

CAMELLIA SINENSIS, A NATURAL PRODUCT TO SUPPORT THE TREATMENT OF MEDICAL AND STOMATOLOGICAL CONDITIONS

Camellia sinensis, un producto natural de apoyo al tratamiento de afecciones médicas y estomatológicas - Revisión Sistemática

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ABSTRACT

Introduction: The tea plant, *Camellia sinensis*, is one of the most popular non-alcoholic beverages in the world. The main components of *Camellia sinensis* include amino acids, fatty acids, phenolic compounds, flavins and purine alkaloids (xanthines). For this reason, in the field of medicine, *Camellia sinensis* has been used as an anticancer, anxiolytic, antidiabetic, antiobesity, anti-inflammatory, analgesic, antipyretic, chemopreventive, cytotoxic and apoptogenic, genoprotective, hepatoprotective, nephroprotective, hemato-protective, and in wound healing, among other uses. **Objective:** To carry out a systematic review of the use of *C. sinensis* as supportive therapy in the treatment of oral disorders.

Materials and Methods: This systematic review was carried out following the PRISMA guidelines. The search was carried out in the *PubMed*, *ScienceDirect* and *Google Academic* databases. Articles from studies of *Camellia sinensis* were reviewed and those from a secondary source, such as literature review articles, were excluded

Results: A total of 12 full-text articles were selected for review, in which the properties of *Camellia sinensis* are detailed.

Conclusions: According to the bibliography reviewed, *C. sinensis* exhibits anticariogenic properties, applications in the treatment of dental erosion, applications in the treatment of gingivitis and bacterial plaque, and applications in the prevention of oral cancer; however, more controlled clinical trials are needed to confirm its effectiveness and safety of use.

Keywords: *Camellia sinensis*; Botany; Functional claim; Therapeutics; Dentistry; Systematic Review.

RESUMEN

Introducción: La planta del té es una de las bebidas no alcohólicas más populares en todo el mundo. Entre los principales componentes de *Camellia sinensis* tenemos los aminoácidos, ácidos grasos, compuestos fenólicos, flavinas y alcaloides de purina (xantinas). Por ello en medicina, la *Camellia sinensis* se ha utilizado como anticancerígeno, ansiolítico, antidiabético, antiobesidad, antiinflamatorio, analgésico, antipirético, quimiopreventivo, citotóxico y apoptógeno, genoprotector, hepatoprotector, nefroprotector, hematoprotector, cicatrizantes de heridas, entre otros. **Objetivo:** Realizar una revisión sistemática del uso de *C. sinensis* como apoyo en el tratamiento de afecciones bucales.

Materiales y Métodos: Esta revisión sistemática se llevó a cabo siguiendo los lineamientos PRISMA. La búsqueda se realizó en las bases de datos *PubMed*, *Science Direct* y *Google Academic*. Se revisaron los artículos de estudios de *Camellia sinensis* y se excluyeron aquellos de fuente secundaria, como los de revisión de la literatura.

Resultados: Se seleccionaron un total de 12 artículos de texto completo para la revisión. En los que se detalla las propiedades de la *Camellia sinensis*.

Conclusión: De acuerdo a la bibliografía revisada, la *C. sinensis* exhibió efecto anticariogénico, aplicación en el tratamiento de la erosión dental, aplicación en el tratamiento de gingivitis y placa bacteriana, y aplicación en la prevención del cáncer bucal, sin embargo, se necesitan realizar más ensayos clínicos controlados que confirmen su efectividad y seguridad de uso.

Palabras Clave: *Camellia sinensis*; Botánica; Alegación de propiedades funcionales; Terapéutica; Odontología; Revisión sistemática.

INTRODUCTION

Camellia sinensis O. Kuntze is native to East Asia, the Indian subcontinent, and Southeast Asia.^{1,2} The exact date *Camellia sinensis* was first grown remains unknown. According to Chinese tradition, around the year 2737 B.C., Emperor Shen Nung, a renowned herbalist, first discovered tea and subsequently claimed that the tea brew could detoxify 72 kinds of poisons.^{2,3} In the Yunnan-Guizhou Plateau (southwest China) about 5,000 years ago, *Camellia sinensis* was used by people only for chewing and eating, in the same way that coffee was first used in those times.^{3,4}

Nowadays, the tea plant is one of the most popular non-alcoholic beverages around the world, with nearly 2 billion cups being regularly consumed.^{4,5} China remains the world's largest tea producer with 1.9 million tons, which in 2013 accounted for 38% of the world's total tea production of 5 million tons.⁶ In 2017, tea production reached almost 2,473,443 tons in China.⁷

