REVIEW

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The effect of monosodium glutamate on the risk of oral cancer: a systematic review

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ABSTRACT

Introduction: Oral cancer is a malignancy, and most cases are diagnosed as oral squamous cell carcinoma. Oral cancer has a multifactorial etiology, one of which is the pattern of food intake. Monosodium glutamate has been widely used by the public as a flavor enhancer. Until now, the safety of MSG has been debated because several studies state that MSG can have both negative and positive effects, so its effect on the risk of developing oral cancer is still unclear. The aim of this study was to find out the effect of MSG on the risk of oral cancer.

Methods: An article search was performed through the Pubmed, ScienceDirect, EBSCOhost, Nature, Scopus, ResearchGate, and Semantic Scholar databases using predefined keywords, inclusion and exclusion criteria, and adapted to the PICO framework. Article writing refers to the PRISMA guidelines.

Results: A total of five selected articles were obtained. Three in vivo study articles describe the effect of MSG, which can cause genotoxicity, a decrease in the quality and quantity of DNA, and changes in the histological structure of the oral mucosa of experimental animals. One case-control study article explained that MSG had the potential to triple the risk of oral cancer, while one cohort study article described the effect of MSG in suppressing post-chemotherapy side effects in head and neck cancer patients.

Conclusion: MSG has the potential to increase the risk of oral cancer because it tends to be more of a carcinogen. It because MSG can induced and increased oxidative stress, which triggers genotoxicity in oral mucosa cells.

Keywords: Monosodium glutamate, oral cancer, carcinogen, chemopreventive, oral squamous cell carcinoma.
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INTRODUCTION

Oral cancer is a malignant condition that affects the lips or mouth cavity; it is a subtype of head and neck cancer (HNC).[1,2] Most oral cancers are diagnosed as oral squamous cell carcinoma (OSCC) because histologically 90% of cancers originate from squamous cells.[1] Oral cancer has a complicated pathophysiology and multifactorial etiology.[3,4] Oral cancer risk factors include smoking, excessive alcohol use, betel chewing, poor oral hygiene, UV irradiation, Human Papillomavirus (HPV) infection, genetic, dietary, and nutritional patterns.[3,5] According to the World Health Organization, thirty percent of malignancies are connected with dietary patterns, which have been investigated according to individual dietary intake.[6]

Monosodium glutamate is a synthetic flavor enhancer derived from L-glutamate, an amino acid present in proteins and an organic component of all living organisms in both bound and unbound forms.[7,8] MSG (*Sodium 2-aminopentanedioate*); with the molecular formula of $C_3H_8NNaO_4$, is available in white crystallin monohidrate consisting of 78% glutamate, 12% natrium, and 10% water.[7,9–12] MSG is one of the most widely used flavor enhancer in the world, and it has used in cooking, commercially processed food, and homemade food with its typical savory flavor or umami for 100 years.[7,13,14] Indonesia is one of the countries in Asia with the highest MSG consumption in the world,[15] in addition, according to Riskesdas 2018, around 77,6 % (from 265 people) Indonesian citizens have been using flavor enhancer such as *vetsin* (MSG), instant stock and additive more than one portion per day.[16,17]

Food safety regulatory agencies like The Food and Drug Administration (FDA) states that MSG is safe for public consumption, however, several studies indicate that monosodium glutamate (MSG) may have negative or good effects on human health, therefore its safety as a flavor enhancer is still debatable.[18] Several studies indicate that MSG can enhance food flavor, stimulate salivary secretion, and has the potential to boost appetite and food consumption; therefore, it may be beneficial to malnourished and elderly people in order to improve their health and nutritional status.[19–21] Other studies claim that chronic MSG consumption with high concentration may cause toxicity, consequently it will develop negative effect on the system of body organs.[15] One *in vitro* study explained that MSG could induce genotoxicity and potentially develop into a carcinogenic substance; it had also been reported to be associated with colorectal cancer (CRC).[22]

A study about the MSG effect to the risk of oral cancer has not been widely practiced in various countries, particularly in Asian countries, which are the highest MSG producer as well as consumer in the world.[23] According to GLOBOCAN 2020, Asian countries have had the highest prevalence rate of oral cancer development globally.[5] Based on this fact,[5,23] it can be

observed that there's MSG contradictive effect on oral cancer, especially in Asia region including Indonesia. However, there are not many articles disscussing the effect of MSG to the risk of oral cancer. The aim of this study was to find out the effect of MSG on the risk of oral cancer in order to spread information and educate the public about its effect on daily consumption.

