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Review

Medicinal plants in the Southeast Asia for treatment and prevention of oral cancer: A systematic review

[Plantas medicinales en el sudeste asiático para el tratamiento y prevención del cáncer bucal: Una revisión sistemática]

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Abstract

Context: Oral cancer is the fourth most common type of cancer among Southeast Asian populations. Despite the existence of numerous anti-cancer drugs, the survival rate of oral cancer patients remains moderate. Furthermore, these drugs often lead to adverse side effects. Southeast Asia has massively underexplored medicinal plants and herbs, and can, therefore, offer a promising avenue for new alternative plant-based drugs against oral cancer.

Aims: To review Southeast Asian medicinal plants with *in vitro* and/or *in vivo* activities against oral cancer, their bioactive compounds, and their mechanisms of actions using a systematic review approach.

Methods: A thorough literature search was conducted in five databases, namely, Google Scholar, PubMed, ScienceDirect, Scopus, and Web of Science, following PRISMA 2020 guidelines and using AXIS quality appraisal tool.

Results: From 30 final articles included in this review, 23 plants and 13 bioactive compounds were found to exhibit activities against oral cancer with various anti-cancer mechanisms, most commonly *via* apoptotic induction. *Azadirachta indica* with the two bioactive compounds (nimbolide and azadirachtin) showed remarkable *in vivo* and *in vitro* anti-cancer properties. *Allium sativum* (garlic), *Zingiber officinale* (ginger), and *Curcuma longa* (turmeric), which are readily available and common in daily cooking, also exhibit anti-cancer activities, which suggest that they can offer good preventive measures against oral cancer.

Conclusions: Southeast Asian medicinal plants with remarkable potential, such as *A. indica,* could be considered for future development of therapeutics for the prevention and treatment of oral cancer.

Keywords: anticancer agents; medicinal plants; oral cancer; phytochemical compounds; Southeast Asia; systematic review.

Resumen

Contexto: El cáncer oral es el cuarto tipo de cáncer más común entre las poblaciones del sudeste asiático. A pesar de la existencia de numerosos medicamentos contra el cáncer, la tasa de supervivencia de los pacientes con cáncer oral sigue siendo moderada. Además, estos medicamentos a menudo provocan efectos secundarios adversos. El sudeste asiático tiene plantas y hierbas medicinales muy poco exploradas y, por lo tanto, puede ofrecer una vía prometedora para nuevos medicamentos alternativos a base de plantas contra el cáncer oral.

Objetivos: Revisar las plantas medicinales del sudeste asiático con actividades *in vitro* y/o *in vivo* contra el cáncer oral, sus compuestos bioactivos y sus mecanismos de acción utilizando un enfoque de revisión sistemática.

Métodos: Se realizó una búsqueda bibliográfica exhaustiva en cinco bases de datos, a saber, Google Scholar, PubMed, ScienceDirect, Scopus y Web of Science, siguiendo las pautas PRISMA 2020 y utilizando la herramienta de evaluación de calidad AXIS.

Resultados: De los 30 artículos finales incluidos en esta revisión, se encontró que 23 plantas y 13 compuestos bioactivos exhiben actividades contra el cáncer oral con varios mecanismos anticancerígenos, más comúnmente a través de la inducción apoptótica. *Azadirachta indica*. con los dos compuestos bioactivos (nimbolide y azadirachtin) mostraron notables propiedades anticancerígenas *in vivo* e *in vitro*. *Allium sativum* (ajo), *Zingiber officinale* (jengibre) y *Curcuma longa* (cúrcuma), que están fácilmente disponibles y son comunes en la cocina diaria, también exhiben actividades anticancerígenas, lo que sugiere que pueden ofrecer buenas medidas preventivas contra el cáncer oral.

Conclusiones: Las plantas medicinales del sudeste asiático con un potencial notable, como *A. indica*, podrían considerarse para el desarrollo futuro de terapias para la prevención y el tratamiento del cáncer oral.

Palabras Clave: agentes anticancerígenos; cáncer oral; compuestos fitoquímicos; plantas medicinales; revisión sistemática; sudeste asiático.

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Abbreviations: 4NQO: 4-nitroquinoline-1-oxide; AgNps-CN: silver nanoparticles *Clinacanthus nutans*; AIF: apoptosis-inducing factor; AMPK: AMP-activated protein kinase; AP-1: activator protein 1; AXIS: Appraisal Tool for Cross-Sectional Studies; BDMC: bis-demethoxycurcumin; COX-2: cyclooxygenase-2; CUR: curcumin; DA: dehydroandrographolide; DMBA: 7,12-dimethylbenz[a]anthracene; DMC: dimethoxycurcumin; DNA: deoxyribonucleic acid; EGFR: epidermal growth factor receptor; ERK1/2: extracellular signal-regulated protein kinases 1 and 2; ETC: electron transport chain; GGT: gamma-glutamyl transferase; GPx: glutathione peroxidase; GSH: glutathione; GSK-3β: glycogen synthase kinase-3β; GST: glutathione s-transferase; HEK: human epidermal keratinocytes; HOTAIR: homeobox transcript antisense intergenic RNA; IL: interleukin; JNK ½: p38, and c-Jun N terminal protein kinases 1 and 2; MAPK: p38a mitogen-activated protein kinase; MMP-2: matrix metalloproteinase-2; MMP-9: matrix metallopeptidase-9; mTOR: Akt-mammalian target of rapamycin; MTS: 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NF-κB: nuclear factor *kappa*-light-chain-enhancer of activated B cells; OSCCs: oral squamous cell carcinomas; p-Akt: phosphorylated Akt; PCNA: proliferating cell nuclear antigen; PGE2: prostaglandin E2; PI3K: phosphoinositide 3-kinases; PICO: Population, Intervention, Control, and Outcomes; PRISMA: Preferred Reported Items for Systematic Reviews and Meta-Analyses; ROS: reactive oxygen species; SAC: S-allylcysteine; SAE: serial acidic ethanol; SAW: serial acidic water; SD: Sprague Dawley; SI: selectivity index; STAT: signal transducer and activator of transcription; TIMP-2: tissue inhibitors of metalloproteinases-2; TNF-α: tumour necrosis factor-alpha; TWIST1: twist-related protein 1; ULK: Unc-51-like kinase; VGEF: vascular endothelial growth factor.

INTRODUCTION

Cancer is a significant health issue and the second leading cause of mortality worldwide. Oral cancer accounts for 48% of all head and neck cancers. According to Global Cancer Observatory 2018, produced by the International Agency for Research on Cancer, Asia has the largest proportion of newly diagnosed cases of oral cancer, totalling up to 64.2% of cases worldwide, and this region has the highest oral cancer mortality rate of 73.3% compared to other regions (Bray et al., 2018). Oral cancer is the fourth most common type of cancer in Southeast Asian populations and is the most common cancer among men in Southeast Asia (Sarode et al., 2020). Ninety percent of oral cancer patients are diagnosed with oral squamous cell carcinomas (OSCCs) in histological examination (Irani, 2020).

Oral cancer develops through multistep processes that begin with normal mucosa alterations, and it progresses to the emergence of invasive cancer and metastases. Multiple genetic and chromosomal abnormalities emerge during this progression. Due to the involvement of several inflammation-related molecular pathways such as cyclooxygenase-2 (COX-2), epidermal growth factor receptor (EGFR), p38a mitogen-activated protein kinase (MAPK), nuclear factor *kappa*-light-chain-enhancer of activated B cells (NF-κB), and signal transducer and activator of transcription (STAT), oral inflammation is suggested to play a significant role in oral cancer development. Several risk factors for oral cancer have been reported, including tobacco and alcohol use, betel quid chewing, chronic inflammation, exposure to ultraviolet radiation (for lip cancer), human papillomavirus or *Candida* infections, immunosuppression, genetic susceptibility, environmental pollution caused by arsenic, chromium, and nickel, and nutritional deficiencies (Irani, 2020; Lee and Tseng, 2020).