In Latin America, Argentina has become the largest tea producer accounting for around 4% of world production. In 2017, 40,500 hectares were cultivated, of which 2,500 were located in the province of Corrientes and 38,000 in the province of Misiones.⁸ In Peru, the production of *Camellia sinensis* began during the first half of the 20th century in the regions of La Convención (Cuzco) and Tingo María (Huánuco). In 2016, Peruvian tea production amounted to 2,316.1 tons, an increase of 16.2% compared to the 1,992.6 tons produced in 2011. It is projected that, in 2021, Peru will produce 2,710.8 tons of tea for a value of US\$ 138.2 million.^{9,10}

Among the main components of *Camellia sinensis* there are amino acids, fatty acids, phenolic compounds, flavins, and purine alkaloids (xanthines). For this reason, *Camellia sinensis* has been used as an anticancer, anxiolytic, antidiabetic, antiobesity, anti-inflammatory, analgesic, antipyretic, chemopreventive, cytotoxic and apoptogenic, genoprotective, hepatoprotective, nephroprotective, hemato-protective, and wound healing substance, among others.²

Consequently, it was decided to carry out a systematic review, with the aim of identifying the studies reporting on the properties of *Camellia sinensis* and its application in the field of general and oral health.

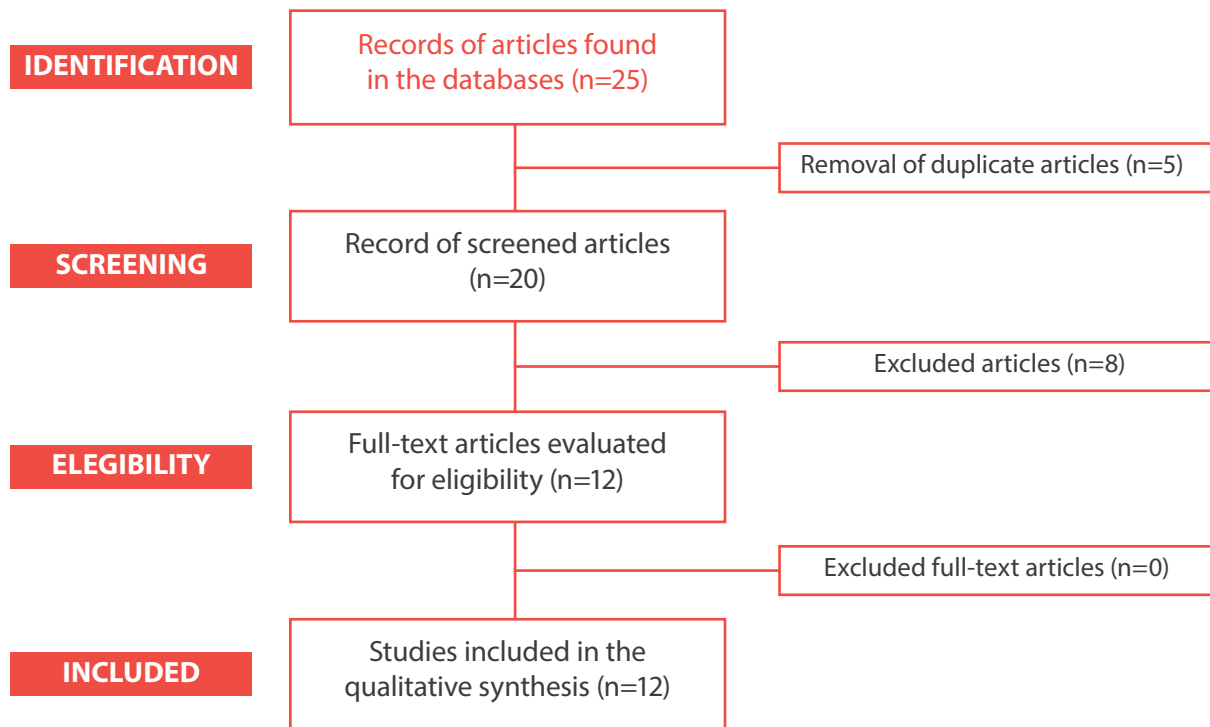
MATERIALS AND METHODS

Selection of original articles

To carry out this systematic review, the following question was formulated: What is the use of *Camellia sinensis* as a therapeutic substance in medical and oral conditions? The available articles on *Camellia sinensis* in relation to the treatment of medical and dental conditions were collected from the electronic databases *PubMed*, *Science Direct*, and *Google Academic* according to the PRISMA guidelines for systematic reviews.

