results

A total of 831 studies were gathered using the search strategy, including 339 from PubMed, 166 from Science Direct, 200 from Google Scholar, 110 from Scopus and 16 from Wiley Online Library. After screening of abstracts and titles, 700 studies that did not meet the inclusion criteria were excluded. The full texts of all the remain-

Table 1 Study characteristics and level of CAT, SOD and GPx in different biological samples.

Study	Country	Study design	Sex	Age range (y)	Sample size	Sample type	Unit	OSCC, mean ± SD	Healthy, mean ± SD	*P* value
Subapriya et al[20]	India	Cohort	M 8, F4	45–60	12	Erythrocyte-lysate	µmole/s/mg Hb	CAT 1.89 ± 0.12; SOD 1.53 ± 0.22; GPx 8.62 ± 0.08	CAT 2.77 ± 0.26; SOD 3.63 ± 0.35; GPx 11.63 ± 1.12	≤ 0.05
Beevi et al[21]	India	Cohort	M 12, F 3	33–72	15	Erythrocyte	µmole/mg/Hb	CAT 14.44 ± 1.63; SOD 10.07 ± 2.93; GPx 33.4 ± 1.38	CAT 33.63 ± 2.59; SOD 21.35 ± 2.80; GPx 13.80 ± 1.22	0.0001
Manoharan et al[23]	India	Case control	M 48, F 0	40–60	48	Erythrocyte-lysate	µmole/mg/Hb	CAT 1.22 ± 0.07; SOD 1.73 ± 0.09; GPx 15.24 ± 1.3	CAT 1.76 ± 0.12; SOD 2.29 ± 0.17; GPx 22.32 ± 1.86	≤ 0.01
Kalayci et al[22]	Turkey	Case control	M 14, F 6	40–76	20	Tissue	U/mg protein	SOD 0.76 ± 0.02; GPx 1.89 ± 1.71	SOD 0.86 ± 0.02; GPx 0.17 ± 0.11	≥ 0.05
Sharma et al[24]	India	Cohort	M 102, F 18	40–60	120	Blood	U/ml	SOD 3.92 ± 1.75; GPx 0.03 ± 0.62	SOD 3.11 ± 1.95; GPx 0.02 ± 0.02	0.001
Srivastava et al[25]	India	Case control	M 27, F 13	38–85	40	Blood	u/g Hb	CAT 1.30 ± 0.02; SOD 1.45 ± 0.11; GPx 0.03 ± 0.62	CAT 1.95 ± 0.49; SOD 2.28 ± 0.30; GPx 0.02 ± 0.02	≤ 0.001
Shilpasree et al[26]	India	Case control	M 15, F 15	40–70	30	Tissue	nmol/min/mg	CAT 0.22 ± 0.31; SOD 1.57 ± 0.14; GPx 7.72 ± 3.96	CAT 0.59 ± 0.04; SOD 2.91 ± 0.35; GPx 19.70 ± 1.49	≤ 0.0001
Sehitogulları et al[27]	Turkey	Case control	M 23, F 42	50–70	65	Serum	U/ml	SOD 7.39 ± 2.62; GPx 22.05 ± 2.73	SOD 25.01 ± 2.83; GPx 47.32 ± 3.75	0.05
Banerjee et al[28]	India	Case control	M 25, F 5	25–50	30	Tissue	mg/min	CAT 2.00 ± 2.09	CAT 6.40 ± 0.29	0.0001
Babiuch et al[29]	Poland	Case control	M 20, F 20	25–70	40	Saliva	U/ml	SOD 7.07 ± 5.30; GPx 20.53 ± 0.73	SOD 2.36 ± 2.42; GPx 15.00 ± 17.00	0.001
Shahi et al[30]	India	Case control	M 86, F 34	26–68	120	Blood	U/min/ml	CAT 14.70 ± 9.80; SOD 4.60 ± 2.24	CAT 29.00 ± 9.20; SOD 10.80 ± 7.40	≤ 0.005
Sushma et al[31]	India	Case control	M 125, F 75	26–70	200	Serum	U/100 mg protein	CAT 2.71 ± 6.51; SOD 1.49 ± 0.49; GPx 10.70 ± 0.73	CAT 4.03 ± 1.48; SOD 6.10 ± 1.12; GPx 13.80 ± 1.25	≤ 0.005

The Granularity-Related Inconsistency of Means (GRIM) test is used to identify potential errors or inconsistencies in the reporting of means of CAT, SOD and GPx markers in the selected studies.