Currently, the main treatment modalities for oral cancer include surgery, radiation, and chemotherapy, either alone or in combination, depending on the individual case (Nandini et al., 2020). Radiotherapy helps to kill the cancer cells in a targeted area by causing deoxyribonucleic acid (DNA) damage, which inhibits cell repair, thereby resulting in cell destruction. Conventional radiotherapy uses high-energy photons to destroy cancer cells; however, during this process, normal cells also get damaged along with cancer cells during radiotherapy. On the other hand, chemotherapy involves the use of chemotherapeutic agents to destroy cancer cells. These chemicals are referred to as anticancer drugs that kill or shrink cancer cells or slow their growth (Ozsahin et al., 2021). The available chemotherapeutic agents for oral cancer include platinum-based cisplatin and carboplatin, antimetabolites like 5-fluorouracil and methotrexate, and taxanes like docetaxel or paclitaxel. However, the available chemotherapeutic agents can affect the quality of life of patients owing to their toxic effects on normal cells and side effects, including nausea, vomiting, diarrhoea, and oral mucositis (Nandini et al., 2020). Furthermore, chemotherapeutic agents that are administered intravenously can also affect the quality of life because the intravenous cannula that remains for a long period may cause discomfort to the patient or, even trigger an infection (Ozsahin et al., 2021). Many useful approaches have been proposed to overcome the aforementioned issues, such as delivering drugs that counteract the side effects. Nevertheless, the problems associated with chemotherapeutic agents remain unresolved (Mosaddad et al., 2021).

With the recent therapeutic modalities for oral cancer, the 5-year survival rate for oral cancer in most countries remains below 50% (Irani, 2020; Nandini et al., 2020; Prakash et al., 2021). This is likely ascribable to the late diagnosis and treatment outcomes in the late stages, which have not been improved in recent years (Lee and Tseng, 2020). In addition to that, the resistance of cancer cells toward conventional treatment makes cancer management more complicated (Akhtar et al., 2020).

Since oral cancer has a poor prognosis, prevention is essential (Irani, 2020). Preventive treatments for

oral cancer include dietary suggestions with antioxidant-rich fruits and vegetables (Prakash et al., 2021). Other than preventive measures using natural resources, there is a growing interest in the research of new alternative anticancer drugs based on medicinal plants with anticancer effects. Certain plant-derived chemicals or phytochemicals have been demonstrated to have anti-cancer effects by a few mechanisms. Suggested mechanisms include regulating epigenetics/epigenomics, targeting cancer stem cells, inhibiting cancer metastasis, boosting the immune system, inhibiting cancer cell-cycle progression, inhibiting cell signal transduction, promoting cancer cell apoptosis, inhibiting cancer cell proliferation and angiogenesis, and exerting antioxidant and anti-inflammatory activities (Lee and Tseng, 2020).

Namdeo (2018) defined medicinal plants as plants that possess therapeutic properties or exert beneficial pharmacological effects on the human or animal body. Recently, several authors have reported the potential of plant-derived natural products and phytochemicals in the treatment of oral diseases. Phytochemicals found in some medicinal plant species have been demonstrated to inhibit the progression and development of oral cancer. These phytocompounds exert antitumour activity by inducing apoptosis and cell-cycle arrest, resulting in cell death. Thus, they could be potentially used for the treatment of oral cancer with less systemic toxicity and side effects in humans. Some of the plants that have been proven to be beneficial against OSCC are curcumin, lycopene, anthocyanin, and artemisinin (Prakash et al., 2021).

Currently, there are few review papers compiling fruits, vegetables, herbs, and their respective phytochemical constituents that potentially act against oral cancer (Butnariu et al., 2022; Lee and Tseng, 2020; Malathi et al., 2024; Mosaddad et al., 2021; Prakash et al., 2021). Among these studies, only Lee and Tseng (2020) utilized a systematic review approach using PRISMA guidelines. However, this review focuses solely on the antioxidant compounds. To the best of our knowledge, there is not much literature available that focuses primarily on Southeast Asian medicinal plants, particularly for oral cancer. The Southeast Asian region comprises countries such as Brunei, Burma (Myanmar), Cambodia, Timor-Leste, Indonesia, Laos, Malaysia, Philippines, Singapore, Thailand, and Vietnam. This region is rich with under-explored medicinal plants, with at least 2,200 medicinal plants reported heretofore. The Southeast Asia region is, therefore, recognized as a vast reservoir for plant-derived drug discovery (Anuar and Ismail, 2020). Furthermore, people in some parts of South Asia still rely on medicinal plants resource as a traditional remedy for ensuring their health and subsistence because of their general perception of natural remedies having minimal side effects at an affordable cost (Astutik et al., 2019; Jeelani et al., 2018). Moreover, many plants are easily accessible, and some of them have interesting therapeutic properties that can potentially be used as adjuvant with conventional therapies or for the development of new drugs in the treatment of oral cancer.

While medicinal plants are widely used in Southeast Asia for their purported anti-cancer properties, there is a pressing need for systematic reviews to gather findings comprising of evidence-based validation, summarize existing knowledge, and identify research gaps to better understand and utilize these natural resources effectively as well as to guide future research and afterward the clinical potential applications. In light of this matter, the aim of this study is to provide a systematic review of studies on medicinal plants and their bioactive compounds in Southeast Asia with potential activity against oral cancer.

MATERIAL AND METHODS

Formulation of research question and systematic searching strategy

A systematic search was conducted in five databases, namely, ScienceDirect, PubMed, Scopus, Web of Science, and Google Scholar, with no limit of timeframe. The first four databases were chosen on account of their high reliability in healthcare and medical-related fields. Since this research focused on Southeast Asian medicinal plants and oral cancer, Google Scholar was also included, as it was expected that not much data could be retrieved from other databases. The keywords for this research were based on the Population, Intervention, Control, and Outcomes (PICO) components. The components of PICO in this study were as follows: oral cancer studies (Population), Southeast Asian medicinal plant (Intervention), control groups or other known anti-cancer compounds/drugs (Control), and anti-cancer activity (Outcome). During the search, the following keywords were used: (‘oral cancer’ OR ’mouth cancer‘ OR ’oral malignancy‘) AND (ethnomedicine OR ’traditional herb‘ OR ’medicinal plant‘) AND (‘Southeast Asia‘ OR Brunei OR Burma OR Myanmar OR Cambodia OR Timor-Leste OR Indonesia OR Laos OR Malaysia OR Philippines OR Singapore OR Thailand OR Vietnam) AND ’anti-cancer‘. The Boolean operators such as ’AND‘ and ’OR‘ were applied to improve the specificity of the retrieved articles.