The following descriptors and terms (according to Descriptores en Ciencias de la Salud) were searched in Spanish: *Camellia sinensis*; botánica; propiedades; tratamiento; odontología; and for articles in English, the following descriptors and terms were used (according to the Medical

Figure 1. Flow diagram of the different phases of the systematic review.



Subject Headings): *Camellia sinensis*; botany; properties; treatment; dentistry.

To further narrow down the search, the following eligibility criteria were included: full-text articles in English and Spanish, published from 2016-2021, original articles from *in vitro* studies, focused on the objective of this review published in indexed dental journals. These criteria were considered crucial to guarantee the quality of the articles included in this review.

The bibliographic references of the consulted articles were also considered as manual search, that is, relevant articles included in other sources if they met the search eligibility criteria. After obtaining the results from both search engines, duplicates were eliminated, then the screening by title and abstract was performed to carry out the

evaluation of the complete texts. Data extraction, data management and analysis consisted of the description of the relevant evidence, which is presented in a flowchart according to the PRISMA guidelines. Results of the literature search in Figure 1.

Eligibility and Exclusion Criteria

Original *in vitro* and *in vivo* studies, articles written in English and Spanish, whose main objective was to evaluate the properties of *Camellia sinensis* in the treatment of medical and dental conditions were included. Only those that had been published between 2016-2021 were considered.

Studies that evaluated other properties of *Camellia sinensis* in fields that were not related to health were excluded. Literature reviews were also excluded.

Table 1. Criteria for the exclusion of the reviewed articles.

Author	Reason for exclusion
Atta <i>et al.</i> , ¹¹	Literature review
Konieczynski <i>et al.</i> , ¹²	Literature review
Mazur <i>et al.</i> , ¹³	Literature review
Saeed <i>et al.</i> , ¹⁴	Literature review
Yang <i>et al.</i> , ¹⁵	Literature review
Jiménez <i>et al.</i> , ¹⁶	Literature review
Omidi <i>et al.</i> , ¹⁷	Evaluated other medicinal plants
Sutini <i>et al.</i> , ¹⁸	Evaluated other properties of <i>Camellia sinensis</i>

Table 2. Synopsis of the articles that identify the properties of *Camellia sinensis* and its application in the medical and stomatological field.

Author and year	Methodology	Results
Thitimuta <i>et al.</i> ¹⁹ (2017)	<i>In vitro</i> study by inhibition of the 5-lipoxygenase with methanolic extract of fresh tea leaves.	Treatment of rats with methanolic tea extract at 2000 mg/kg/day for 28 consecutive days reversed CCl ₄ -induced oxidative damage in liver tissues by reducing alanine aminotransferase levels by 69% and malondialdehyde by 90%.
Ardiana <i>et al.</i> ²⁰ (2018)	Study of the antidiabetic activity of white tea extract carried out in diabetic male rats	Administration of ethanolic extract of white tea for 14 days showed a decrease in fasting blood glucose level in diabetic rats. The dose of 100 mg/kg of body weight of white tea has a greater effect in lowering the fasting glucose level.
Wang <i>et al.</i> ²¹ (2018)	<i>In vitro</i> study of the anticancer effects of tea saponins using human ovarian cancer cell lines.	Tea flower saponins (1.5 µg/ml) produced significant antiproliferative effects against A2780/CP70 and OVCAR-3 cells by inducing p53-dependent apoptosis and S-phase arrest.
Unno <i>et al.</i> ²² (2018)	<i>In vivo</i> study, the stress-reducing effect of green tea was evaluated in mice suffering from suppressed adrenal hypertrophy.	Anxiety, a reaction to stress, was significantly lower in the test group than in the placebo group. Reducing stress was only possible when the molar ratio of caffeine and epigallocatechin gallate (EGCG) to theanine and arginine was less than two.
Cayo <i>et al.</i> ²³ (2018)	<i>In vitro</i> study, consisting of 15 discs soaked in green tea or propolis at different concentrations, 0.12% aqueous chlorhexidine and distilled water. Diffusion disks were placed on Mueller-Hinton agar, seeded with <i>Streptococcus mutans</i> .	The maximum inhibitory halo diameter achieved by 0.12% aqueous chlorhexidine, 20% ethanolic extract of green tea (<i>Camellia sinensis</i>) and 20% ethanolic extract of propolis was at 24 h with values of 10.64 mm ± 0.924mm, 6.82mm ± 0.982mm, and 8.36mm ± 1.286mm, respectively. The 20% ethanolic extract of green tea (<i>C. sinensis</i>) presented statistically significant differences with respect to the 20% ethanolic extract of propolis, both at 24 h (p= 0.013) and 48 h (p= 0.011).