METHODS

This article is a systematic review that has been written according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[24] The questions in this study were identified by PICO (Population, Intervention, Comparison, and Outcome) framework[25] as follows: (1) Population: oral cancer; (2) Intervention: monosodium glutamate; (3) Comparison: other types of glutamate such as monopotassium glutamate, calcium diglutamate, monoammonium glutamate, and magnesium diglutamate; (4) Outcome: oral cancer risk. This systematic review protocol is also registered on PROSPERO (Prospective Register of Systematic Reviews) with registration number CRD42023442973.

Search Strategies

The article search related to the research questions in this study used the keywords "oral cancer" OR "oral squamous cell carcinoma" OR "oral potentially malignant disorders" AND "monosodium glutamate" OR "umami" AND "carcinogenic activity" OR "toxicity" OR "chemoprevention" OR "effect" through digital databases like Pubmed, ScienceDirect, EBSCOhost, Nature, Scopus, ResearchGate, dan Semantic Scholar. Additional article searches also used manual hand searching method, i.e. checking the reference list of articles that have been obtained and will be used if relevant to the research topic.

Inclusion and Exclusion Criteria

The inclusion criteria for this study were articles published within the last 112 years (1909-2021), available in English and Indonesian, with full-text access, and discussing the effect of monosodium glutamate on the risk of oral cancer using in vivo, in vitro, cohort, cross-sectional, case-control, or randomized controlled trial (RCT) study designs. The review article is included among the exclusion criteria.

Quality of Study Assessment

The risk of bias was assessed for each of the included articles based on their study designs. JBI's Critical Appraisal Tools were used to evaluate the quality of articles with cohort, cross-sectional, case-control, and randomized controlled trial (RCT) study designs, while SYRCLE's RoB tool was used to assess the quality of articles with in vivo and in vitro study designs.

Data Extraction and Analysis

All selected articles were subjected to data extraction in order to obtain significant findings from each article based on the anticipated outcome. The selected articles will be analyzed using thematic analysis, a data-identification, classification, explanation, and reporting technique.[26] Data integration will be conducted to obtain a deeper understanding of the effect of MSG on the risk of oral cancer.

RESULTS

The Search Results

Based on the search results that matched the keywords, 17.804 articles were retrieved from seven databases (Pubmed, ScienceDirect, EBSCOhost, Nature, Scopus, ResearchGate, and Semantic Scholar), in addition to the additional articles collected through manual hand searching. The subsequent double-checking of articles produced 718 articles, bringing the total number of articles examined based on title and abstract to 17.086. The exclusion of 17.016 articles because they did not meet the inclusion criteria (irrelevant, in the form of review articles, and inaccessible as full-text) resulted in 70 articles being evaluated as a whole context (full-text). In addition, five selected articles were further analyzed and evaluated based on the assessment result. The article selection process is depicted in Figure 1.

The Characteristics of the Study

Table 1 provides an overview of the article identities that were evaluated based on inlusion criteria by categorizing the data according to the author's name, the