CAT level was measured in eight studies. In five studies,[21,26,28,30,31] the statistical means were inconsistent. SOD level was measured in 11 studies (Table 1). The GRIM statistical test showed that three studies[24,27,29] and the five abovementioned studies of CAT levels are inconsistent due to the differences in biological sample collection method and sample sizes.

GPx level was measured in 10 studies. The GRIM statistical test showed that statistical means were inconsistent in all studies.

Thus, there is the possibility of publication bias between studies in which statistical means were inconsistent.

ing 131 studies relevant to the present studies were screened. Finally, only 12 studies had data compatible with a meta-analysis (Fig 1).

All study characteristics and the levels of CAT, SOD and GPx in various biological samples are presented in Table 1.[20-31] The NOS was used to assess the quality of the studies (Table 2).[20-31]

The biological samples of CAT levels in eight studies (n = 567) were reported. The mean values for the OSCC and control groups were 4.81 ± 2.57 and 10.02 ± 1.81, respectively. The overall SMD in the random model was 3.18 (Z = 4.92, 95% CI 1.01 to 1.42; $P = 0.0001$). There was severe heterogeneity between the studies ($I^2 = 96.3\%$, $Q = 188.47$, $\tau^2 = 3.01$, variance 5.41; $P = 0.0001$). There was an increase in CAT level in all studies with respect to CAT activity (Fig 2). The study publication bias was measured in a funnel plot (Fig 3).

The level of SOD was evaluated in 11 studies (n = 762). The mean values for the OSCC and control groups were 3.78 ± 1.45 and 7.34 ± 1.79, respectively. The overall level of SOD in biological samples showed an SMD in the random model of 3.66 (Z = 4.10, 95% CI 1.51 to 1.94; $P = 0.001$). There was severe heterogeneity between the studies ($I^2 = 98.2\%$, $Q = 556.37$; $\tau^2 = 8.42$, variance 28.11;

Table 2 Quality of studies assessed using the NOS.

Selection					Comparability		Exposure				
Study	Case definition	Case represents	Control selection	Control definition	Known cont. factor	Potentialcont. factor	Secure patient	Interviewer blinded to case and control	Similarity case and control	No response	Total
Subapriya et al[20]	1	1	1	1	NA	NA	1	NA	1	NA	6
Beevi et al[21]	1	1	1	NA	1	NA	1	NA	NA	NA	5
Kalayci et al[22]	1	1	1	1	NA	NA	1	NA	1	NA	6
Monohara et a[l23]	1	1	1	NA	NA	NA	1	NA	1	1	6
Sharma et al[24]	1	1	1	1	1	NA	1	NA	1	1	8
Srivastava et al[25]	1	1	1	1	NA	1	1	NA	1	1	8
Shilpasree et al[26]	1	1	1	1	NA	NA	1	NA	1	1	7
Sehitogulları et al[27]	1	1	1	1	1	1	1	NA	NA	1	8
Banerjee et al[28]	1	1	1	1	NA	NA	1	NA	1	1	7
Babiuch et al[29]	1	1	1	1	NA	NA	1	NA	NA	1	6
Shahi et al[30]	1	1	1	1	NA	NA	1	NA	1	1	7
Sushma et al[31]	1	1	1	1	NA	NA	1	NA	1	NA	6

Note: For cohort studies, the NOS classes a score of up to 3 as high risk of bias, a score between 4 and 6 as moderate risk of bias, and a score between 7 and 9 as low risk of bias. For cross-sectional studies, the NOS classes a scoreof up to 4 as high risk, a score between 5 and 6 as moderate risk of bias, a score between 7 and 8 as low risk of bias, and a score between 9 and 10 as very low risk of bias. NA, not available.