Author and year	Methodology	Results
Melok <i>et al.</i> ²⁴ (2018)	<i>In vitro</i> study, an esterified derivative of epigallocatechin-3-gallate (EGCG), epigallocatechin-3-gallate-stearate (EGCG-S), was used to evaluate its ability to inhibit the growth and formation of <i>S. mutans</i> biofilm.	The results indicated that EGCG-S was able to completely inhibit growth and biofilm formation at concentrations of 250 µg/mL. Its effectiveness was also compared to chlorhexidine gluconate mouthwash.
Passos <i>et al.</i> ²⁵ (2018)	<i>In vitro</i> study, the potential of <i>Camellia sinensis</i> and derived active compounds for use as a treatment to prevent dentin wear was explored.	Data on wear were analyzed by ANOVA followed by Tukey's test ($p < 0.05$). EGCG, theaflavin gallate derivatives, and both regular teas significantly suppressed erosive dentin loss (38-47%, $p < 0.05$). No obvious changes in the Raman spectra were detected in the samples. However, the control group had a lower ratio of 2880/2940 cm^{-1} . The phenolic contents in green and black tea and the important catechins seem to have protective effects on dentin loss.
Hagiu <i>et al.</i> ²⁶ (2019)	<i>In vitro</i> cell viability study using MTT to determine non-toxic levels of green tea in human keratinocyte epithelial cells. Cells were treated with liposaccharide (1 µg/ml) and green tea extract (1 mg/ml, 2.5 mg/ml, 5 mg/ml, and 10 mg/ml) to assess inflammation.	Green tea at concentrations of 2.5 mg/ml, 5 mg/ml, and 10 mg/ml significantly improved cell viability ($p < 0.05$). IL- β 1, IL-6, and TNF α were decreased by up to 10-fold compared to liposaccharide-treated cells. The mechanistic results showed that green tea elicited the anti-inflammatory response by activating the nuclear factor, erythroid-related factor 2 (Nrf2) 2 pathway, and increasing the level of the antioxidant protein heme oxygenase-1 (HO-1).
Belobrov <i>et al.</i> ²⁷ (2019)	<i>In vitro</i> study, oral cancer cells (H400 and H357) were treated with 10 µg/ml and 20 µg/ml EGCG for 72 hours. Phenotypic changes were assessed by performing cell proliferation assays and cell migration assays (Transwell).	Cell proliferation of both cell lines was significantly reduced at 48 hours when treated with 20 µg/ml EGCG. However, after 72 hours of treatment, the effect of EGCG on cell proliferation ceased. Treatment of both cell lines with 10 µg/ml and 20 µg/ml EGCG resulted in a significant reduction in cell migration. EGFR expression did not change significantly after EGCG treatment; however, there was a reduction in its phosphorylated form.
Yoshimura <i>et al.</i> ²⁸ (2019)	<i>In vitro</i> and <i>in vivo</i> study to evaluate the therapeutic potential of EGCG to target oral squamous cell carcinoma (OSCC).	In <i>in vitro</i> experiments, EGCG suppressed the viability of HSC-3 cells in a dose- and time-dependent manner. Cell cycle analysis revealed that EGCG induced G1 phase arrest of tumor cells. In the <i>in vivo</i> xenograft experiment in mice, EGCG treatment resulted in a 45.2% reduction in tumor size compared to the control group without weight loss.