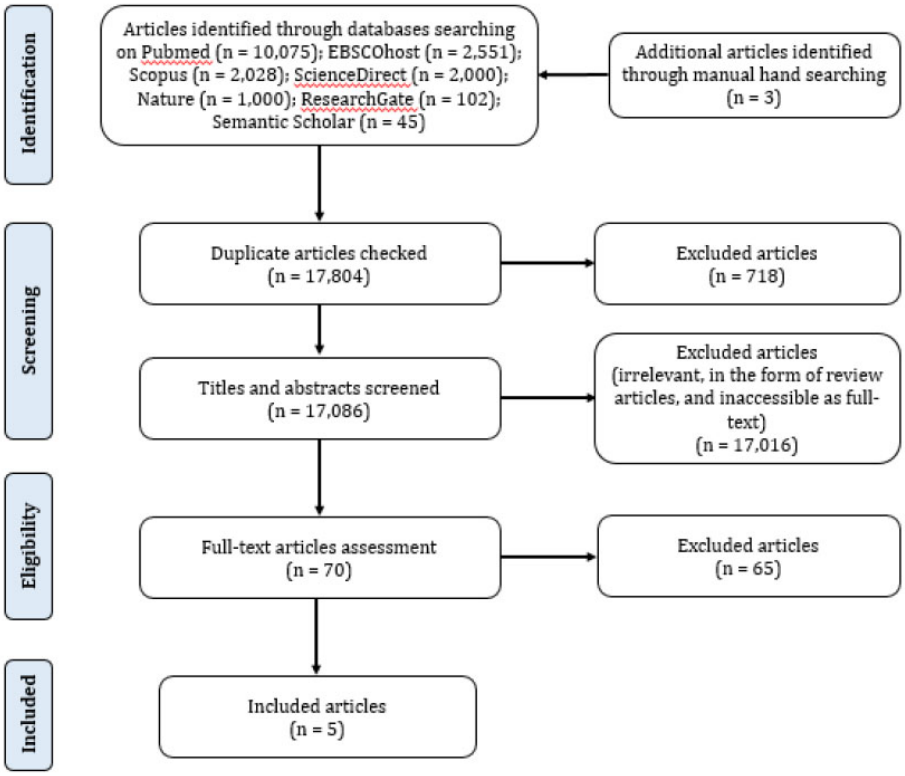

Figure 1. PRISMA flow diagram.

Table 1. The general summary of the identity of the reviewed articles based on inclusion criteria

No	Author (Year)	Title	Country	Study design
1	Shono et al. (2021)[27]	Dietary supplementation with *monosodium glutamate* suppresses chemotherapy-induced downregulation of the T1R3 taste receptor subunit in head and neck cancer patients	Japan	Cohort study
2	El Imam & El Salam (2019)[28]	Evaluation of the effect of *monosodium glutamate* administration on buccal mucosa of adult male albino rats: histological and immuno-histochemical study	Egypt	In vivo study
3	Shredah (2017)[29]	Molecular study to the effect of *monosodium glutamate* on rat gingiva	Egypt	In vivo study
4	Mohammed (2017)[30]	*Monosodium glutamate*-induced genotoxicity in rat palatal mucosa	Egypt	In vivo study
5	Amtha et al. (2009)[31]	Dietary patterns and risk of oral cancer: A factor analysis study of a population in Jakarta, Indonesia	Indonesia	Case-control study

publication year, the article's title, the country, and the study design. These five articles were published in Japan[27], Egypt[28–30] and Indonesia[31], and included cohort study, in vivo study, and case-control study. Table 2 shows the result of data extraction from the reviewed article by categorizing them according to the author's name, research design, sample, glutamate dose or concentration, administration time, result, and conclusion.

Assessment of Study Quality

Utilizing indicators from JBI's Critical Appraisal Tools, the quality of selected cohort and case-control study articles will be assessed. The answers for each indicator are Yes, No, Unclear, and N/A (Not applicable).[32,33] The quality of selected articles with in vivo study designs will be assessed using indicators from SYRCLE's RoB tool for animal studies. This assessment perceives 10 criteria pertaining to 6 types of bias, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias.[34] The answers for each indicator are Yes, No, and Unclear.[34] The results of the assessment of each article will then be categorized into three categories: (1) Low risk of bias (meets > 75% of the overall assessment); (2) Moderate risk of bias (meets 50%–74% of the overall assessment); and (3) High risk of bias (meets < 49% of the overall assessment).[35] Based on the findings of the study, the quality of cohort study and case-control study articles fell into the low risk of bias category, while in vivo study articles fell into the moderate risk of bias category. Tables 3, 4, and 5 show the complete assessment results.

DISCUSSION

Monosodium glutamate produces an umami flavor that can be perceived over a broad area of the tongue, as evidenced by the results of biochemical and neurophysiological studies that show that there are specific peripheral receptors for umami flavor.[36] The findings of studies using immunocytochemical methods for light microscopy reveal that glutamate is present in taste buds and surrounding epithelium, as well as acting as an excitatory neurotransmitter for chemosensory signaling.[36,37] One recent study found that glutamate receptors play a critical role in the pathogenesis of MSG, as evidenced by the neurotoxicity caused by glutamate receptor overexpression after high-dose MSG administration, which can lead to the onset of various neurodegenerative diseases and excitotoxicity.[21,38,39] Cancer development has been attributed to the stimulation of voltage-gated sodium channels, glutamate excitatory, and non-neural excitatory receptors that mediate cell hyperexcitability.[40]