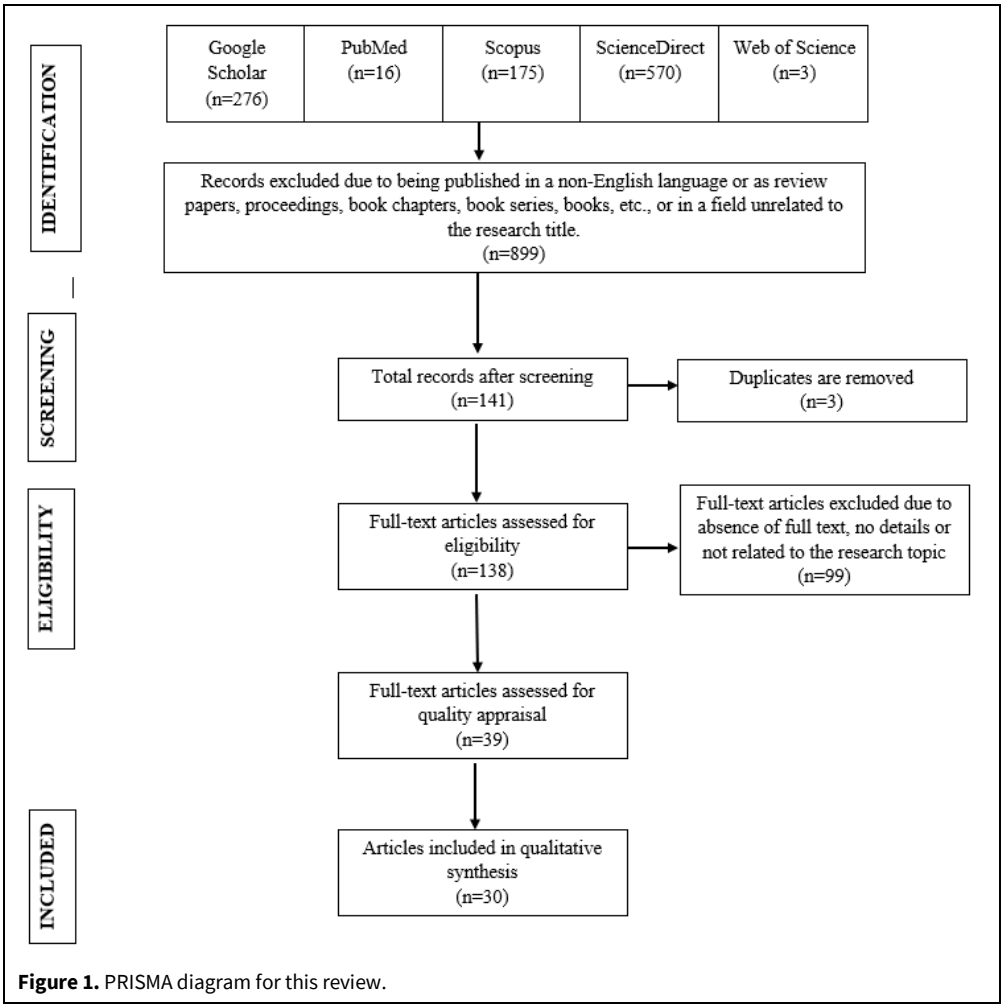

Figure 1. PRISMA diagram for this review.

Selection procedure

Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 was used as the guideline for the selection of related articles (Page et al., 2021). Articles that were identified through the database search were screened to match the inserted keywords, and duplicates were removed. The articles deemed relevant to the intended objectives were assessed and reviewed in full text for eligibility. Only articles that suit and meet the inclusion criteria were selected for this systematic review. The PRISMA diagram flow for this review is shown in Fig. 1.

Screening

The initial step was conducted using the sorting and filter function that can be accessed in each database. This feature helped in the initial screening process that involved hundreds of articles by automatically sorting the results based on criteria of interest set by authors. The following inclusion criteria were used: (i) The articles must be published in the English language, and (ii) The articles must be original research articles. Articles that did not fulfil this inclusion criteria were excluded from this study. Duplicates found from different databases were also removed.

Eligibility

The eligibility process was performed to ensure that the selected articles that have undergone the screening process were consistent with the inclusion criteria established by the authors. This process was performed manually by reading the full text of the articles by two reviewers, and the opinion of a third reviewer was consulted in case of discrepancy. The articles that were not available for full text and did not specify the main scope of study, such as oral cancer and medicinal plants, were excluded.

Quality assessment

Articles that passed the eligibility stage were assessed for their quality by using the Appraisal Tool for Cross-Sectional Studies (AXIS) critical appraisal tool. This tool was utilized to assess the quality and

integrity of the articles and to avoid any biases that may have been present in the study (Downes et al., 2016). It was developed through a Delphi panel that is comprised of 20 components. Only items that were suitable for the articles were applied. Components 7, 13, and 14 were not included because they involved responders, which was not applicable to the articles included in this review. There were two reviewers for this review. Each reviewer chose either 'Yes' or 'No' for each item or 'Don't know' when they were unsure about their judgment. 'Yes' was scored as '1', 'No' was scored as '0', and both reviewers came to a consensus for the 'Don't know' answer. The average score of each question from reviewers was then calculated and categorized into high, moderate, or low quality according to the score range. The quality was considered 'high' if the average score was more than 15, 'moderate' if it was between 12.5 and 15, and 'low' if it was less than 12.5. Only articles in 'high' and 'moderate' categories were accepted. The papers that were ranked as 'low' by both reviewers were rejected. In the case when only one reviewer ranked the article as 'low', both reviewers decided whether the article should be included or excluded upon mutual agreement.

Data abstraction and analysis

Data from eligible and accepted articles were taken and listed in tables. The data that were extracted were as follows: i) Southeast Asian medicinal plants with *in vitro* and *in vivo* activities against oral cancer, their main plant parts and methods of preparation, ii) their bioactive compounds, and iii) their mechanism of action.

RESULTS AND DISCUSSION

Study selection

A comprehensive search across five major databases: Google Scholar, PubMed, Scopus, ScienceDirect, and Web of Science yielded an initial total of records of 1,040 articles. A total of 899 articles were excluded for reasons such as being published in non-English languages, in forms like review papers, proceedings, book chapters, book series, and content irrelevant to the research theme. After screening 141 articles, duplicate articles were found and eliminated, leaving 138 articles for full-text eligibility assessment. The content of each article was scrutinized, resulting in the exclusion of 99 articles that lacked full-text availability, detailed information, or relevance to the research topic. The remaining 39 articles were then subjected to quality appraisal using the AXIS tool to ensure that they met the necessary standards for inclusion in the synthesis. A final total of 30 articles were included in the qualitative synthesis, representing the most relevant and high-quality studies identified in this systematic review process.

Study characteristics

Types of medicinal plants in the Southeast Asia region with potential activity against oral cancer

Table 1 shows the details of plant species that were included in this review. These medicinal plants were originated from the family of *Acanthaceae, Amaryllidaceae, Apocynaceae, Arecaceae, Balsaminaceae, Caricaceae, Cucurbitaceae, Hypericaceae, Lamiaceae, Moringaceae, Melastomataceae, Meliaceae, Moraceae, Phyllanthaceae, Piperaceae, Poaceae, Polygonaceae, Solieriaceae,* and *Zingiberaceae* (Fig. 2). Out of these families, each *Acanthaceae, Apocynaceae, Meliaceae,* and *Zingiberaceae* family contributed to two plant species, accounting for 36% of the plant species in this review. Other families contributed to only one type of plant species, making up to 64% of the remaining plant species included in this review.

A large proportion of these plants comprised herbs (29%), trees (25%), and shrubs (25%), while a small portion was made up of vines (8%), algae (4%), and grass (4%) (Fig. 3). Herbs are the most common type of plant used as traditional medicine worldwide because they contain different types of phytochemicals with various therapeutic functions. Shrubs and trees are also feasible sources of natural medicines as they can be easily found and are usually accessible throughout the year (Tariq et al., 2017).

In vitro and in vivo studies on medicinal plants in Southeast Asia with potential activities against oral cancer

The potential activities against oral cancer for any testing agents (plant-based extracts or compounds or chemicals or drug candidates) may be investigated in two phases, beginning at the *in vitro* level. The *in vitro* study phase is a crucial preliminary step in preclinical study prior to the subsequent step involving *in vivo* studies (Tariq et al., 2017). In this review, 15 plants, including *Andrographis paniculata, Clinacanthus nutans, Areca catechu, Impatiens balsamina*, *Carica papaya, Momordica charantia, Bridelia retusa, Imperata cylindrica*, *Cratoxylum formosum subsp. prunifolium*, *Osbeckia octandra*, *Azadirachta indica*, *Piper betle*, *Persicaria odorata*, *Soliera robusta*, and *Curcuma longa* were analysed in 13 *in vitro* studies as shown in Table 2. The most common part of plant materials used in these studies was the leaf, as it contains several medicinally important active compounds and can easily be harvested with less harmful effects on the plant's life cycle, which is important for plant species conservation (Tariq et al., 2017).

Table 1. Types of medicinal plants in Southeast Asia with potential activity against oral cancer.