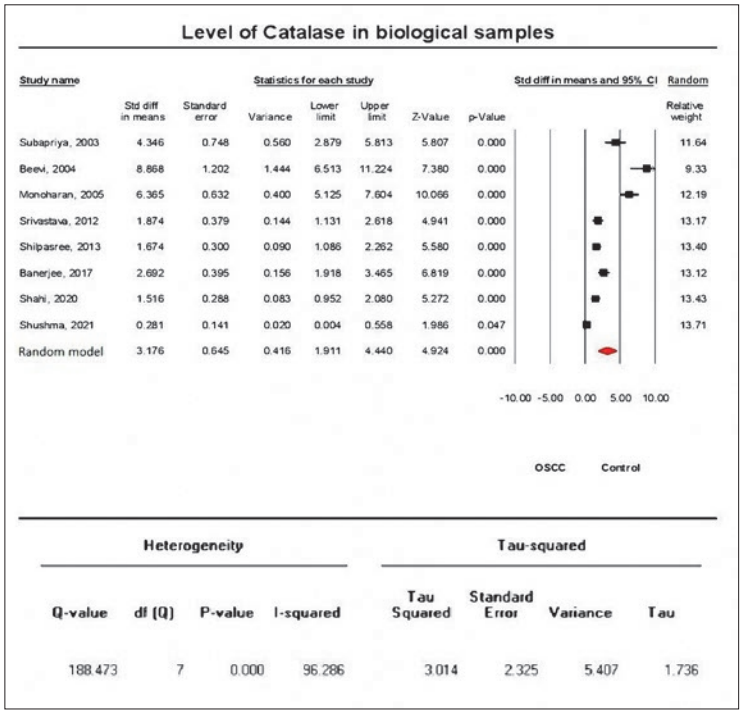

Fig 2 Forest plot showing weighted mean/relative weight (random) and SMD estimates with 95% CI for the differences in CAT levels between the OSCC group and the healthy control group. To estimate the variance of true effect size between the studies, τ^2 was applied (value: 3.01).

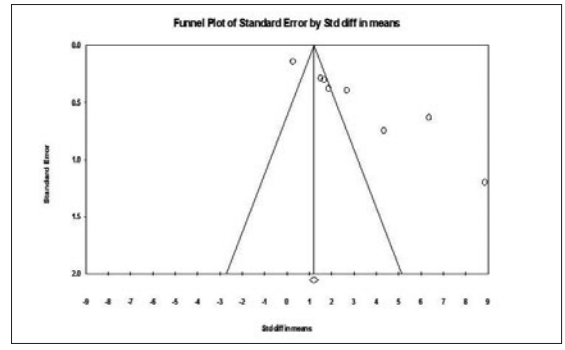

Fig 3 Publication bias between the studies. The funnel plot shows that only three studies were significant, perhaps due to the inconsistencies between the biological sample types and means of the studies. The margin of error was 10% between the studies' level of publication bias.

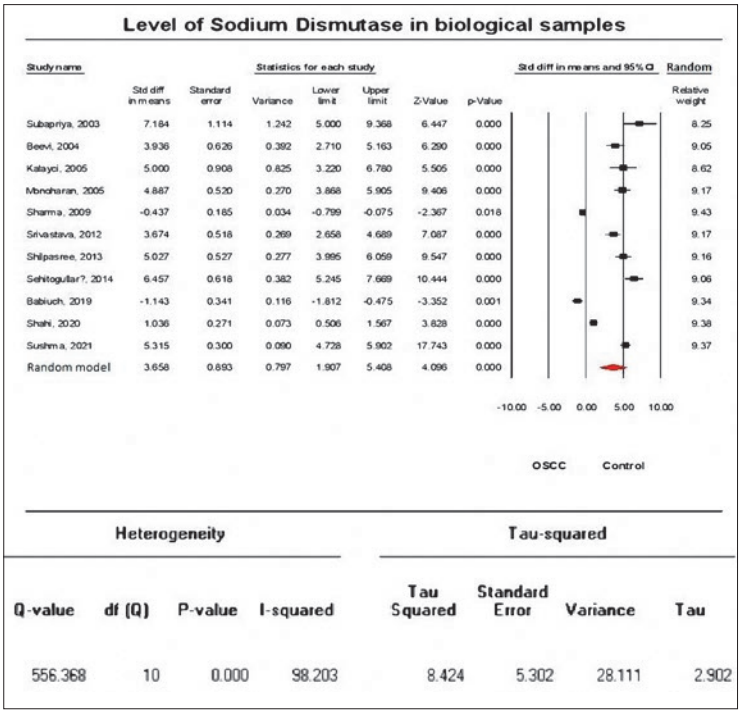

Fig 4 Forest plot showing weighted mean/relative weight (random) and SMD estimates with 95% CI for the differences in SOD levels between the OSCC group and the healthy control group. To estimate the variance of true effect size between studies, τ^2 was applied (value: 8.42).