MSG administration, according to the findings of three articles, can induce changes in molecular mechanisms such as genotoxicity and decreased DNA quality[29,30] furthermore, MSG may trigger degenerative changes in the histological structure of the oral mucosa (buccal, gingival, and palatal).[28–30] Another article discovered that MSG with the "chemically related" label has the potential to triple the risk of oral cancer when compared to the other three labels (preferred, combination, and traditional).[31] Meanwhile, one article mentions that MSG administration can alleviate dysgeusia caused by chemotherapy by increasing T1R3 expression in the tongue, VAS scores, and daily energy intake in patients with head and neck cancer.[27]

Based on the findings of the articles that have been analyzed, the average maximum dose of MSG that has the effect of increasing the risk of oral cancer is about 30 mg/kg bw, with consecutive administration for 6-8 weeks.[28–30] According to Shredah (2017)[29] and Mohammed (2017)[30], MSG administration especially at high doses (30 and 40 mg/kg bw) can cause genotoxicity and a decrease in the quality of DNA in the gingival and palatal mucosa of experimental animals; this is supported by the findings of several studies that show that consuming MSG, particularly at high doses, can cause metabolic syndrome and increased production of reactive oxygen species (ROS), triggering oxidative stress.[15,41,42] MSG-induced oxidative stress can cause genotoxicity by damaging DNA, RNA, proteins, and lipids. Furthermore, MSG can cause chromosomal instability, affecting cell division and growth, causing alterations in gene expression, and inducing mutations that lead to malignancies.[38,43] The decrease in DNA quality is characterized by a decrease in DNA integrity, which is manifested as fragmented DNA that is not intact (sheared DNA), and a decrease in relative DNA concentration as compared to the control group.[29,30,44]

MSG can cause genotoxicity through two mechanisms, which are direct and indirect mechanisms.[15] Based on the direct mechanism stage, MSG can trigger nuclear damage in the host by affecting genetic material through the induction of chromosomal aberrations, causing interference with protein adhesion or DNA/RNA metabolism resulting in clumping and stickiness of chromosomes

at the anaphase stage.[15,41] In the indirect mechanism stage, MSG can increase oxidative stress and decrease the levels of antioxidant defense enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH), resulting in genetic damage by affecting the nuclear components of the cell.[15,30,41,45] The findings of one in vivo study stated that MSG can stimulate an increase in ROS associated with cellular lipids and DNA molecules, thus causing lipid peroxidation and DNA alterations (single-strand to double-strand breaks in DNA).[46]

Ataseven et al. (2016)[38] showed that MSG can cause genotoxicity effects on human peripheral blood lymphocytes along with an increase in the concentration of administration, it is characterized by a decrease in mitotic index (MI), and an increase in chromosomal abnormalities, SCE / cell ratio (sister chromatid exchanges), and micronucleus frequency (MN).[38] The comet assay results showed that the comet tail intensity, tail length and tail moment appeared to increase significantly, while the random amplified polymorphic DNA-polymerase chain reaction (RAPD-PCR) results showed that there were different patterns in band intensity indicating the occurrence of DNA damage.[38] Al Hargan et al. (2023)[22] discovered that MSG may have a pro-proliferative effect on CRC cells at both the genetic and cellular levels, as evidenced by an increase in the viability of human colorectal adenocarcinoma cells SW620 and SW480 induced by increased expression of APC and BECN1 and decreased expression of TP53.

Histopathological findings in buccal, gingival, and palatal mucosa samples from experimental animals corroborated the results of the molecular test.[28–30] Administration of MSG at a dose of 30 mg/kg bw might result in degenerative changes to the histological structure of the buccal mucosa, El Imam & El Salam (2019)[28] reported the presence of atrophic epithelium, disruption of intercellular bridges in epithelial cells, cell degeneration with pyknotic nuclei, thinning or shortening of the rete ridge, and destruction of some basal cells, in addition to collagen fiber deposition in the lamina propria and capillary blood vessel congestion. These findings are consistent with those of Damiano et al. (1990),[47] who discovered that damaged epithelial cells can cause fibroblast activation, cell division, and deposition of collagen fiber, and that collagen fiber deposition in the lamina propria, particularly around blood vessels, causes a decrease in blood flow to the buccal mucosa, triggering ischemia and degeneration.[28] Other findings by El-Aziz et al. (2014)[48] revealed that MSG administration, particularly over an extended period of time (6 weeks), can cause damage to to the histological structure of the stomach in the form of partial loss of surface epithelium, an increase in cells undergoing destruction, blood vessel congestion, and a clear increase in connective tissue in the lamina propria and around the basal part of the gastric glands. According to research conducted by Olowofolahan et al. (2021),[49] the histological structure of uterine tissue in experimental animals fed by MSG appeared to exhibit substantial collagen fiber deposition in the endometrial layer and severe uterine hyperplasia in the myometrium.