Family	Plant name	Type	Parts of plants used	Types of extract	Identified compounds (dose/concentration used)	Local name	Specific country localities in Southeast Asia	Reference
Acanthaceae	*Andrographis paniculata* (Burm.f.) Wall. ex Nees	Herb	-	-	Dehydroandrographolide (DA), 0–40 (μM)	Sambiloto, pepaitan (Indonesia) Hempedu bumi, pokok cerita (Malaysia) Fah talai jone (Thailand) Bitterweed, king of bitters (English)	Indonesia, Malaysia, Thailand	(Hsieh et al., 2017)
	Clinacanthus nutans (Burm.f.) Lindau	Shrub	Leaf	Aqueous		Dendang gendis, ki tajam (Indonesia) Belalai gajah (Malaysia) Phaya yo (Thailand)	Indonesia, Malaysia, Thailand	(Yakop et al., 2018)
Amaryllidaceae	*Allium sativum* L.	Herb	Bulb	-	S-allylcysteine, 200 mg/kg/day for 98 days	Bawang putih (Malaysia) Kra Tiam (Thailand) Garlic (English)	Indonesia, Malaysia, Thailand	(Balasenthil et al., 1999)
Apocynaceae	*Pergularia daemia* (Forssk.) Chiov.	Herb	Aerial parts	Methanolic	-	Trellis-vine (English) Bunga Siam (Malaysia)	Indonesia, Malaysia, Philippines	(Mirunalini et al., 2013)
	Rauvolfia serpentina Benth. ex Kurz	Shrub	-	-	Reserpine, 10 mg/kg/day for 112 days	Akar tikus, pulai pandak (Malaysia) Indian snakeroot, devil peppers (English)	Cambodia, Laos, Indonesia, Malaysia, Myanmar, Thailand, Vietnam	(Ramu et al., 2021)
Arecaceae	*Areca catechu* L.	Tree	Leaf	Methanol	-	Pinang, pinang siri (Malaysia) Betel-nut palm, areca palm (English)	Indonesia, Malaysia	(Sari et al., 2017; 2020)
Balsaminaceae	*Impatiens balsamina* L.	Herb	Leaf	Methanol	-	Bunga tabo, inai air, inai ayam (Malaysia) Pancar banyu, paru inai (Indonesia) Garden balsam, rose balsam (English)	Indonesia, Malaysia, Myanmar	(Shin et al., 2015)
Caricaceae	*Carica papaya* L.	Tree	Leaf	Basic ethanolic Acidic ethanolic Basic aqueous Acidic aqueous	-	Betik, kates, tembi (Malaysia) Papaya, pawpaw (English)	Malaysia, Philippines	(Nguyen et al., 2015)

Table 1. Types of medicinal plants in Southeast Asia with potential activity against oral cancer (continued...)

Family	Plant name	Type	Parts of plants used	Types of extract	Identified compounds (dose/concentration used)	Local name	Specific country localities in Southeast Asia	Reference
Cucurbitaceae	*Momordica charantia* L.	Vine				Peria (Malaysia) Bitter gourd, bitter melon (English)	Indonesia, Malaysia, Philippines, Thailand, Vietnam	(Sur et al., 2019)
Hypericaceae	*Cratoxylum formosum subsp. pruniflorum* (Kurz) Gogelein	Tree	Leaf	Hexane Ethyl acetate Methanol	-	Teawdang, pink mempat, derum, gerunggung, kemutun, mempitis	Indonesia, Malaysia, Thailand, Singapore, Vietnam	(Promraksa et al., 2015)
Lamiaceae	*Ocimum sanctum* L.	Shrub	Leaf	Fresh leaf paste Aqueous Ethanolic	-	Ruku (Malaysia) Kala-pi-sein, pin-sein-net (Myanmar) Holy basil, sacred basil (English)	Malaysia, Myanmar	(Karthikeyan et al., 1999; Li et al., 2021)
Moringaceae	*Moringa oleifera* Lam.	Tree	-	-	Vicenin-2, 30 mg/kg/day for 98 days	Kelor (Indonesia) Gemunggai, meringgai, muringa (Malaysia) Dandalonbin (Myanmar) Marum (Thailand) Horse-radish tree, behen tree (English)	Indonesia, Malaysia, Myanmar, Thailand	(Li et al., 2021)
Melastomataceae	*Osbeckia octandra* DC.	Shrub	Leaf	*O. octandra* extract	-	Heen bovitiya, bovitiya (Sinhala)	Malaysia	(Kim et al., 2022)
Meliaceae	*Azadirachta indica* A. Juss.	Tree	*Azadirachta indica*	-	-	Nimbolide	Indonesia, Malaysia, Myanmar	(Balasenthil et al., 1999; Harish Kumar et al., 2010; Manikandan et al., 2008; Sophia et al., 2018; Subapriya et al., 2006)
	Toona sinensis (A.Juss.) M.Roem.	Tree	Leaf	TSL extract	-	Chinese mahogany, Chinese cedar, Chinese toon (English)	Indonesia, Malaysia, Thailand	(Wang et al., 2016)

Table 1. Types of medicinal plants in Southeast Asia with potential activity against oral cancer (continued...)

Family	Plant name	Type	Parts of plants used	Types of extract	Identified compounds (dose/concentration used)	Local name	Specific country localities in Southeast Asia	Reference
Moraceae	*Ficus deltoidea* Jack	Shrub	Leaf	Aqueous	-	Tabat barito (Indonesia) Mas cotek (Malaysia) Mistletoe fig (English)	Indonesia, Malaysia, Thailand	(Al-Koshab et al., 2020)
Phyllanthaceae	*Bridelia retusa* (L.) A.Juss.	Tree	Leaves, shoot-tips		Anthocyanin, 25, 50, 100, 200 µg/mL	Rang thon, teng nam (Thailand) Kasi, seikchi (Myanmar)	Myanmar, Thailand	(Madanakumar et al., 2018)
Piperaceae	*Piper betle* L.	Vine	Leaf	Aqueous	-	Sireh (Malaysia) Betel (English)	Malaysia, Indonesia	(Veettil et al., 2022)
Poaceae	*Imperata cylindrica* (L.) Raeusch.	Grass	Leaf	Methanol	-	Thatch grass, cogon grass (English) Lalang (Malaysia)	Cambodia, Laos, Indonesia, Malaysia, Philippines, Singapore, Thailand, Vietnam	(Keshava et al., 2016)
Polygonaceae	*Persicaria odorata* (Lour.) Soják	Herb	Aerial	Methanolic	-	Chi krasang tomhom (Cambodia) Daunkesom (Indonesia) Phak phaew (Laos) Kesum (Malaysia) Laksa plant (Singapore) Phak phai (Thailand) Rau rdm (Vietnamese)	Cambodia, Indonesia, Laos, Malaysia, Singapore, Thailand, Vietnam	(Khwairakpam et al., 2020)
Solieriaceae	*Soliera robusta* (Greville) Kylin 1932	Algae	Algae	Methanolic	-	Red algae (English)	Indonesia, Malaysia	(Yen et al., 2014)

Table 1. Types of medicinal plants in Southeast Asia with potential activity against oral cancer (continued...)

Family	Plant name	Type	Parts of plants used	Types of extract	Identified compounds (dose/concentration used)	Local name	Specific country localities in Southeast Asia	Reference
Zingiberaceae	*Zingiber officinale* Roscoe	Herb	-	-	[6]-Shogaol, 10,20,49 mg/kg/day for 98 days	Ginger (English) Halia (Malaysia)	Malaysia, Philippines	(Annamalai and Suresh, 2018)
	Curcuma longa L.	Herb	Rhizomes	-	Curcumin (CUR), dimethoxy-curcumin (DMC), and bisdemethoxycurcumin (BDMC), 1 % in turmeric diet for 82 days	Turmeric, haldi	Indonesia, Malaysia, Philippines, Thailand	(Garg et al., 2008; Hsiao et al., 2018)

Source of scientific names of species were obtained from https://www.worldfloraonline.org/

Table 2. The *in vitro* cytotoxic effects of Southeast Asian medicinal plants on oral cancer cell lines.

