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REVIEW

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Can a cup a day keep cancer away? A systematic review exploring the potential of coffee constituents in preventing oral squamous cell carcinoma

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Abstract

Background: Coffee is one of the most consumed beverages in the world. Containing an abundance of bioactive molecules including polyphenols and flavonoids, the constituents of this beverage may exert antiproliferative, antioxidant and anti-inflammatory effects.

Methods: We conducted a systematic review to summarise the available evidence on the anticancer effects of coffee constituents and their potential therapeutic use for oral squamous cell carcinoma (OSCC). Studies were identified through a comprehensive search of OVID MEDLINE, OVID EMBASE and Web of Science, including articles from any year up to 15 May 2023.

Results: Of the 60 reviewed papers, 45 were in vitro, 1 was in silico and 8 were in vivo exclusively. The remaining studies combined elements of more than one study type. A total of 55 studies demonstrated anti-proliferative effects, whilst 12 studies also investigated migration and invasion of neoplastic cells. The constituents studied most frequently were quercetin and epigallocatechin gallate (EGCG), demonstrating various cytotoxic effects whilst also influencing apoptotic mechanisms in cancer cell lines. Dose-dependent responses were consistently found amongst the studied constituents.

Conclusion: Whilst there was heterogeneity of study models and methods, consistent use of specific models such as SCC25 for in vitro studies and golden hamsters for in vivo studies enabled relative comparability. The constituents of coffee have gained significant interest over the last 30 years, particularly in the last decade, and present an area of interest with significant public health implications. Currently, there

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This study is not registered in the International Prospective Register of Systematic Reviews (PROSPERO) database.

is a paucity of literature on utilization of active coffee constituents for the therapeutic treatment of oral cancers.

KEYWORDS
cancer, coffee, flavonoids, oral cancer, polyphenols

1 | INTRODUCTION

Coffee, a highly varied beverage made from the beans of over 100 species of plants, dates to the 15th century.[1] Through the centuries, accompanied by cultural expansion and internationalisation, it has grown to be one of the most consumed drinks in the world, with 2.25 billion cups consumed worldwide every day.[2,3]

Despite the *Coffea* genus consisting of over 120 species, worldwide coffee consumption relies heavily on two species, *Coffea arabica* and *Coffea canephora*, known commonly as Arabica and Robusta coffee, respectively.[4] The harvested beans are fermented, dried and roasted to varying levels. The roasting process triggers the release of volatile compounds giving coffee its characteristic scents and flavours and contributes to the relative abundance of different compounds in alternate coffee varieties.[4] Similarly, to the roasting process, the brewing process can also produce marked differences in the final chemical composition.[4] Additionally, cultural variance and practices can alter the chemical profile of coffee.[5]

Coffee consists of a diverse and complex array of biochemicals. Polyphenols such as chlorogenic acid and caffeic acid, diterpenes, flavonoids and lignans can all be found in a cup of coffee to varying degrees.[6] This diverse composition can contribute to the antioxidant, anti-inflammatory and anti-carcinogenic potential of the beverage.

OSCC is the most common cancer of the oral cavity, accounting for 90% of oral malignancies, which continues to trend upwards.[7–9] OSCC often stems from preneoplastic lesions of the oral epithelium following insult by carcinogens.[10]

Various factors increase OSCC risk including betel nut consumption, socioeconomic status, tobacco use, alcohol consumption, diet, certain infections and other oral conditions such as lichen planus.[11]

Due to its diverse aetiology and progression, equally diverse therapies to counter cancer are being explored as potential adjuncts to current treatment protocols.[12] One such agent showing potential benefits is coffee, possessing numerous bioactive molecules that have demonstrated effects in modulating various processes implicated in cancer.[12] Coffee contains an abundance of polyphenols, which have exhibited immunomodulatory, anti-inflammatory and antioxidant properties.[12] Key constituents, such as caffeic acid, kahweol and caffeine, have been reported to inhibit pathways involved in the expression of cytokines, growth factors and immunoreceptors, alongside regulating immune cell function.[12]

Inflammatory markers, notably Il-6, have been associated with numerous cancer types, including OSCC.[13] In OSCC, chronic inflammatory states have been implicated in tumour progression, invasion and metastasis.[14] Hence anti-inflammatory properties of coffee could support novel mechanisms for therapeutic treatment.[14] Relatedly other constituents, such as melanoidins and caffeine, boast prominent antioxidant potential, scavenging free radicals generated through oxidative stress.[15] Therefore, in combination with its widespread consumption, defining the factors that contribute to coffee's beneficial properties could provide the basis for novel, targeted approaches to oncological treatment.

The objective of this study was to review relevant literature and to assess the specific processes through which coffee constituents interact with oral cancerous cells. This study aims to determine the extent to which the diverse compounds present in coffee contribute to these outcomes and identify the molecules that generate the greatest protective effect. To achieve this, the review will address the following questions as a framework for synthesising the existing literature:

1. What is the extent of literature regarding coffee and its antiproliferative effects on oral cancer cells **in vitro, in silico and** in **animal studies**?
2. Are the constituents of coffee associated with OSCC prevention pathways?
3. Do the constituents of coffee impact OSCC development or progression?
4. Among the constituents of coffee, which ones have been shown to possess the greatest potential for exerting anticancer or antiproliferative effects?