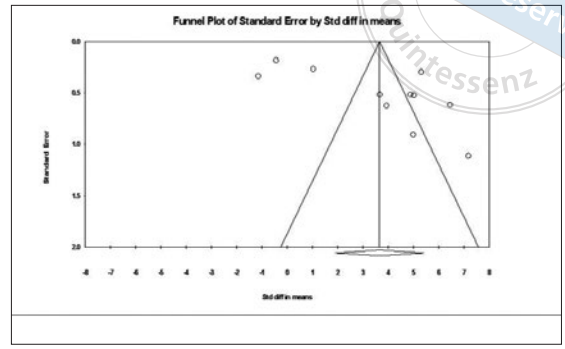

Fig 5 Publication bias between the studies. The funnel plot shows that only three studies were significant, perhaps due to the inconsistencies between the means of the studies. The margin of error was 10% between the studies' level of publication bias.

P = 0.0001). The level of SOD was significantly decreased in biological samples with OSSC compared to healthy ones (Fig 4). The study publication bias was measured in a funnel plot (Fig 5).

The GPx level was calculated in 10 studies (n = 697). The mean for the OSCC and control groups was 13.33 ± 1.42 and 16.54 ± 2.90, respectively. There was a significant decrease in GPx levels in biological samples with OSSC. The overall SMD in GPx level in the random model was 1.91 (Z = 2.13, 95% CI 1.34 to 1.77; *P* = 0.03). There was severe heterogeneity between the studies (I^2 = 98.1%, *Q* = 471.57, τ^2 = 7.50, variance 29.96, P = 0.0001); however, the GPx level was significantly decreased in biological samples with OSCC compared to healthy ones (Fig 6). The study publication bias was measured in a funnel plot (Fig 7).

The high heterogeneity in this meta-analysis showed I^2 values of CAT 96.3, SOD 98.2 and GPx 98.1 (Figs 2, 4 and 6). The different methods used in reporting studies to measure antioxidant enzyme levels could be the reason for high heterogeneity. When meta-regression analysis was performed on sample size and types, insignificant R^2 (9%, P = 0.211) was recorded.

The R^2 value was very low and insignificant in the meta-regression model, and indicates that the sample size and types of samples were also potential reasons for heterogeneity.

Discussion

This study investigated the role of antioxidant enzymes in OSCC. A total of 12 studies were included in the analysis. Most of the studies reported that the statistical means of CAT, SOD and GPx levels in biological sample were inconsistent. The combined analysis of the studies of antioxidant enzymes is considered severely heterogenous. The overall quality of the evidence is "average to good".

Oxidative stress occurs when there is an imbalance between the production of ROS and the body's ability to counteract or repair the damage caused by them.[32] Prolonged exposure to oxidative stress and sustained inflammation can lead to the accumulation of genetic damage, which can increase the risk of cancer development. This is because oxidative stress can cause damage to DNA and other cellular components, and if the damage is not repaired or removed, it can accumulate over time and lead to genetic mutations and other changes that contribute to cancer initiation.[33] ROS are associated with high free radicals and reactivity that are