Family	Plant name	Plant part	Extract	Compound	Cell line	Concentration	Inhibition %	Viability %	IC_{50} (µg/mL)	Selectivity index	Reference drug	Method	Reference
Acanthaceae	*Andrographis paniculata* (Burm.f.) Wall. ex Nees	-	-	Dehydroandrographolide (DA)	SCC-9	0-40 µM	0	-	-	-	-	MTT assay	(Hsieh et al., 2017)
	Clinacanthus nutans (Burm.f.) Lindau	Leaf	Aqueous	-	HSC-4	0.75 to 3 µg/mL	90	-	1.61	-	-	MTT assay	(Yakop et al., 2018)
Arecaceae	*Areca catechu* L.	Seed	Areca nut extract	-	HSC-2 HSC-3	160, 320, 640, 1280, 2560 µg/mL	-	-	629.50 164.06	-	-	MTS assay	(Sari et al., 2017)

Table 2. The *in vitro* cytotoxic effects of Southeast Asian medicinal plants on oral cancer cell lines (continued...)

Family	Plant name	Plant part	Extract	Compound	Cell line	Concentration	Inhibition %	Viability %	IC_{50} (µg/mL)	Selectivity index	Reference drug	Method	Reference
Balsaminaceae	*Impatiens balsamina* L.	Leaf	Methanol	-	HSC-4 OSC-20	0, 20, 40 nM	-	100, 40, 20	-	-	YM155 (20 and 40 nM)	MTS assay	(Shin et al., 2015)
Caricaceae	*Carica papaya* L.	Leaf	Basic ethanolic Acidic ethanolic Basic aqueous Acidic aqueous	-	SCC25	5 to 100 µg/mL	-	-	172.9 77.18 40.14 57.72	-	-	MTT assay	(Nguyen et al., 2015)
Hypericaceae	*Cratoxylum formosum subsp. prunifolium* (Kurz) Gogelein	Leaf	Hexane Ethyl acetate Methanol	-	ORL-48 ORL-136	50-400 µg/mL	-	-	Ranged from 44.82 to 400.0 depending on extract used		-	MTT assay	(Promraksa et al., 2015)
Melastomataceae	*Osbeckia octandra* DC.	Leaf	*O. octandra* extract	-	HSC-2	50 to 300 µg/mL	-	-	100	-	-	MTT assay	(Kim et al., 2022)
Meliaceae	*Azadirachta indica* A. Juss.	-	-	Nimbolide	SCC131 SCC4	0 to 10 µg/mL	-	-	6 6.2	-	-	MTT assay	(Sophia et al., 2018)
Phyllantaceae	*Bridelia retusa* (L.) A.Juss.	Leaves, shoot tips	-	Anthocyanin	SCC4 SCC9 SCC25	25, 50, 100, 200 µg/mL	-	-	52.7 49 37.8	-	-	MTS assay	(Madanakumar et al., 2018)

Table 2. The *in vitro* cytotoxic effects of Southeast Asian medicinal plants on oral cancer cell lines (continued...)

Family	Plant name	Plant part	Extract	Compound	Cell line	Concentration	Inhibition %	Viability %	IC $_{50}$ (µg/mL)	Selectivity index	Reference drug	Method	Reference
Piperaceae	*Piper betle* L.	Leaf	Aqueous	-	KB	6.25, 12.5, 25, 50, 100 µg/mL	-	65.72 57.70 56.96 54.27 43.42	-	-	-	MTT assay	(Veettil et al., 2022)
Poaceae	*Imperata cylindrica* (L.) Raeusch.	Leaf	Methanol	-	SCC-9	10 to 640 µg/mL	20 (10-40 µg/mL) 20-25 (80 and 160 µg/mL) 50 (320 µg/mL) 60 (640 µg/mL)	-	138.9	-	-	MTS assay	(Keshava et al., 2016)
Polygonaceae	*Persicaria odorata* (Lour.) Soják	Aerial	Methanolic	-	SAS HSC-3 SCC-9	0 to 200 µg/mL	-	-	75.0 ~350 ~350	-	-	MTT assay	(Khwairakpam et al., 2020)
Solieriaceae	*Soliera robusta* Greville) Kylin 1932	Algae	Methanolic	-	Ca9-22 CAL 27	0 to 2.5 mg/mL 0 to 1 mg/mL	-	-	1.89 (mg/mL) 0.296 (mg/mL)	-	-	MTS assay	(Yen et al., 2014)

Source of scientific names of species were obtained from https://www.worldfloraonline.org/

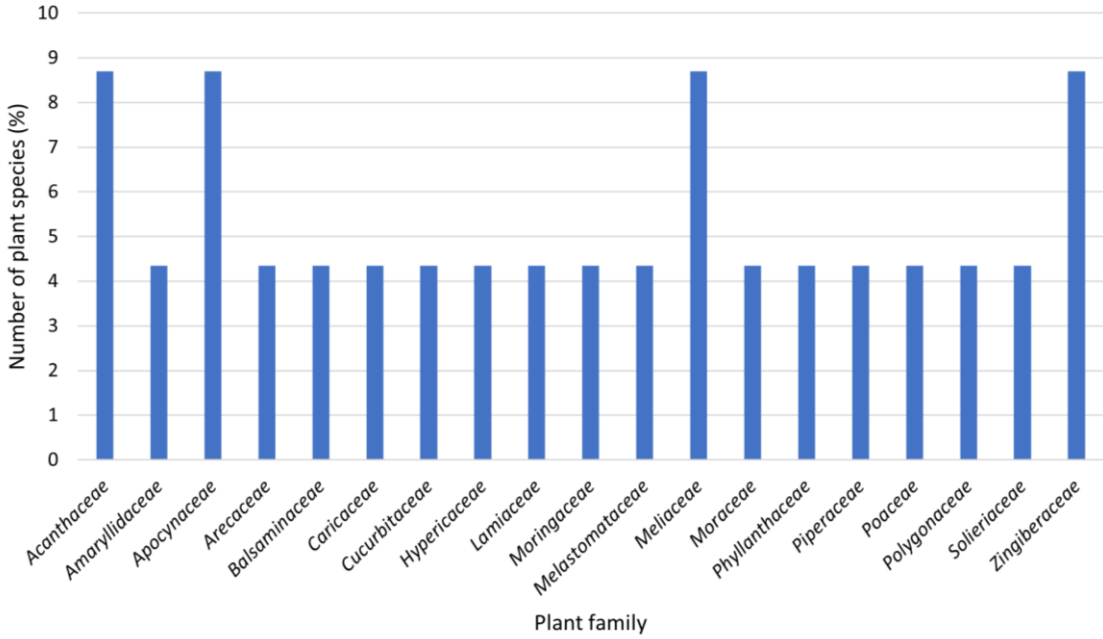

Figure 2. Distribution of plants according to plant families.

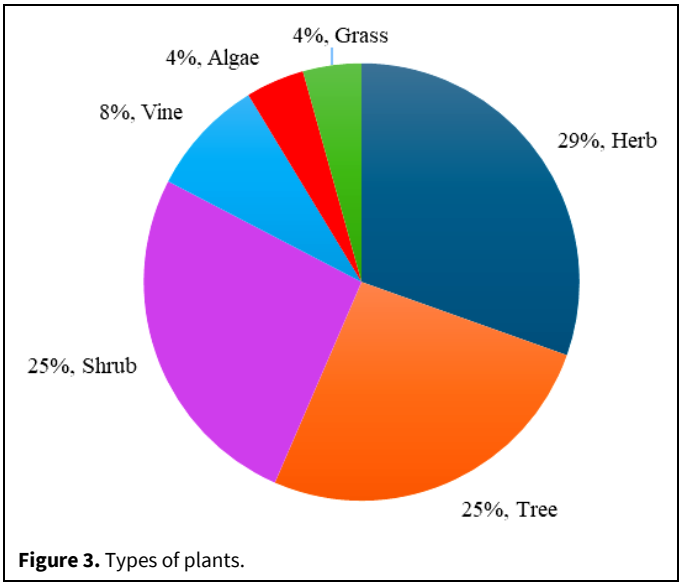

Figure 3. Types of plants.

Other than the leaf, the seed and the aerial parts of plants were also being tested. Most of the plant materials were extracted using water or alcoholic solvents such as ethanol or methanol before being exposed to cancer cell lines.