2 | METHODS

This systematic review used the 2020 version of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) as guidelines for screening and data collection processes.[16]

2.1 | Literature search

A comprehensive online literature search from databases including Web of Science, OVID MEDLINE and OVID EMBASE was conducted on 15 May 2023. The search strategy shown in the Supporting information was employed across all databases to collect studies about constituents found in coffee and Oral Squamous Cell Carcinoma (OSCC)-related terms.

2.2 | Selection criteria

Search criteria included publications in any language and date of publication. We sought papers investigating the relationship between

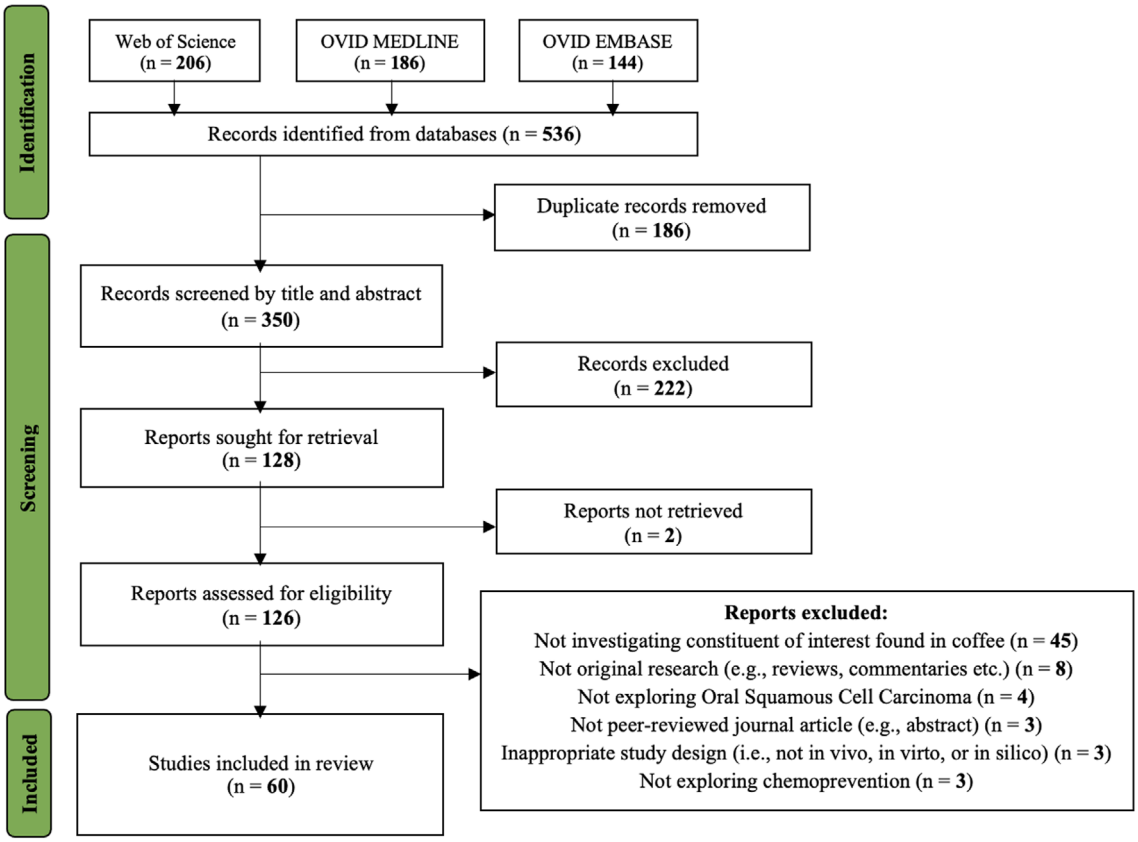

FIGURE 1 PRISMA flowchart of the screening and data selection process.

coffee constituents and oral squamous cell carcinoma (OSCC), which included in vitro, in vivo and in silico research. Studies investigating constituents found in coffee but utilising samples from other plant species were also included. Studies assessing extracts or fractions were also included. Studies that were not investigating constituents found in coffee and their relation to oral squamous cell carcinoma were excluded. Case reports, letters, conference abstracts, reviews, epidemiological studies and retracted studies were also excluded.

2.3 | Statistical analysis

Cohen's kappa coefficient and inter-rater reliability (IRR) was calculated for the two independent reviewers conducting the title and abstract screening and the full-text screening using IBM Statistics 29 (SPSS).

2.4 | Quality assessment

All 60 included studies were assessed for internal validity using the Office of Health Assessment and Translation (OHAT) risk of bias tool.[17] The answers for each question were assigned as either 'definitely low', 'probably low', 'probably high' or 'definitely high'.