According to Shredah (2017),[29] the administration of MSG especially at high doses (30 mg/kg bw) can induce alterations in the histological structure of the gingival mucosa, as evidenced by the appearance of acanthosis and hyperkeratosis. In addition, a higher magnification of the same histological field showed the presence of deformed and hyperchromatized sulcular epithelium, basal cells with pleomorphic hyperchromatic nuclei, and intracellular vacuolization in spinous cells.[29] In line with this statement, Mohammed (2017)[30] mentioned that administration of MSG at a high dose (40 mg/kg bw) can affect changes in the histological structure of the palatal mucosa as indicated by the presence of acanthosis and hyperkeratosis; in addition, through higher magnification, the same histological field showed a picture of pleomorphic basal cells with atypical cellular changes, increased mitosis in basal and spinous cells of the palatal mucosa, as well as the presence of bulbous rete pegs with pleomorphic basal cells.

Based on some data from scientific articles,[50–52] the most common characteristics of the development of oral precancerous lesions (oral epithelial dysplasia) are described as acanthosis, hyperkeratosis, hyperchromatic nuclei, variations in cell size and shape (cell and nuclear pleomorphism), increased cell mitosis, and bulbous rete pegs.[29,30] Another finding by Ortiz et al. (2006)[53] also discovered that MSG can cause degenerative changes in the hepatic and renal tissues of experimental animals and that histologically, the presence of hyperchromatic nuclei and variations in the size and shape of cells and cell nuclei in hepatocytes and glomerular cells is a manifestation of elevated oxidative stress triggered by MSG.

The results of histopathological analysis are supported and reinforced by immunohistochemical (Proliferating Cell Nuclear Antigen) tests performed on buccal mucosa samples of experimental animals by El Imam and El Salam (2019)[28], which revealed a positive PCNA reaction with a bright brown picture in basal cells. PCNA can determine dysregulation in cell proliferation as well as increased PCNA immunoreactivity linked with increased cell proliferation, hence, an increase in PCNA expression is a marker of alterations in normal epithelial tissue to hyperplasia, dysplasia, premalignant, and malignant lesions.[28,54]

Shono et al. (2021)[27] stated that MSG administration for 1 week at a dose of 2.7 g/kg bw/day (2700 mg/kg bw) can suppress chemotherapy-induced dysgeusia by inducing an increase in T1R3 expression in the tongue, Visual Analog Scale (VAS) score and daily energy intake in patients with head and neck cancer. On the other hand, the results of a randomized control trial (RCT) study conducted by Noel et al. (2018)[55] showed that continuous exposure to MSG for 4 weeks at a dose of 3.8 g/kg bw/day (3800 mg/kg bw) can cause a significant decrease in the intensity of perceived umami. This is consistent with the findings of Shahbandi et al. (2016)[56] which showed that long-term administration of MSG can reduce the expression of T1Rs thereby inducing a reduction in umami taste perception in experimental rats. The increase in demand for MSG was most noticeable among the group of people who consume MSG frequently, as they have a strong desire

for a higher intake of MSG compounds.[57] Glutamate (especially contained in MSG) can act as a proxy in the habitual consumption of umami stimuli since it is the main source of umami flavor in food.[55]

Epigenetic alterations or an unstable epigenetic state can also lead to an increased risk of oral cancer.[58] The epigenetic state is more reversible and is not associated with modification of DNA structure, and can be inherited and maintained for generations.[59] Epigenetic modifications usually occur due to changes in DNA methylation, histone modifications, and non-coding RNA-mediated regulation.[60,61] Epigenetic modifications can lead to abnormal gene expression and unique pathophysiological characteristics.[60] Risk factors of oral cancer such as tobacco and alcohol consumption, chronic inflammation of the oral mucosa, and dietary/nutrition patterns have been associated with dysregulation in epigenetic patterns.[4,59,62] A number of small-scale preliminary studies stated that the habit of eating foods that contain flavor-enhancing chemicals such as MSG combined with a high lipid diet (HLD), known as fast food, can trigger alterations in gene expression.[40] The combination of MSG-containing foods with a high lipid diet is also often associated with the formation of human nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) that triggers inflammation and progression of primary tumors to hepatocellular carcinoma through mechanisms of altered redox balance, inflammatory response, and programmed cell death, as well as activating NF-kB and mitochondrial caspase-mediated pathways.[40,41,46,63,64]