The cancer cell line was the basic *in vitro* model system that was frequently used, especially in cancer research and drug discovery (Mirabelli et al., 2019). Table 2 also lists the various types of oral cancer cell lines used in these studies which include those derived from humans' and rats' OSCCs such as the HSC series (HSC-2, HSC-3, HSC-4), SCC series (SCC-4, SCC-9, SCC-25, SCC-131), ORL series (ORL 48 and ORL 136), SAS, Cal 27, OSC 20, H400, JHU022, KB, and Ca9-22 cell lines. However, most of these studies were carried out on the SCC series. All SCC series originated from humans except for the SCC-131 cell line in which it was isolated from a rat's (*Rattus norvegicus*) squamous cell carcinoma. Likewise, SCC-131 is the only cell line that originated from rats in this present review. The rest of the SCC series originated from tongue squamous cell carcinoma of male humans of different ages: SCC-4 (55-year-old), SCC-9 (25-year-old), and SCC-25 (70-year-old) (Duvaud et al., 2021).

Other than the variation in the types of cancer cell lines, variabilities in the types of cell cytotoxicity and viability assay were also observed. The cell viability assays usually measure the number of viable cells in a sample and indirectly inform about the number of dead cells (Kamiloglu et al., 2020). In these studies, two types of viability assays were identified which include 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay. MTT is the most common type of assay found across all studies in the present review. MTT is a yellow dye that can only be reduced to purple colour by viable cells (Kanagamani et al., 2019; Tsao et al., 2021). The formazan production is proportional to the viable cells and inversely proportional to the degree of cytotoxicity (El-Naggar et al., 2017). This assay is widely applied in proliferation and cytotoxicity studies to screen the chemo-preventive potential of natural products, thus providing preliminary data for further *in vitro* and *in vivo* investigations (Nguyen et al., 2015). As this assay has high sensitivity, it has been recognised as a high-throughput assay for cytotoxicity screening (Van Tonder et al., 2015). MTT assay is a common assessment method with high positivity and can penetrate the eukaryotic cells effectively.

Alternatively, some studies used the MTS assay, which is also known as the 'one-step' MTT assay. The MTS assay is a simplified form of MTT assay in which the intermittent steps of MTT assay are excluded, thus making it more convenient. This method was performed in studies by Shin et al. (2015), Keshava et al. (2016), Madanakumar et al. (2018), and Yen et al. (2014). However, it was observed that the simplified step caused the MTS assay to become susceptible to colorimetric interference as the intermittent steps in the MTT assay actually help in removing the traces of coloured compound, whereas these would remain in the microtiter plate in one-step MTS assay (Kuete et al., 2017). While most studies did not employ any positive control in the MTT/MTS assay, only one study by Shin et al. (2015) utilized YMM155 at concentrations of 20 and 40 nM as positive control in the MTS assay. YMM155 is a sepantronium bromide, a small-molecule inhibitor that suppresses the expression of survivin, a protein that inhibits apoptosis and is overexpressed in various cancers. Future studies are recommended to complement the findings of MTT/MTS assay results with other cytotoxicity assessment methods that involve demonstrating cell membrane damage, for example, the lactate dehydrogenase (LDH) cytotoxicity assay. This assay is based on the release of intracellular enzymes into the culture medium after cell membrane damage (Setiawati et al., 2022), which could be an alternative to the MTT test. The use of MTT assay for *in vitro* toxicity assessment alone is not sufficient, and the results obtained by this test may not be reliable owing to the inability of the MTT assay to detect cells at an interface between a metabolically inactive state and death. This is because the MTT cytotoxicity assay is based on the reduction of MTT by mitochondrial enzymes (Hoogstraten et al., 2022), which could falsify the results of cytotoxicity.

Most of these cytotoxicity studies reported the half-maximal inhibitory concentration (IC_{50}), which indicates the amount of drug required to inhibit a biological process by half, thus providing a measure of the potency of a drug in pharmacological research (Patel and Pathak, 2022). Only a minority of studies reported the findings as inhibition or viability percentages (Table 2). None of these studies reported a selectivity index (SI), which reflects the specificity of a compound in targeting cancer cells over normal cells, despite its importance in investigating an anticancer drug candidate. A higher SI indicates the potential for targeted action with reduced toxicity to normal cells, making it a promising candidate for cancer treatment (Mansour et al., 2022). This could be another gap in the previous studies, which needs to be fulfilled in future studies.

In addition to *in vitro* studies, *in vivo* studies are performed to understand the effect of plant extracts, compounds, or any drug candidates in the body under cancerous conditions (Tariq et al., 2017). Some of the plants studied *in vitro* have been extended for *in vivo* studies. In this review, 10 plant species from the Southeast Asian region were examined in 13 studies using *in vivo* approach. These include *Allium sativum*, *Rauvolfia serpentina*, *Pergularia daemia*, *Ocimum sanctum*, *Moringa oleifera*, *Azadirachta indica*, *Toona sinensis*, *Ficus deltoidea*, *Zingiber officinale*, and *Curcuma longa* (Table 3).

All these *in vivo* studies used the same organism model, namely, male Syrian hamster, except for one study by Al-Koshab et al. (2020), in which the authors used Sprague Dawley (SD) rats. Hamster buccal pouches are highly distensible, making them easy to be everted with little or no risk of trauma. There are also similarities between its lining mucosa and the epithelium covering the hard palate, tongue, and gingiva of the human oral cavity. It also supports the long-term survival of transplanted foreign tissue without immunological rejection (Abdel Hamid et al., 2021; Fox et al., 2015; Melo et al., 2018). The presence of immunologically privileged and large, highly distensible cheek pouches makes hamsters a preferred model for oral carcinogenesis (Nagarajan et al., 2021).

Table 3. The anticancer properties of Southeast Asian plants in animal models of oral cancer.

Family	Plant name	Plant part	Extract	Compound	Model organism	Dose (mg/kg/day)	Route of administration	Time (days)	Inhibition %	Use of control group or placebo	Tumour system	Method	Findings	Reference
Amaryllidaceae	*Allium sativum* L.	Bulb	-	S-allylcysteine	Male Syrian hamster	200	Oral	98	-	Untreated control group received neither DMBA (7,12-dimethylbenz[a]anthracene) nor S-allylcysteine (SAC), serving as an untreated baseline.	DMBA-induced hamster buccal pouch carcinogenesis	Tumour incidence Histopathological changes	No malignant transformation, only mild hyperplasia with normal keratin and normal connective tissue was observed.	(Balasenthil and Nagini, 2000)
Apocynaceae	*Pergularia daemia* (Forssk.) Chiov.	Aerial parts	Methanolic	-	Male Syrian golden hamster	200	Intragastric Topical	105	-	Negative control group was pasted with paraffin alone, without DMBA or *P. daemia* methanolic extract (PDME).	DMBA-induced hamster buccal pouch carcinogenesis	Histopathological observation	Mild to moderate preneoplastic lesion (hyperplasia, hyperkeratosis, and dysplasia).	(Mirunalini et al., 2013)
	Rauvolfia serpentina Benth. ex Kurz	-	-	Reserpine	Male Syrian golden hamster	10	-	112	-	Vehicle control group received only basal diet without DMBA or reserpine treatment.	DMBA-induced hamster buccal pouch carcinogenesis	Tumour incidence Histopathological observation	No tumour formation in reserpine treated groups with only mild hyperplasia and dysplasia.	(Ramu et al., 2021)

Table 3. The anticancer properties of Southeast Asian plants in animal models of oral cancer (continued...)