3 | RESULTS

3.1 | Data collection and sorting

As illustrated in Figure 1, the literature search of Web of Science, EMBASE and Medline identified 536 articles.[18] Search results were imported into Covidence, and duplicates were removed, and then further reviewed individually to remove duplicates manually ($n = 186$). A total of 350 articles were screened. Two independent and blinded reviewers sorted articles by title.

3.2 | Article screening

Two reviewers evaluated 350 articles and 126 were unanimously accepted for full-text review with an IRR of 83.43% and Cohen's kappa of 0.63 (95% confidence interval [CI]: 0.54–0.71). Contentious articles were discussed between the reviewers until a consensus was achieved. The same protocol was applied to articles for data extraction. A total of 126 full-text articles were assessed for eligibility and 60 were included with an IRR of 84.25% and Cohen's kappa of 0.69 (95% CI: 0.56–0.81). The article screening process and reasons for exclusion are summarised in the PRISMA chart (Figure 1).

Articles included were published in the last three decades with the oldest study published in 1994. Of the studies screened,

18 (30.0%) were published between 1994 and 2003, whilst 16 (26.67%) were between 2004 and 2013. Interest in the effects of coffee has nearly doubled in the last decade, from 2014 to 2023, as we were able to identify an additional 28 articles to include. As illustrated in Figure 2, majority of the studies were conducted mostly in the United States then followed by Japan, India and then by China.

3.3 | Quality assessment (OHAT results)

The questions were categorised into five domains 'selection', 'performance', 'detection', 'selective reporting' and 'other biases' under the OHAT guidelines.[17] A 'definitively low' risk of bias rating was found for domain 'selection', 'performance', 'detection', 'selective reporting' and 'other biases' in 82.76%, 57.63%, 8.33%, 6.67%, 46.67%, 5.00% of the extracted studies, respectively (Figure 3). A bias rating of 'definitely high' was found for 'selection' (1.72%), 'performance' (1.69%) and 'detection' (3.33%). The rating of 'probably low' was given for 6.90%, 16.95%, 90.00%, 63.33%, 43.33% and 60.00% of the extracted paper, respectively, and the rating of 'probably high' was 8.62%, 23.73%, 1.67%, 26.67%, 10.00% and 35.00%, respectively, for the 'selection', 'performance', 'detection', 'selective reporting' and 'other biases' domain.

TABLE 1 Frequency of active coffee constituents investigated in extracted articles.

Constituent family	Total
Flavonoids	50
Phenols	21
Melanoidin	3
Other (quinolines)	1
Not reported	1

TABLE 2 Frequency of in vivo animal models and strains in extracted articles.

Animal model	Strain	Frequency
Mice	BALB/c	3
	Swiss	1
Rat	Wistar	2
Hamster	Syrian	5

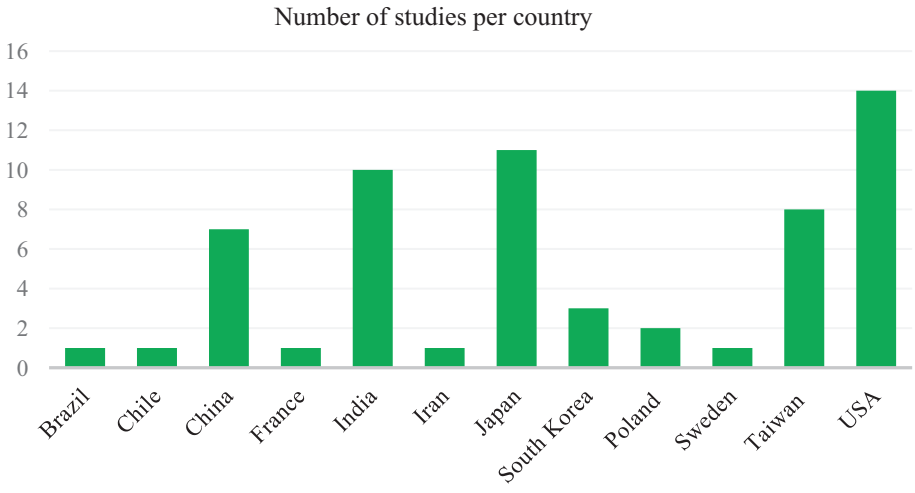

FIGURE 2 Geographic distribution of the included studies.