MSG administration has the potential to raise the risk of oral cancer due to its ability to induce an increase in oxidative stress and hence promote genotoxicity in the oral mucosa. Compared to other organ systems such as the digestive system (GIT), the central nervous system (CNS), the cardiovascular system, the reproductive system, the excretory system, and body metabolism, research on the effects of MSG on the risk of oral cancer is relatively uncommon. Based on the findings of the studied articles,[27–31] the majority of MSG was only administered at certain doses, and its administration was not continuous. Thus, there were no deposits attached to the oral mucosal tissue, and there was no significant damage that led to malignancy. To reinforce the evidence-based approach to the use of MSG, it is hoped that further clinical research will be conducted on the effects of monosodium glutamate on the risk of oral cancer, particularly in the Asian region.

This study has several limitations, including that some of the articles that have been analyzed still have a moderate risk of bias, besides the number of articles discussing the effect of monosodium glutamate on the risk of oral cancer is still limited. Another limitation is that there are no articles with in vitro, cross-sectional, and randomized controlled trial (RCT) study designs that investigate the effect of monosodium glutamate on the risk of oral cancer.

CONCLUSION

MSG has the potential to increase the risk of oral cancer because it tends to be more of a carcinogen. It because MSG can induced and increased oxidative stress, which triggers genotoxicity in oral mucosa cells.

ETHICAL CONSIDERATION

This literature review has followed ethical guidelines in scientific publications based on the COPE and ICMJE protocols.

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CONFLICT OF INTEREST

All authors declare there were no conflicts of interest in the making of this manuscript.

AUTHORS' CONTRIBUTION

SNIW responsible for definition of intellectual content, literature search, data acquisition, data analysis, manuscript preparation, and manuscript editing. JAA and SW responsible for concept of the study, design of the study, definition of intellectual content, data analysis, manuscript editing, manuscript review, and guarantor.

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Table 2. Data extraction result from the reviewed articles

No	Author (Year)	Research Design	Sample	Glutamate Dose or Concentration	Administration time	Result	Conclusion
1	Shono et al. (2021)[27]	Cohort study	Lingual mucosa from a patient with advanced head and neck cancer which consists of laryngeal, hypopharyngeal, pharyngeal, maxillary, paranasal, and other types of head and neck cancers.	MSG at a dose of 2.7 g/kg bw/day (2700 mg/kg bw).	1 week	Analysis of the change on lingual gene expression T1R3: 1. The first cycle of chemotherapy: MSG was not given for the MSG group patients during the first round of chemotherapy during CRT. A week after first-dose chemotherapy, gene expression T1R3 in the tongue showed significant decrese compared to one that was measured before chemotherapy, both in the MSG group and in control. 2. T1R3 level mesurement was soon performed before second round chemotherapy. The result revealed that the gene expression has recovered in both groups. 3. The second cycle of chemotherapy: - Pasient in MSG group was give rice with MSG three time a day at a total dose of 2.7 g/kg bw/day on the first seven days during this second cycle of chemotherapy. While control group was not given any. - A week after second cycle of chemotherapy, the gene expression T1R3 in the tongue was also significantly lower in both groups than it was before the administration of the second dose lidah. However, it could be observed that the T1R3 level in MSG group was higher than in control. The Analysis of Visual Analog Scale (VAS) and daily energy intake: 1. VAS: - One week after the first dose of chemotherapy, VAS scores for taste sensitivity appeared to decrease significantly in both groups compared to before chemotherapy, then the scores returned to baseline before the second round of chemotherapy and finally decreased again at 1 week after the administration of the second dose of chemotherapy. 2. VAS score was considerably higher in the MSG group one week following the second cycle of chemotherapy compared to the control group. Daily energy intake:	MSG administration was able to suppress chemotherapy-induced dysgeusia by increasing T1R3 expression in the tongue, the score of Visual Analog Scale (VAS), and daily energy intake in head and neck cancer patients.