Family	Plant name	Plant part	Extract	Compound	Model organism	Dose (mg/kg/day)	Route of administration	Time (days)	Inhibition %	Use of control group or placebo	Tumour system	Method	Findings	Reference
Lamiaceae	*Ocimum sanctum* L.	Leaf	Fresh leaf paste Aqueous Ethanolic	-	Male Syrian golden hamsters	30-1000	Oral Topical	70	-	Liquid paraffin/olive oil-treated DMBA groups were used as baseline control groups. There were also non-DMBA treated groups given various preparations of O. sanctum in the form of leaf paste, aqueous extract, and ethanolic extract form, applied topically or orally (serving as the baseline control group).	DMBA-induced hamster buccal pouch carcinogenesis	Tumour incidence Histopathological observation	Significant reduction in the incidence of papillomas and carcinomas.	(Karthikeyan et al., 1999)
Lamiaceae, Moringaceae	*Ocimum sanctum* L., *Moringa oleifera* Lam.	-	-	Vicenin-2	Syrian golden hamster	30	Topical	98	-	Healthy control group without exposure to DMBA or vicenin-2.	DMBA- induced hamster buccal pouch carcinogenesis	Tumour incidence and volume Histopathological observation	Absence of tumour formation. Moderate keratosis and mild hyperplasia were noted.	(Li et al., 2021)

Table 3. The anticancer properties of Southeast Asian plants in animal models of oral cancer (continued...)

Family	Plant name	Plant part	Extract	Compound	Model organism	Dose (mg/kg/day)	Route of administration	Time (days)	Inhibition %	Use of control group or placebo	Tumour system	Method	Findings	Reference
Meliaceae	*Azadirachta indica* A. Juss.	Seed kernels, leaves and flowers	-	Azadirachtin, nimbolide	Male Syrian hamsters	10, 100	Topical	98	-	Control group received no treatment, serving as a baseline.	DMBA-induced hamster buccal pouch carcinogenesis	Tumour burden Histopathological observation	Group (DMBA + Azadirachtin 10) - 3 out of 10 hamsters developed SCC, others exhibited severe dysplasia: Group (DMBA + azadirachtin 100) - no tumour: Group (DMBA + nimbolide 10) - no tumour: Group (DMBA + nimbolide 100) - moderate to severe dysplasia.	(Harish Kumar et al., 2010)
		Leaf	Ethanolic	-	Male Syrian hamsters	200	Topical	98	112	Control group was treated with paraffin oil alone, without exposure to DMBA or ethanolic neem leaf extract, provided a baseline reference for experimental group.	DMBA-induced hamster buccal pouch carcinogenesis	Tumour incidence and burden Histopathological changes	Effectively suppressed the development of carcinomas, but hyperplasia and dysplasia continued to persist.	(Subapriya et al., 2006)

Table 3. The anticancer properties of Southeast Asian plants in animal models of oral cancer (continued...)

Family	Plant name	Plant part	Extract	Compound	Model organism	Dose (mg/kg/day)	Route of administration	Time (days)	Inhibition %	Use of control group or placebo	Tumour system	Method	Findings	Reference
		Leaf	Crude ethanolic extract (CEE) ethyl acetate fraction (CEF) methanolic fraction (MF)	-	Male golden Syrian hamster	100 (CEE),1 (EAF1), 10(EAF 2), 100 (EAF 3), 1 (MF1), 10 (MF2), 100 (MF3)	Intragastric	98	-	Control group received only a basal diet without exposure to DMBA or any neem leaf fraction.	DMBA-induced hamster buccal pouch carcinogenesis	Tumour incidence, histopathological observations	No tumours were observed. There were varying degrees of hyperplasia, hyperkeratosis, and dysplasia.	(Manikandan et al., 2008)
		Leaf	-	-	Male Syrian hamster	100	Intragastric	98	-	Control group received neither DMBA nor neem extract, serving as a baseline reference.	DMBA-induced hamster buccal pouch carcinogenesis	Tumour incidence	Reduced tumour incidence.	(Balasenthil and Nagini, 1999)
	Toona sinensis (A.Juss.) M.Roem.	Leaf	TSL extract	-	Male Syrian golden hamster	1000	Intragastric	154	-	Control group treated with mineral oil as a vehicle control without DMBA or TSL extract.	DMBA-induced hamster buccal pouch carcinogenesis	Tumour incidence, volume and burden Histopathological observations	Decreased tumour incidence, volume, and burden.	(Wang et al., 2016)

Table 3. The anticancer properties of Southeast Asian plants in animal models of oral cancer (continued...)

Family	Plant name	Plant part	Extract	Compound	Model organism	Dose (mg/kg/day)	Route of administration	Time (days)	Inhibition %	Use of control group or placebo	Tumour system	Method	Findings	Reference
Moraceae	*Ficus deltoide* Jack	Leaf	Aqueous	-	Sprague-Dawley rats	250, 500	Topical	154	-	Control group received only 4NQO to induce oral cancer without the *F. deltoidea* extract, serving as a positive control for cancer induction. Untreated group received regular water, served as a baseline comparison, acting as the negative control group.	4NQO-induced oral cancer rat model	Tumour volume Histopathological observations	Significant reduction in the incidence from 100% to 14.3% in the high-dose group.	(Al-Koshab et al., 2020)
Zingiberaceae	*Zingiber officinale* Roscoe	-	-	[6]-Shogaol	Male golden Syrian hamsters	10, 20, 40	Topical	98	-	Control group was treated with liquid paraffin alone without DMBA or [6]-shogaol.	DMBA-induced hamster buccal pouch carcinogenesis	Tumour incidence Histopathological observation	Significant reduction in the tumour volume and tumour burden.	(Annamalai and Suresh, 2018)
	Curcuma longa L.	Rhizomes	-	Curcumin (CUR), dimethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC)	Male Syrian hamsters	(1% turmeric diet)	Oral	82	-	Control group received only the vehicle (oil) without DMBA or turmeric treatment.	DMBA-induced hamster buccal pouch carcinogenesis	Tumour incidence and burden	Significant reduction in tumour incidence by 45%. Decrease in tumour burden and multiplicity.	(Garg et al., 2008)

DMBA: 7,12-dimethylbenz[a]anthracene, NQO: 4-nitroquinoline-1-oxide. Source of scientific names of species were obtained from https://www.worldfloraonline.org/

In the present review, it was observed that the studies conducted on Syrian hamsters involved 7,12-dimethylbenz[a]anthracene (DMBA) treatment, while studies conducted on SD rats utilized 4-nitroquinoline-1-oxide (4NQO) to induce oral cancer carcinoma.

The overall process of *in vivo* experiment includes model organisms being treated with a carcinogenic solution such as DMBA or 4NQO to develop the buccal pouch cancer as a model for human oral carcinogenesis, proceeding with the treatment of plant extracts or pure compounds based on the predetermined dose *via* designated route of administration of either topical, oral, intraperitoneal, or intragastric, then followed by tissue evaluation. Evaluation of the treated buccal cells was assessed through the measurement of tumour volume, incidence, and burden, assisted by histopathological observations.

Southeast Asian medicinal plants with activities against oral cancer

In summary, there were 23 different plants with various *in vitro* and/or *in vivo* activities with interesting potentials to be considered either for prophylaxis and/or treatment of oral cancer such as follows.

Allium sativum L. *(Amaryllidaceae)*

Allium sativum is known as '*bawang putih*' in Malaysia, '*kra Tiam*' in Thailand and garlic in English. It has been used as a spice in cooking and as a medicinal herb for centuries. S-allylcysteine (SAC) is a naturally occurring, non-toxic, water-soluble, organosulphur compound regarded as one of the important biologically active constituents of garlic. Balasenthil and Nagini (2000) demonstrated that an intragastric administration of SAC at the dose of 200 mg/kg thrice a week on days alternate to DMBA application has shown chemopreventive activity towards DMBA-induced hamster buccal pouch carcinogenesis. The study found that in these treated hamsters, there was no malignant transformation, but only mild hyperplasia with normal keratin and normal connective tissue was observed, which is indicative of the absence of neoplasms. The same study also showed that SAC exerted its chemopreventive mechanism by diminishing the level of lipid peroxidation, as well as by enhancing the level of glutathione (GSH) and glutathione peroxidase (GPx) and the elevation of carcinogen-detoxifying enzymes such as glutathione s-transferase (GST).