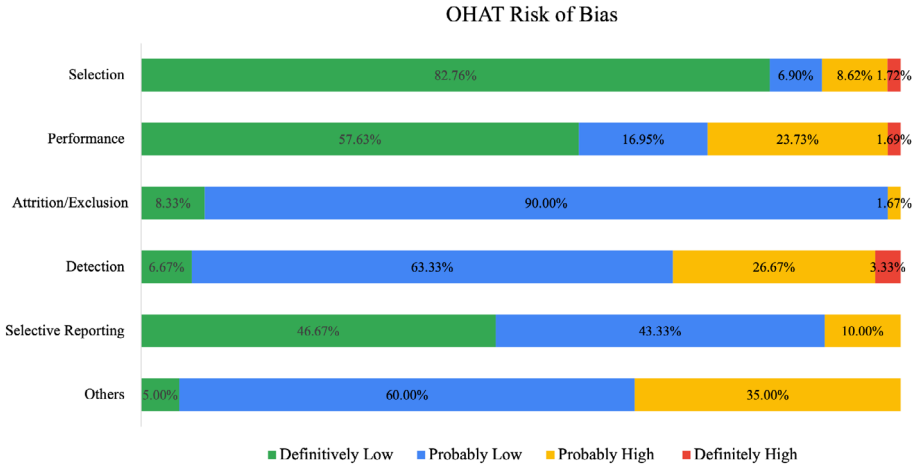

FIGURE 3 Risk of bias result summary for 60 extracted studies based on the OHAT guidelines.

TABLE 3 Major cancer-associated effects of active coffee constituents in extracted articles.

Coffee constituent	Cancer-associated effects
Caffeic acid	• Reduced the viability and migration rate of SCC25 cells.[1] • Pro-apoptotic effects observed in CAL27 cells in a dose-dependent manner, with synergistic cytotoxic effects being induced with other polyphenols.[2] • Coffee bean roast type affected the caffeic acid content alongside total phenolic concentration, with lighter roast extracts exhibiting greater antioxidant activity and growth inhibitory effects.[3] • Grape skin extract containing caffeic acid demonstrated a reduction in epithelial dysplasia.[4] However, the isolated effects of caffeic acid could not be determined due to the use of extracts in Cornelis[2] and Gancarz et al.[4]
Catechin	• Reduce the incidence of both benzo[a]pyrene (BP) and methyl-(acetoxymethyl > nitrosamine (DMN-OAC) induced oral tumours in Swiss mice.[5] • However, these antiproliferative effects were substantially enhanced upon concomitant treatment with 5% turmeric diets and may be explained by elevated forestomach and hepatic glutathione S-transferase activity.[5] • Purified catechin extracts also exhibit cytotoxicity against Kb cell lines similar to vinblastine, a chemotherapeutic agent.[6] In the same study, it also promoted the growth of protective mice splenocytes. • Grape skin extracts containing catechin produced anti-inflammatory effects on Wistar rats through the downregulation of pNFkBp50 and MYD88.[4]
Chlorogenic acid	• Demonstrated cytotoxicity towards various human squamous cell carcinoma lines (HSC 2-4, Ca9-22), which may be due to its ability to cause DNA fragmentation and apoptosis, as well as its capacity as a free radical scavenger.[7,8] • Effects were dose-dependent, with higher doses correlating with increased anti-oxidant potential and reduced cell viability.[9,10] • Downregulate tumour suppressor genes p54 and p21.[10]
Daidzein	• Exhibits weaker cytotoxicity against HSC2 and HSG cells when compared to genistein.[11] • Extracts containing daidzein, such as soy and pigeon pea root, inhibited cancer cell proliferation through the regulation of apoptosis initiator and effector proteins alongside anti-proliferative effects.[12,13] • Anti-proliferative effects were seen in SCC25 and SCC26 cell lines, with the latter also illustrating significantly reduced migration and invasion when administered with incumbent therapeutic agents such as cisplatin or taxol.[13]
Epigallocatechin gallate (EGCG)	• When tested in isolation, demonstrated potent apoptotic effects on oral cancer cell lines, inducing caspase-3 in mitochondria.[14] • Inhibited the volume and number of tumours, whilst also preventing invasion.[15] This was complemented by significant antioxidant effects, reducing ROS molecule concentrations to baseline levels. • However, responses were cell line-dependent, with ROS production being suppressed for the most part but induced in one study.[15] • EGCG present in extracts such as Polyphenon E and B, a mixture of eight polyphenols found in tea, which are also found in coffee, demonstrated varying effects. Cytotoxic effects were observed in CAL27 cells but were also accompanied by increased ROS generation and decreased BCL2/Bax ratio.[16,17] • Significant ROS-scavenging ability and the prevention of oxidative DNA damage.[17] • Contradictory results were observed with regard to effects on cancerous cells.[16,17]
Epicatechin	• Demonstrated cytotoxic activity against HSC2.[18] • Also displayed binding potential for human CyPD protein, which is involved in mitochondrial membrane pore opening and the promotion of apoptosis.[19] • Green tea extracts containing epicatechin (which is also found in coffee) demonstrated cytotoxic effects on CAL27 cells in vitro and inhibitory effect on hamster buccal pouch carcinogenesis.[16,17] These effects, however, were not observed in isolation.
Fisetin	• Induced cell apoptosis in varying OSCC cell lines via the intrinsic pathway.[20] • Inhibited RTK signalling activation, reducing the proliferation of cancerous cells through DNA damage, ROS production, Ca2+ release and decreased mitochondrial membrane potential.[21,22] • Induces cell morphological changes, induces G2/M cell cycle arrest and increases the activity of caspases thereby increasing apoptosis via intracellular pathways.[23] • Increased pro-apoptotic proteins such as Bax, AIF and Endo G and decreased anti-apoptotic protein Bcl-2.[22] • Depending on the level of autophagy induced by fisetin, the sensitivity of apoptosis may differ.[24]
Gallic acid	• In isolation, exhibited cytotoxic activity against HS2.[25] • Within *Juglans regia* leaf extracts, demonstrated antiproliferative effects towards BHY through induction of G0/G1 cell cycle arrest.[26] • Grape skin extracts containing gallic acid possessed anti-inflammatory effects on Wistar rats through the downregulation of pNFkBp50 and MYD88.[4]
Genistein	• Exhibited anti-proliferative effects on cancerous epithelial cells.[27,28] • Together with daidzein, downregulated mRNA expression in the oral cancer cell-cycle promoter ornithine decarboxylase (ODC), while upregulating caspase-2 and -8.[12]