Author and year	Methodology	Results
Mi-Ah et al. ²⁹ (2020)	<i>In vitro</i> study, <i>Streptococcus mutans</i> and <i>Streptococcus sobrinus</i> were cultivated and treated with extracts of green or black tea prepared under different maceration conditions. Biofilm formation, glycosyltransferase (GTF) levels, bacterial growth, and acidogenicity were evaluated.	All extracts with hot soaking showed greater inhibitory effects on biofilm formation and cell viability and lower GTF levels compared to those with cold soaking ($p < 0.05$). Hot soaking significantly reduced bacterial growth ($p < 0.05$) and maintained pH. Within the limits of this study, cold macerated extracts showed less inhibitory effects on oral biofilms.
Kanbarkar et al. ³⁰ (2020)	Study on tea polyphenols and their ability to inhibit matrix metalloproteinase (MMP) against the main protease of SARS-CoV-2 using the GLIDE docking module of the Schrodinger Suite software.	Analysis showed a docking score for all five polyphenols, that is, theaflavin, 1-O-caffeoylquinic acid, genistein, epigallocatechin 3-gallate, and ethyl trans-caffeate. Furthermore, theaflavin, EGCG and 1-O-caffeoylquinic acid have been identified as inhibitors of MMPs involved in various pathological conditions such as cancer and lung diseases.

RESULTS

The search yielded 25 references in total, resulting in 20 articles after removing duplicates, eight articles were excluded for not meeting the selection criteria, the reasons for their exclusion are detailed in Table 1. Finally, a total of 12 full-text articles were selected for the review whose analysis is included in Table 2.

DISCUSSION

USE IN MEDICINE

Antidiabetic effect

Ardiana et al.,²⁰ evaluated the effect of the ethanolic extract of white tea on the reduction of blood glucose levels in fasting diabetic rats. These studies show that consumption of ethanolic white tea extract for 14 days reduced fasting blood glucose levels in streptozotocin-induced diabetic rats. However, these data did not show any correlation between dose and response. The greatest decrease in fasting

blood levels is at the 100 mg/kg body weight dose, which is statistically different compared to the negative control.

Antioxidant effect

According to Wang et al.,²¹ tea flower saponins at 1.5×g/ml showed significant antiproliferative effects against human ovarian cancer A2780/CP70 and OVCAR-3 cells by inducing p53-dependent apoptosis and S-phase arrest. The mechanistic intervention of saponins in apoptosis is through the Cdc25A-Chk2-CyclinE/A pathway. In addition, the tea flower extract has the best antiproliferative and apoptotic effects in MCF-7 cells of breast cancer.

Likewise, Thitimuta et al.,¹⁹ showed the ability of catechins to inhibit tyrosinase, an enzyme that limits the rate of melanogenesis and is involved in the oxidation of excess dopamine to produce DOPA quinones, in the treatment of rats with extract of methanolic tea at 2000 mg/kg/day for 28 consecutive days rever-

sing CCl-induced oxidative damage in liver tissues by reducing alanine aminotransferase levels by 69% and malondialdehyde by 90%.

Antiviral effect

Kanbarkar *et al.*,³⁰ conducted a study in which polyphenols such as theaflavin, 1-O-caffeoylquinic acid, genistein, EGCG, and ethyl trans-caffeate showed a higher docking score in silico against the main protease enzyme of SARS-CoV-2. These polyphenols have been identified as inhibitors of MMPs involved in various pathological conditions such as cancer and lung diseases. Furthermore, *in silico* molecular docking research suggests that *C. sinensis* could target the main protease of SARS-Cov-2 in the management of COVID-19.

Anti-stress effect

Unno *et al.*,²² evaluated the stress-reducing effect of green tea rich in theanines in mice, evaluated as suppressed adrenal hypertrophy. The results show that adrenal hypertrophy was significantly suppressed in mice that ingested more than 33 mg/kg of green tea. The stress-reducing effect was then compared between the seven green tea samples. Adrenal hypertrophy was significantly suppressed in mice consuming green tea sample numbers 1, 2, 4, and 6, which had a lower content of total amino acids.

USE IN DENTISTRY

Anti-cariogenic application

Cayo *et al.*,²³ analyzed concentrations of green tea and propolis, 0.12% chlorhexidine, and distilled water in diffusion disks on Mueller-Hinton agar seeded with *S. mutans*. The maximum inhibitory halo diameter achieved by 0.12% aqueous chlorhexidine, 20% ethanolic