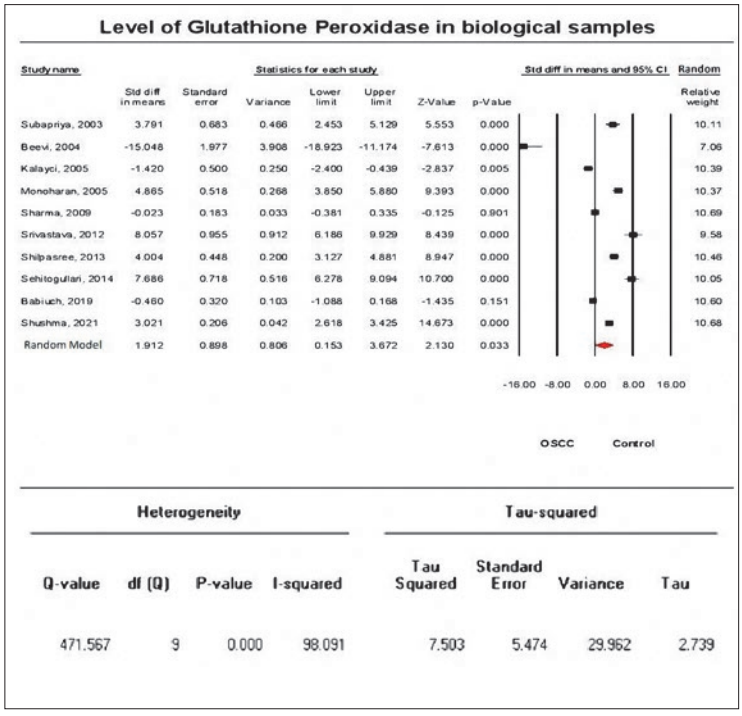

Fig 6 Forest plot showing weighted mean/relative weight (random) and SMD estimates with 95% CI for the differences in GPx levels between the OSCC group and the healthy control group. To estimate the variance of true effect size between studies, τ^2 was applied (value: 7.50).

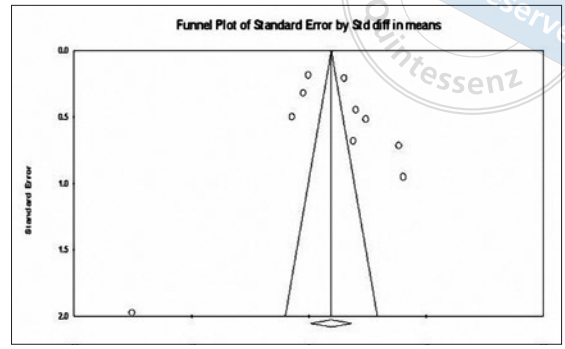

Fig 7 Publication bias between the studies. The funnel plot shows that no studies were significant, perhaps due to the inconsistencies between the mean data of the studies. The margin of error was 10% between the studies' level of publication bias.

involved in different processes, especially in the initiation and promotion of OSCC.[34] A network of antioxidant enzymes controls the cellular maintenance of the redox system. Amongst the enzymes, the most common are CAT, SOD and GPx.[35] Despite the existence of diverse protection mechanisms against oxidant injuries, redox homeostasis is altered within tumour cells. Excessive ROS production is associated with alteration of gene expression and genetic instability, favouring cancer cell proliferation.[36]

In the present study, levels of CAT, SOD and GPx were analysed in different biological samples taken from patients with OSCC and healthy patients. In a study performed by Subapryia et al,[20] the activity of CAT, SOD and GPx was decreased by 58%, 33% and 59%, respectively, in preoperative OSCC patients as compared to normal subjects. The findings showed that an imbalance in the redox status of patients with oral cancers may be due to the compromised antioxidant levels. Decreased levels of CAT, GPx and SOD in erythrocyte lysate of oral cancer patients as compared to healthy patients has also been reported.[21,23] Furthermore, GSH-Px levels were reported to increase significantly in cancerous patients' tissue as compared with cancer-free tissues ($P \leq 0.05$), whereas an insignificant difference was reported between SOD activities ($P \geq 0.05$).[22,23]

Overall, a decline in the enzymatic and non-enzymatic antioxidant enzyme level in oral cancer patients has been a common finding in various studies.[21-24] Antioxidant levels decreased gradually in oral cancer patients from stage II to stage IV.[25] Further experimental evidence also demonstrated a significantly low level ($P = 0.001$) of SOD and GPx in cancer patients compared to healthy patients.[26] Similarly, the mean levels of antioxidant enzymes CAT, SOD and GPx were lower in study cases, and the difference was highly statistically significant.[27,28] These findings suggest the presence of oxidative stress in oral cancer patients; however, analysis of correlation (r) showed a significantly negative correlation between antioxidant and pro-oxidant levels in patients ($P \leq 0.05$).[27] Hence, it is postulated that OSCC is closely associated with a marked increase in oxidative stress and a decrease in antioxidant enzyme activities.[28] On a similar note, a decrease in antioxidant level was reported in the blood of patients diagnosed with OSCC as compared with healthy controls ($P \leq 0.001$).[26] Meanwhile, GSH showed a significant positive correlation with SOD ($P \leq 0.001$), GPx and CAT ($P \leq 0.01$).[26] Likewise, oral cancer

patients demonstrated significantly reduced levels of SOD and GPX ($P \leq 0.005$), with no significant difference observed with regard to catalase level.[31] The findings further suggested the role of superoxide dismutase and glutathione peroxides in the progression and development of oral carcinogenesis.[31]