(Continues)

TABLE 3 (Continued)

Coffee constituent	Cancer-associated effects
	• iNOS/COX-2/NF-kB signalling pathways are downregulated through increased levels of MMP-2 and VEGFR2, inducing cell proliferation inhibition.[13] • Arrested cells in the G2/M phase, which was associated with a reduction in PGE2 levels and COX-2 activity, promoting an anti-inflammatory effect.[29] • Contrastingly, whilst the other studies testing genistein inducted the dose-dependent induction of apoptosis, Ye et al.[29] suggested no significant apoptotic effect on cells other than arrest.
Kaempferol	• Exhibited anti-proliferative effects on squamous carcinoma cells via several signalling pathways.[30,31] • Alters the expression and enzymatic activity of MMP-2, MMP-9, TIMP-2 and VEGF.[30,32] • Possesses strong binding affinity for the anti-apoptotic CyPD protein and the ability to produce radicals in alkaline conditions, promoting apoptosis in cancerous cells.[19] • Two studies[25,31] suggested that these effects are dose-dependent.
Luteolin	• Cell lines such as SCC4 and SCC25 were found to have suppressed cell viability.[33,34] • OSC cell lines such as OSC2 were also found to display decreased levels of anti-apoptotic proteins.[34]
Tannic acid and Rutin	• Examined in a total of two in vitro and in silico studies.[10,35] • Ocimum sanctum (holy basil) extracts, exhibited antioxidant activity within rat PC12 cell lines.[35] • Both exhibit high binding energy towards EGFR, β2-AR and keap1/nrf2 receptors, which are pivotal in the progression and metastasis of OSCC.[35] • *A. indica* (Indian lilac) and *M. charantia* (bitter melon) extracts demonstrated antioxidative effects towards KB cell lines through increased superoxide dismutase (SOD), catalase (CAT), and Glutathione S-transferase (GST) activity, as well as increased glutathione (GSH) levels and lipid peroxidation.[10]
Quercetin	• In isolation, irreversibly inhibited SCC9 growth, DNA synthesis and the cell cycle progression through inhibiting thymidylate synthase.[36] • Reduced cell viability and antiproliferative effects on cancer cell lines, often in a dose-dependent manner.[10,31,37,38] • In *J. Regia* leaf extracts containing quercetin induced G0/G1 phase cell cycle arrest of oral cancer cell lines and anti-proliferative properties.[26] • In contrast, one study found quercetin showed no effect on proliferation but minimal effect on cellular uptake.[27] • Demonstrated pro-apoptotic properties.[19,37,39,40] • Several factors involved in apoptosis were shown to interact with quercetin, including Bax, caspase 3, 7, 8, and 9, alongside the JNK and ERK pathways.[37,39,41] • Suppressed anti-apoptotic factors such as xIAP and demonstrated a synergistic effect between quercetin and cisplatin.[20] • Migration and invasion are impaired in HSC-6 and SCC-9 cell lines. by increasing miR-16 production and downregulating HOXA10 levels.[38] • Anti-inflammatory and antioxidant effects were observed in oral cancer cells.[4,35]
Other compounds (hydroxycinnamic acid, delphinidin, cyanidin, caftaric acid, ferulic acid, p-coumaric acid, troxerutin, myricetin, lignin F and neochlorogenic acid)	• Hydroxycinnamic acid, delphinidin, cyanidin, caftaric acid and ferulic acid were evaluated from grape skin extract.[4] Though an anti-inflammatory effect was observed, due to the non-isolated nature of each of the compounds, a precise indication of which contributed to and the relative proportion of its contributing effect could not be determined. • Ferulic acid is also observed in Cornelis,[2] where it was tested alongside caffeic acid and p-coumaric acid, displaying a synergistic cytotoxic effect on CAL27 cell lines. • Troxerutin exhibited dose-dependent cytotoxicity and anti-proliferative effects on KB cells.[2] • Lignin F displayed anti-proliferative effects on HSC2 cell lines, also in a dose-dependent manner, whilst Myricetin reduces cell viability in SiHA cells through the induction of caspase 3/7, and 8 activity.[2] • Myricetin was also found to synergistically act with incumbent cytotoxic drugs such as doxorubicin and cisplatin.[2] • Neochlorogenic acid suppressed HSC-4 cell proliferation and induced apoptosis in OSCC cell lines, whilst also scavenging free radicals.[2]