Table 2. **Data extraction result from the reviewed articles**

No	Author (Year)	Research Design	Sample	Glutamate Dose or Concentration	Administration time	Result	Conclusion
						- Daily energy intake of both groups appeared to decrease significantly at one week following first-dose chemotherapy, it began to recover before the second chemotherapy, then daily energy intake recovered before the second round of chemotherapy and finally decreased significantly again at 1 week after the second dose of chemotherapy. - - Daily energy intake was significantly higher in the MSG group than the control group at 1 week after the second dose of chemotherapy. The analysis of T1R3 gene and VAS association: 1. Upregulated T1R3 expression showed significantly positive correlation with VAS taste sensitivity score of patients with head and neck cancer from both MSG group and control during chemotherapy. The correlation coefficient became lower for both patient groups after administration of the second dose of chemotherapy. 2. After the second dosage of chemotherapy, there was a strong positive connection between taste sensitivity VAS score and daily energy intake in both patient groups.	
2	El Imam & El Salam (2019)[28]	In vivo study	Buccal mucosa in adult male albino rats.	MSG at a dose of 30 mg/kg bw.	6 weeks	The Histological analysis with H&E staining: 1. There was a picture of atrophic epithelium, disruption of intercellular bridges in epithelial cells, degeneration of cells with pyknotic nuclei, thinning or shortening of the rete ridge, and destruction of some basal cells. 2. There was collagen fiber deposition in the lamina propria as well as capillary blood vessel congestion. The Immunohistochemical analysis (Proliferating Cell Nuclear Antigen): Positive PCNA reaction with strong brown color in basal cells.	MSG administration can induce degenerative changes in the histological structure of the buccal mucosa of experimental animals as well as positive PCNA reactions.

No	Author (Year)	Research Design	Sample	Glutamate Dose or Concentration	Administration time	Result	Conclusion
3	Shredah (2017)[29]	In vivo study	Gingival tissue in adult wistar rats	MSG at a dose of 15 and 30 mg/kg bw	6 weeks	1. The histological analysis with H&E staining MSG at a dose of 15 mg/kg bw: - There is a picture of atrophic eptiel cells and a keratinized layer. - Higher magnification of the same histological field showed a basal cell layer with pleomorphic hyperchromatic nuclei, invasion of hyperchromatized epithelial cells in the lamina propria, basophilic cytoplasm in some basal cells and sulcular epithelial cells, and edema in the lamina propria. 2. MSG dosis 30 mg/kg bw: - There were features of acanthosis and hyperkeratosis. - Higher magnification of the same histological field showed deformed and hyperchromatized sulcular epithelium, basal cells with pleomorphic hyperchromatic nuclei, and intracellular vacuolization in spinous cells. Moleculer analysis: 1. There was a decrease in DNA quality in both experimental groups compared to the control group. 2. The genotoxicity effect of MSG was higher in the group given MSG at a dose of 30 mg/kg bw.	MSG administration can cause changes in histological structure, decreased DNA quality, and genotoxicity to the gingival mucosa of experimental animals, especially if given at high doses.

No	Author (Year)	Research Design	Sample	Glutamate Dose or Concentration	Administration time	Result	Conclusion
4	Mohammed (2017)[30]	In vivo study	Palatal mucosa in adult albino mice.	MSG at a dose of 20 dan 40 mg/kg bw.	8 weeks	Histological analysis with H&E staining dan Mallory's trichrome staining: 1. MSG dose of 20 mg/kg bw : - There is a picture of acanthosis, hyperkeratosis, and blood vessels in the connective tissue appear dilated and crowded by blood cells (congestion). - Higher magnification of the same histological field showed pleomorphic basal cells with deformation and disruption of the basement membrane, as well as hyperchromatized pyknotic nucleated basal cells and binucleated spinous cells, both with intracellular vacuolization. 2. MSG dose of 40 mg/kg bw: - There were features of acanthosis and hyperkeratosis, and papillary folds were found in the epithelium of the palate durum. - Higher magnification of the same histological field showed pleomorphic basal cells with atypical cellular changes. There was an increased mitotic rate in the basal and spinous cells of the palatal mucosa, and bulbous rete pegs were found with pleomorphic basal cells. Moleculer analysis: 1. There was a decrease in DNA quality in both experimental groups compared to the control group. 2. The genotoxicity effect of MSG was higher in the group that was administered by MSG at a dose of 40 mg/kg bw.	MSG administration can trigger genotoxicity, decreased DNA quality and quantity, and changes in the histological structure of the palatal mucosa of experimental animals, especially if given at high doses.