However, in a different study performed on OSCC samples, post-hoc analysis showed that patients with OSCC had a markedly increased level of SOD compared with the control groups.[30] Different approaches have been used by researchers to evaluate the amount of SOD, GPX and catalase in diverse biological samples, which may have different results. The majority of the OSCC group patients in those studies were categorised using various clinical staging methods and histological grading systems. Future research intending to evaluate the impact of oxidative stress on tumours should consider these details in the OSCC group's antioxidant enzymes assessment.

Limitations

This analysis has several limitations. The Begg test failed to find a statistically significant publishing bias. It was also challenging to compare the research to determine the relationship between the results due to the wide variety of sample sizes in the different studies. Further analysis of the effect of antioxidant enzymes on tumour tissue should be carried out to better understand the relationship between the different treatments and outcomes. Biological samples should be preferred as they experience the greatest enzymatic changes in patients with tumours compared to normal samples.

Conclusion

The majority of investigations showed that individuals with OSCC had significantly lower antioxidant levels than healthy controls. Antioxidant enzymes are possible biomarkers for oxidative stress and a reliable prognostic predictor of OSCC.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Drs Zainab NIAZI and Norhayati YUSOP contributed to the research design and data collection; Drs Farah FARHAN and Sadia MUNEER contributed to the statistical analysis and manuscript draft; Drs Hasan MUJTABA and Zainab NIAZI contributed to project management and manuscript revision; Dr Nurul IBRAHIM contributed to the critical revision of the manuscript.

(Received June 20, 2023; accepted May 30, 2024)

References

1. Young IS, Woodside JV. Antioxidants in health and disease. J Clin Pathol 2001;54:176–186.
2. Roy Z, Bansal R, Siddiqui L, Chaudhary N. Understanding the role of free radicals and antioxidant enzymes in human diseases. Curr Pharm Biotechnol 2023;24:1265–1276.
3. Rogers NM, Seeger F, Garcin ED, Roberts DD, Isenberg JS. Regulation of soluble guanylate cyclase by matricellular thrombospondins: implications for blood flow. Front Physiol 2014;5:134.
4. Zuo L, Zhou T, Pannell BK, Ziegler AC, Best TM. Biological and physiological role of reactive oxygen species--the good, the bad and the ugly. Acta Physiol (Oxf) 2015;214:329–348.
5. Ighodaro OM, Akinloye OA. First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. Alexandria J Med 2018;54:287–293.
6. He L, He T, Farrar S, Ji L, Liu T, Ma X. Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species. Cell Physiol Biochem 2017;44:532–553.
7. Hayes JD, Dinkova-Kostova AT, Tew KD. Oxidative stress in cancer. Cancer Cell 2020;38:167–197.
8. Jiang WG, Sanders AJ, Katoh M, et al. Tissue invasion and metastasis: Molecular, biological and clinical perspectives. Semin Cancer Biol 2015;35(suppl):S244–S275.
9. Bugshan A, Farooq I. Oral squamous cell carcinoma: metastasis, potentially associated malignant disorders, etiology and recent advancements in diagnosis. F1000Res 2020;9:229.
10. Abati S, Bramati C, Bondi S, Lissoni A, Trimarchi M. Oral cancer and precancer: a narrative review on the relevance of early diagnosis. Int J Environ Res Public Health 2020;17:9160.
11. Kumar SA, Indu S, Gautami D, VarRuchi S. Oral squamous cell carcinoma (OSCC) in humans: Etiological factors, diagnostic and therapeutic relevance. Res J Biotechnol 2020;15:141–151.
12. Pastushenko I, Blanpain C. EMT transition states during tumor progression and metastasis. Trends Cell Biol 2019;29:212–226.
13. Vo TT, Wu CZ, Lee IT. Potential effects of noxious chemical-containing fine particulate matter on oral health through reactive oxygen species-mediated oxidative stress: Promising clues. Biochem Pharmacol 2020;182:114286.
14. Weydert CJ, Cullen JJ. Measurement of superoxide dismutase, catalase and glutathione peroxidase in cultured cells and tissue. Nat Protoc 2010;5:51–66.
15. Jablonska E, Gromadzinska J, Peplonska B, et al. Lipid peroxidation and glutathione peroxidase activity relationship in breast cancer depends on functional polymorphism of GPX1. BMC Cancer 2015;15:657.
16. Scher RL. Role of nitric oxide in the development of distant metastasis from squamous cell carcinoma. Laryngoscope 2007;117:199–209.
17. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg 2021;88:105906.