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3.4 | Constituents investigated

Of the studies screened, 54 (90.0%) investigated lab-derived compounds or constituents isolated from other plants. The constituents investigated are nonetheless found in coffee. Additionally, two studies reported on the constituents extracted from coffee. For the remaining studies, the origin was not reported or not available from the literature.

The active constituents were tested in isolation or with other compounds. 43 (71.67%) studies observed the active constituents in isolation, 13 (21.67%) tested the active constituents in association with others and 4 (6.67%) studies looked at the constituent concurrently in isolation and in association with other constituents.

The distribution of constituent families investigated is summarised in Table 1. Majority of the studies investigated either flavonoids, phenols or both concurrently. This may be due to the classification of the biomolecules or due to ease of access to physical resources. One study did not report the specific constituents it investigated and instead assessed a coffee extract.[19]

3.5 | Study design

The great majority of the 60 included studies were in vitro ($n = 51$, 85.0%), with a smaller portion ($n = 9$, 15.0%) consisting of in vivo or in silico studies. Six (10.0%) of studies incorporated multiple study designs.[20–24] This distribution aligns with our initial research question and search strategy. During our preliminary literature search, we observed a higher frequency of cell culture studies. Finally, the reliance on in vitro studies enhances the likelihood that the collected data will be more comparable and provide consistent insights.

Moreover, the frequency of cell lines utilised by the collated studies is summarised in Appendix A. The most frequently utilised neoplastic cells were the HSG, SCC25 and HSC2 lines.

3.6 | Assay types

Varying assay types were employed to explore the effects of coffee constituents on cancerous cell lineages, including proliferation, cell viability, migration and invasion. Studies often investigated multiple elements within a single experimental design, including the assessment of proliferation, cell viability and apoptotic activity following exposure to the treatment agent. A total of 26 (43.33%) studies investigated apoptosis, and these were framed most commonly through the activity of caspase 3, mitochondrial membrane potential and succinate dehydrogenase activity. Proliferation and cytotoxicity assays were also frequently explored in 18 (30.0%) and 19 (31.67%) studies, respectively. Antioxidant activity and interactions with reactive oxygen species were examined in nine (15.0%) studies, measured through determinations of ROS levels prior to and post agent administration and through catalase activity.

3.7 | Study duration

In vivo study duration ranged from 4 weeks[21] to a maximum of 26 weeks.[25] As this is a short follow-up period, this could possibly limit the accuracy of the study findings given that oral cancer can take substantial time to develop. Interestingly four studies progressed for 14 weeks and utilised the same model organism, golden hamsters. This therefore improves some comparability between these studies.

3.8 | In silico studies

There were only four in silico studies in total within those studies, all were docking studies investigating the binding affinity of proteins involved in cancer pathways.

3.9 | Animal models and strains (in vivo)

The frequency of in vivo animal models and their associated strains is summarised in Table 2. More than half of in vivo studies utilised Syrian hamsters or BALB/c mice.

4 | DISCUSSION

Frequent consumption of coffee and its therapeutic potential for a diverse array of conditions has led to growing interest in its application within oncology.[2,26] In previous literature, coffee constituents, such as caffeine, chlorogenic acid, kahweol and trigonelline, have all demonstrated anti-proliferative and prophylactic effects on cancer cell lines.[27–31] There is also increasing interest in the dose-dependent relationship between coffee consumption and its impact on cancer. For example, high and/or intermediate coffee may impart protection against cancers of the oral cavity.[32]

We aimed to evaluate the potential anti-cancer properties of these constituents, their associated mechanisms as well as determining which constituent had the greatest potential for exerting anti-cancer effects.

Analysis of the literature included studies of constituents obtained commercially, extracted from coffee, and from a non-coffee origin. As summarised in Table 3, the active constituents were analysed in isolation and/or in association with other compounds and were then assessed on their ability to inhibit (i) cancer proliferation, (ii) cancer migration and (iii) cancer invasion. Moreover, the carcinogenic potential of active constituents was also investigated.

5 | EXTENT OF LITERATURE

5.1 | Pro-cancer effects

Extracted articles predominantly reported anti-cancer effects (95%), with only two studies (3.33%) demonstrating pro-cancer mechanisms.

This result suggests a trend in the literature relating to anti-cancer effects. However, it is unclear whether this was due to targeted nature of the search query, which specified certain compounds used or whether it was due to the inherent anti-proliferative capabilities of compounds themselves. In other words, our perception of the extent of the literature may be skewed by the specificity of our search strategy. The remaining 1.67% of articles did not directly investigate the anti-cancer and/or pro-cancer effects of active coffee constituents. For example, Singh et al.[33] utilised an in silico docking study to investigate the binding affinity of various coffee constituents (Quercetin, Kaempferol, Epicatechin) towards CyPD, an anti-apoptotic protein.