No	Author (Year)	Research Design	Sample	Glutamate Dose or Concentration	Administration time	Result	Conclusion
5	Amtha et al. (2009)[31]	Case-control study	Patients with diagnosed OSCC / oral squamous cell carcinoma (age 23-74 years, n = 81) and non-cancer patients as controls (age 22-79 years, n = 162).	Not applicable	Not applicable	Factor analysis using Kaiser-Meyer-Olkin (KMO) measurement and Bartlett test of sphericity.: 1. The first factor labeled "preferred" accounted for 27% of the total variance, this component consisted of fast food, fermented food, canned food, high-fat and sugar snacks, raw and cooked vegetables, and seafood. 2. The second factor labeled "combination" accounted for 11% of the total variance, this component consisted of intake of dairy products, red meat, white meat and fruits. 3. The third factor labeled "chemical related" accounted for 9% of the total variance, this component consisting of processed foods and monosodium glutamate (MSG). 4. The fourth factor labeled "traditional" accounted for about 8% of the total variance, this component consisting of beverages and grains. 5. The highest communality is shown in "fast food" (0.818) which belongs to the first factor labeled "preferred". Analysis of dietary patterns and oral cancer risk: 1. The highest tertile of the "preferred" pattern appeared to show a twofold increased risk of oral cancer, while the "chemical related" pattern showed an approximately threefold higher risk after adjusting for controls. 2. The highest tertile of the "combination" pattern appears to show a protective effect in relation to oral cancer, before and after adjusting for predefined variables. 3. The highest tertile of the "traditional" pattern appears to show a two-fold increased risk of oral cancer after looking at ethnic habits and dietary intake.	MSG, which is a component of the "chemical related" label, has been shown to increase the risk of oral cancer by three times compared to the other three labels.

Table 3. Quality assessment of included cohort study articles

No	Assessment indicators JBI[32]	Shono et al (2021)[27]
1	Were the two groups similar and drawn from the same population?	Yes
2	Was exposure measured in the same way to assign participants to exposed and unexposed groups?	Yes
3	Was the exposure measured in a valid and reliable way?	Yes
4	Were confounding factors identified?	Unclear
5	Were strategies to address confounding factors mentioned?	Yes
6	Were the groups/participants free of the outcomes at the start of the study (or at the time of exposure)?	Yes
7	Were the outcomes measured in a valid and reliable way?	Yes
8	Was the follow-up time reported, and was it long enough to obtain the outcomes?	Yes
9	Was follow-up completed, and if not, were the reasons explained and explored?	Yes
10	Was there a strategy to handle follow-ups that were not completed?	Unclear
11	Was appropriate statistical analysis used?	Yes
	Result	81,8 %

Table 4. Quality assessment of the included case-control study articles

No	Assessment indicators JBI[33]	Amtha *et al.* (2009)[31]
1	Can the groups be compared in aspects other than the presence or absence of disease in cases and controls?	Yes
2	Were cases and controls matched appropriately?	Yes
3	Were the same criteria used to identify cases and controls?	Yes
4	Was exposure measured in a standardized, valid, and reliable way?	Yes
5	Was exposure measured in the same way for cases and controls?	Yes
6	Were confounding factors identified?	Yes
7	Were strategies to address confounding factors specified?	Yes
8	Were the outcomes assessed in a standardized, valid, and reliable way for cases and controls?	Yes
9	Was the exposure time long enough to influence the results?	Yes
10	Was appropriate statistical analysis used?	Yes
	Result	100 %

Table 5. Quality assessment of covered in vivo study articles

No	Domain *SYRCLE's RoB tool*[34]	El Imam & El Salam (2019)[28]	Shredah (2017)[29]	Mohammed (2017)[30]
1	Sequence generation (selection bias)	Yes	Yes	Yes
2	Baseline characteristics (selection bias)	Yes	Yes	Yes
3	Allocation concealment (selection bias)	Unclear	Unclear	Unclear
4	Random housing (performance bias)	Yes	Yes	Unclear
5	Blinding of personel (performance bias)	Unclear	Unclear	Unclear
6	Random outcome assessment (detection bias)	Yes	Yes	Yes
7	Blinding of outcome assessment (detection bias)	Yes	Yes	Yes
8	Incomplete outcome data (attrition bias)	Unclear	Unclear	Unclear
9	Selective outcome reporting (reporting bias)	Yes	Yes	Yes
10	Other sources of bias	Yes	Yes	Yes
	Result	70%	70%	60%