18. Andrade C. Mean Difference, Standardized Mean Difference (SMD), and Their Use in Meta-Analysis: As Simple as It Gets. J Clin Psychiatry 2020;81:20f13681.
19. Bae JM. A suggestion for quality assessment in systematic reviews of observational studies in nutritional epidemiology. Epidemiol Health 2016;38:e2016014.
20. Subapriya R, Kumaraguruparan R, Nagini S, Thangavelu A. Oxidant-antioxidant status in oral precancer and oral cancer patients. Toxicol Mech Methods 2003;13:77–81.
21. Beevi SS, Rasheed AM, Geetha A. Evaluation of oxidative stress and nitric oxide levels in patients with oral cavity cancer. Jpn J Clin Oncol 2004;34:379–385.
22. Kalayci A, Ozturk A, Ozturk K, Karagozoglu E, Dolanmaz D. Superoxide dismutase and glutathione peroxidase enzyme activities in larynx carcinoma. Acta Otolaryngol 2005;125: 312–315.
23. Manoharan S, Kolanjiappan K, Suresh K, Panjamurthy K. Lipid peroxidation & antioxidants status in patients with oral squamous cell carcinoma. Indian J Med Res 2005;122: 529–534.
24. Sharma M, Rajappa M, Kumar G, Sharma A. Oxidant-antioxidant status in Indian patients with carcinoma of posterior one-third of tongue. Cancer Biomark 2009;5:253–260.
25. Srivastava KC, Austin RD, Shrivastava D, Sethupathy S, Rajesh S. A case control study to evaluate oxidative stress in plasma samples of oral malignancy. Contemp Clin Dent 2012;3: 271–276.
26. Shilpasree AS, Kumar K, Itagappa M, Ramesh G. Study of oxidative stress and antioxidant status in oral cancer patients. Int J Oral Maxillofac Surg 2013;4:2–6.
27. Sehitogulları A, Aslan M, Sayır F, Kahraman A, Demir H. Serum paraoxonase-1 enzyme activities and oxidative stress levels in patients with esophageal squamous cell carcinoma. Redox Rep 2014;19:199–205.
28. Banerjee S, Mukherjee S, Mitra S, Singhal P. Altered expression of mitochondrial antioxidants in oral squamous cell carcinoma. J Oral Sci 2017;59:439–446.
29. Babiuch K, Bednarczyk A, Gawlik K, et al. Evaluation of enzymatic and non-enzymatic antioxidant status and biomarkers of oxidative stress in saliva of patients with oral squamous cell carcinoma and oral leukoplakia: a pilot study. Acta Odontol Scand. 2019;77:408–418.
30. Shahi Y, Samadi FM, Mukherjee S. Plasma lipid peroxidation and antioxidant status in patients with oral precancerous lesions and oral cancer. Oral Sci Int 2020;17:86–93.
31. Sushma PS, Jamil K, Udaykumar P, et al. Analysis of CCND1 protein and circulatory antioxidant enzyme activity association in oral squamous cell carcinoma. Saudi J Biol Sci 2021;28:6987–6991.
32. Pizzino G, Irrera N, Cucinotta M, et al. Oxidative stress: harms and benefits for human health. Oxid Med Cell Longev 2017;2017:8416763.
33. George S, Abrahamse H. Redox potential of antioxidants in cancer progression and prevention. Antioxidants (Basel) 2020;9:1156.
34. Menegon S, Columbano A, Giordano S. The dual roles of NRF2 in cancer. Trends Mol Med 2016;22:578–593.
35. Juneja S, Rathore AS, Sharma K, Shetty D, Jain A. Antioxidant-oxidant index as a biomarker in oral potentially malignant disorders and oral squamous cell carcinoma: a biochemical study. J Clin Diagn Res 2017;11:ZC05–ZC08.
36. Flohé L. Looking back at the early stages of redox biology. Antioxidants (Basel) 2020;9:1254.