5.2 | Inhibition of cancer proliferation

Amongst the 60 extracted articles, 55 (91.67%) reported anti-proliferative effects, and 1 (1.67%) reported no effect on oral cancer cell lines. These results indicate two important trends in the literature. First, that an overwhelming majority of the literature is focused on cancer proliferation, and second, is that most coffee constituents observed exhibit anti-proliferative effects towards oral cancer cell lines. The remaining four articles (6.67%) did not directly investigate the antiproliferative effects of coffee constituents. For example, Lin et al.[34] only studied the effect of kaempferol on SCC-4 invasion/migration and not on cell viability.

5.3 | Inhibition of cancer migration and invasion

Majority of extracted articles did not explore the effects of active coffee constituents on cancer invasion and migration (83.33% and 81.67%, respectively). It can be inferred that current research is more interested in the prevention of cancer growth and pathogenesis rather than the inhibition of metastasis highlighting a clear gap in the existing literature that should be addressed. Nevertheless, within the remaining articles, 9 and 10 (15.0% and 16.67%) reported inhibitory effects towards cancer migration and invasion respectively, and only 1 (1.67%) reported promotive effects.

6 | CONSTITUENTS AND OSCC DEVELOPMENT OR PROGRESSION

Our results indicate that flavonoids, especially quercetin and EGCG, were the most represented in the literature, followed by phenols (Table 1). From our analysis, quercetin was found to demonstrate anti-proliferative effects via antioxidant activity and the induction of apoptosis in certain oral cancer cell lines.[22,35–40] Although it is unclear why there is an emphasis on quercetin and EGCG in the literature, it may be due to an increased potential in these constituents to affect cancer development or progression. Alternatively, the nature of the constituents may be more feasible to test in a laboratory setting due to ease of access, stability and/or lability, costs, and so forth.

Additionally, there was a paucity of data exploring the impact of caffeine on OSCC. Caffeine's therapeutic potential is well-documented in the literature as a neuroactive and analgesic.[41–43] These properties also extend to anti-cancer potential in skin cancer, neuroblastoma and oral cancers.[26] Despite caffeine's potential in reducing the development or progression of cancers, we did not identify studies exploring this relationship between OSCC and the biochemical mechanisms through which it acts.[26]

Moreover, a significant proportion of studies investigated compounds in combination with others as opposed to in isolation. This study design made it challenging to identify the individual impact of a constituent. Hence, it is unclear whether the impact of cancer development or progression observed resulted from the coffee constituent alone, whether it was due to other compounds in the extract and which specific biochemical or physiological processes were involved.

7 | CONSTITUENTS AND OSCC PREVENTION PATHWAYS

A diverse array of cancer prevention pathways was identified in the literature. Induction of apoptosis, alteration of oxidative state, and induction of cell cycle arrest were the most represented pro-apoptotic mechanisms across the studies. Additionally, the data assessed the influence of coffee constituents on chemotherapeutic sensitivity, DNA synthesis, enzymatic inhibition and its influence on signalling and anti-inflammatory pathways.

The overrepresentation of apoptosis in the literature may be attributed to methodological homogeneity. Anti-cancer effects were predominantly evaluated through cell viability and cell cytotoxicity assays such as MTT. We found that several coffee constituents were associated with the induction of apoptosis. These include: chlorogenic acid, daizein, EGCG, epicatechin, fisetin, genistein, green tea polyphenols, kaempferol, myricetin and quercetin. There was homogeneity in the mechanistic action of these constituents, namely the activation of pro-apoptotic caspase 2, 3, 7, 8 and 9.[21,35,36,38,39,44–49] In addition to increased caspase activation, upregulation of pro-apoptotic proteins Bax, AIF and Endo G[35,49] as well as downregulation of anti-apoptotic proteins BCl-2, xIAP, were also observed.[20,35,38,46,49] These modalities ultimately increase mitochondrial membrane permeability, resulting in DNA fragmentation and the formation of apoptotic bodies.[50]

8 | FUTURE DIRECTIONS AND LIMITATIONS

One of the most well-known constituents of coffee, caffeine, was sparsely documented in the literature in relation to oral cancer. Hence, future studies could further investigate the association between caffeine and oral carcinogenesis. Moreover, some studies looked at active constituents tested in association with other compounds or extracted from a non-coffee origin. It would be enlightening to see further studies on compounds tested alone and samples from coffee

extracts to reduce potential confounds. Few studies investigated the effect the coffee constituents on metastasis; hence this area still warrants research. Moreover, due to the vast number of constituents found in coffee as well as compositional differences amongst different coffee blends, it was not feasible to include all constituents in the literature search. Hence, only the most represented and abundant coffee constituent families were investigated in this paper. Consequently, it is highly probable that certain coffee constituents with potential antiproliferative effects were missed in our search query. Some examples include trace components in coffee such as minerals, proteins and carbohydrates.