extract of green tea (*C. sinensis*) and 20% ethanolic extract of propolis was at 24 hours with values of 10.64 mm 40.924mm, 6.82mm 40.982mm, and 8.36mm 41.286mm, respectively. The 20% ethanolic extract of green tea (*C. sinensis*) presented statistically significant differences with respect to the 20% ethanolic extract of propolis, both at 24 and 48 hours. Likewise, Melok *et al.*,²⁴ used an esterified derivative of epigallocatechin-3-gallate (EGCG), epigallocatechin-3-gallate-stearate (EGCG-S), to evaluate its ability to inhibit the growth and formation of biofilms of *S. mutans*. The results indicated that EGCG-S was able to completely inhibit growth and biofilm formation at concentrations of 250 µg/mL. Its effectiveness was also compared to chlorhexidine gluconate mouthwash. Mi-Ah *et al.*,²⁹ cultivated *S. mutans* and *S. sobrinus* and treated them with extracts of green or black tea prepared under different maceration conditions. Biofilm formation, glycosyltransferase levels, bacterial growth, and acidogenicity were evaluated. All extracts with hot soaking showed greater inhibitory effects on biofilm formation and cell viability and lower GTF levels compared to those with cold soaking ($p < 0.05$). Hot soaking significantly reduced bacterial growth ($p < 0.05$) and maintained pH.

Application in dental erosion

Passos *et al.*,²⁵ explored the potential of *C. sinensis* and its active compounds for use as a treatment to prevent dentin wear. EGCG, theaflavin gallate derivatives, and both regular teas were shown to significantly suppress erosive dentin loss (38%-47%, $p < 0.05$). No obvious changes in the Raman spectra were detected in the samples. However, the control group had a lower ratio of 2880/2940 cm⁻¹.

The phenolic contents in green and black tea and the important catechins seem to have protective effects on dentin loss.

Application in the treatment of gingivitis and bacterial plaque

Hagiu *et al.*,²⁶ performed a cell viability assay using MTT to determine non-toxic levels of green tea extract (GTE) in human gingival epithelial keratinocytes (HGEK). Cells were treated with liposaccharides (1×g/ml) and GTE (1 mg/ml, 2.5 mg/ml, 5 mg/ml, and 10 mg/ml) to assess inflammation. Gene expression levels of the inflammatory markers IL-1, IL-6, and TNF were measured by RT-PCR, and their protein production was assessed by ELISA. The scratch assay, also known as wound healing assay, was used to study the effects of different concentrations of GTE on cell migration.

They also explored the effect of GTE on the induction of the Nrf2/HO-1 pathway in cells with or without LPS. The results of the mechanism showed that GTE produced the anti-inflammatory response by activating the nuclear factor, erythroid-related factor 2(Nrf2)2 pathway and increasing the level of the antioxidant protein heme oxygenase-1 (HO-1). *C. sinensis* can potentially be used as an anti-inflammatory mouthwash for the treatment and prevention of inflammatory diseases, due to its ability to reduce inflammation and increase cell migration depending on the dose.

Application in the prevention of oral cancer Belobrov *et al.*,²⁷ performed an *in vitro* study, in which they treated oral cancer cells (H400 and H357) with 10×g/ml and 20×g/ml of

EGCG for 72 hours. Cell proliferation of both cell lines was significantly reduced at 48 hours when treated with 20×g/ml EGCG.

However, after 72 hours of treatment, the effect of EGCG on cell proliferation ceased. Treatment of both cell lines with 10×g/ml and 20×g/ml EGCG resulted in a significant reduction in cell migration. Mechanistically, epidermal growth factor receptor expression was not significantly changed after EGCG treatment; however, there was a reduction in its phosphorylated form. Yoshimura *et al.*,²⁸ used EGCG to suppress the viability of HSC-3 cells in a time and dose dependent manner. Cell cycle analysis revealed that EGCG induced G1 phase arrest of tumor cells. In the *in vivo* xenograft experiment in mice, EGCG treatment resulted in a 45.2% reduction in tumor size compared to the control group without weight loss.

CONCLUSION

C. sinensis O. Kuntze has been evaluated in multiple studies because catechins such as EGCG, GC and CG; flavonoids, theanines, caffeine, saponins, xanthine, theophylline, among others, are included in its composition. *Camellia sinensis* has been shown to have anticancer, anxiolytic, antidiabetic, anti-inflammatory, chemopreventive, and apoptogenic effects. Its anticariogenic property has been studied in the dental field, as well as its application in the treatment of dental erosion, its application in the treatment of gingivitis and bacterial plaque, and its application in the prevention of oral cancer. However, conducting more controlled clinical trials is recommended to confirm its effectiveness and safety, as well as to validate the currently available data.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

ETHICS APPROVAL

Not applicable.

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AUTHORS' CONTRIBUTIONS

Reyes-Mansilla R: Conceptualization, review and analysis of the literature, draft and final writing.

Cuentas-Robles A: Writing – Original Draft.


Ramos-Perfecto D: Conceptualization, review and analysis of the literature, final writing.

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PEER REVIEW

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