9 | CONCLUSION

This literature review aimed to assess the anti-cancer and anti-proliferative potential of constituents found in coffee. Most literature identified an inhibition of cancer proliferation, migration and invasion, with a limited proportion suggesting pro-cancer effects. Quercetin and EGCG had the largest evidence base in support of their anti-cancer and anti-proliferative effects. The existing literature suggests that these constituents have therapeutic potential as an adjunct to existing cancer therapies. We also noted a paucity of literature assessing the effects of constituents in isolation or in a standardised manner, which allows for comparison between studies. Based on our findings, we recommend that future research should evaluate the anti-cancer and anti-proliferative potential of constituents found in coffee in isolation to better assess their impact and test their specific mechanisms of action.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

"N/A" as all the data produced by this systematic review have already been included in the accepted manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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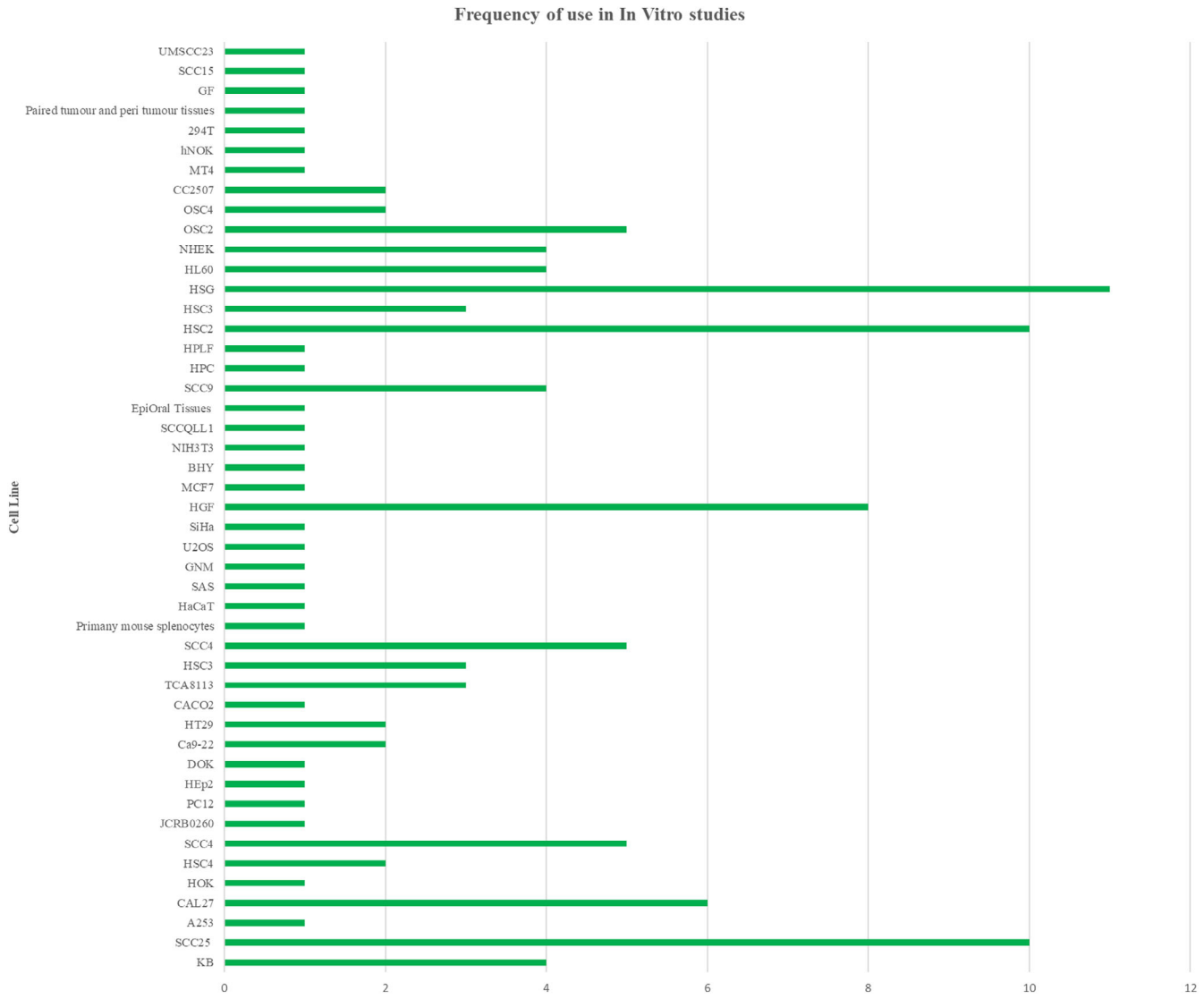

APPENDIX A Frequency of cell line-use in-vitro studies.