Andrographis paniculata (Burm.f.) Wall. ex Nees *(Acanthaceae)*

Andrographis paniculata is known as '*sambiloto*' or '*pepaitan*' in Indonesia, '*hempedu bumi*' or '*pokok cerita*' in Malaysia, '*fah talai jone*' in Thailand, and bitterweed or king of bitters in English. Dehydroandrographolide (DA), is one of the principal components of *A. paniculata* that mainly contributes to its therapeutic properties. When DA was tested at various concentrations (0–40 μM) on the human oral cancer cell line, SCC9, it did not display any reduction in the cell viability even after 72 hours of treatment as compared to untreated cells (Hsieh et al., 2017). Subsequent studies have been conducted to elucidate the potential effects of DA on wound closure, migration, and invasion abilities of SCC9 cells. In the wound closure assays, DA treatment at 24 hours reduced the number of migrating SCC9 cells by 33%. In the subsequent Boyden chamber assays on SCC9 cells, DA at 40 μM reduced the cell invasion and migration by 40% and 45%, respectively. This is indicative of the ability of DA to inhibit the SCC9 cells' invasion and migration. In the next assay, the anti-metastatic potential of DA was investigated by examining its effect on matrix metalloproteinase-2 (MMP-2) activity and expression, which is known to be correlated with the metastatic potential of tumour cells. In DA-treated SCC9 cells, it was shown to inhibit the MMP-2 expression and activity and to increase the expression of tissue inhibitors of metalloproteinases-2 (TIMP-2), a specific inhibitor for MMP-2. DA suppressed the MMP-2 expression by inhibiting the IKKα/β/γ expression, thus affecting the NF-κB and the activator protein 1 (AP-1) expression. DA also inhibited the phosphorylation of extracellular signal-regulated protein kinases 1 and 2 (ERK1/2), p38, and c-Jun N terminal protein kinases 1 and 2 (JNK 1/2), which are crucial for cell migration. In addition, DA suppressed carcinoma-associated epithelial-mesenchymal transition in SCC9 cells, a vital developmental program for cancer invasion and metastasis. Finally, DA administration at 40 mg/kg for 24 days effectively suppressed the MMP-2 expression and tumour metastases in the *in vivo* oral carcinoma xenograft mice model (Hsieh et al., 2017). Altogether, the finding has indicated the potential of DA as a preventive and therapeutic agent for cancer metastasis.

Areca catechu L. *(Arecaceae)*

Areca catechu is known as *'pinang'* in Malaysia and betel-nut palm or areca palm in English. The plant can be found in Southeast Asia and is particularly common in Indonesia and Malaysia. *Areca* nut (betel) chewing is one of the folkloric practices among Indi-

ans and Malays (Sari et al., 2017). *Areca* nut has been classified as a human carcinogen according to the International Agency for Research on Cancer (IARC, 2004). Furthermore, epidemiological studies have established a correlation between areca nut chewing and the development of OSCCs. Despite this evidence, the *Areca* nut on its own does not contain carcinogenic substances, but this carcinogenic effect is caused by prolonged and uncontrollable exposure to nitrosamines. Nitrosation of alkaloids in the nuts inside the mouth, in combination with the acid conditions of the stomach, and in the presence of nitric oxide generated by bacteria produces nitrosamines, which was proven to be carcinogenic in animal studies according to the IARC (2004). Previous studies found that this nitrosamine product was markedly higher in people with poor oral hygiene (Nagao et al., 2000) and was much higher in people chewing *Areca* nuts together with tobacco (Carossa et al., 2001). Nevertheless, some studies on *Areca* nut itself have demonstrated the selective cytotoxicity against human oral squamous carcinoma cell lines, the HSC-3 and HSC-2 cells with IC_{50} of 164.06 µg/mL in HSC-3 and 629.50 µg/mL in HSC-2, respectively, with no cytotoxic effect on human keratinocytes, the HaCaT cells (Sari et al., 2017). Furthermore, the *Areca* nut extract caused cell-cycle arrest in HSC-3 cells after 24 hours of extract treatment, and it inhibited cell proliferation by reducing the Ki-67 activity after 24 hours of *Areca* nut extract treatment in both HSC-2 and HSC-3 cells (Sari et al., 2020). The Ki-67 protein is a non-histone nuclear protein expressed by the cells in G_1, S, G_2, and M phases but not observed in cells at G_0 phase, and it is a prognostic marker of OSCC and oral premalignant lesions. The well-differentiated OSCC usually expresses Ki-67 as a proliferation marker. By inhibiting this Ki-67, this has indicated an antiproliferative effect of *Areca* nut. Since there is a potential risk of also creating the carcinogenic product upon *Areca* nut chewing (especially upon combination with certain other conditions), it is best to avoid this accustomed practice, unless the *Areca* nut extract is consumed by other means that does not result in production of the carcinogenic nitrosamines.

Azadirachta indica A. Juss. *(Meliaceae)*

Azadirachta indica, which is known as '*mimba*' in Indonesia, '*nim*' or '*intara*' or '*mambu*' in Malaysia, and neem tree or Indian lilac in English, can be found in Indonesia, Malaysia, and Myanmar. In the present review, five articles evaluated the anticancer effect of *A. indica* on oral cancer. One of them studied the *in vitro* activities of *A. indica*, while the rest studied its *in vivo* activities. Balasenthil and Nagini (2000) demonstrated the chemo-preventive effects of *A. indica* on DMBA-induced hamster buccal pouch carcinogenesis. This chemo-preventive activity was based on its ability to modulate lipid peroxidation, antioxidants, and detoxification systems. This was indicated through the decreased lipid peroxidation and the elevated GSH, GPx, GST, and GGT in the oral cancer model. A subsequent study by Subapriya et al. (2006) discovered that ethanolic *A. indica* leaf extract exerted its anticancer properties by inhibiting cell proliferation and inducing differentiation and apoptosis evidenced by decreased expression of proliferating cell nuclear antigen (PCNA), mutant p53 and Bcl-2 and overexpression of cytokeratin. Manikandan et al. (2008) also suggested that the antioxidant properties of neem leaf fractions may be responsible for modulating the capabilities of cancer cells for cell proliferation, angiogenesis, and apoptosis in the hamster buccal pouch carcinogenesis model. Following that, Harish Kumar et al. (2010) found that two bioactive compounds of *A. indica*, which include azadirachtin and nimbolide mediate their antiproliferative effects by downregulating proteins involved in cell cycle progression and apoptosis by both the intrinsic and extrinsic pathways. According to the latest study by Sophia et al. (2018), nimbolide induced apoptosis of oral cancer cell lines by overcoming the shielding effects of cytoprotective autophagy through modulation of the phosphorylation status of Akt and glycogen synthase kinase-3β (GSK-3β), as well as the ncRNAs miR-126 and homeobox transcript antisense intergenic RNA (HOTAIR). Nimbolide negatively regulates PI3K/Akt signaling with the consequent increase in p-GSK-3βTyr216, the active form of GSK3β that inhibits autophagy. Downregulation of HOTAIR, a competing endogenous RNA that sponges miR-126, may be a major contributor to the inactivation of PI3K/Akt/GSK3 signaling by nimbolide.

Bridelia retusa (L.) A.Juss. *(Phyllanthaceae)*

Bridelia retusa, which is known as '*rang thon*' or '*teng nam*' in Thailand and '*kasi*' or '*seikchi*' in Myanmar, can be found in those two countries. Madanakumar et al. (2018) revealed that anthocyanin, an isolated compound of *B. retusa* has the ability to induce apoptosis. This was evidenced by the morphological alterations in SCC cells after treatment with *B. retusa* anthocyanin, which include nuclear condensation, fragmentation, and apoptosis. In addition, the study has revealed that *B. retusa* anthocyanin was able to cause cell-cycle arrest of SCC-25 cells which are the epithelial-like cells that were isolated from the tongue of a 70-year-old male patient with squamous cell carcinoma. The arrest mostly occurs in the G_0/G_1 and S-G_2/M stages with a concomitant upregulation of sub-G_1 fraction, indicating cell death by apoptosis. Apoptosis was further proven by an increased level of

caspase-3 expression in the treated SCC-25 cells (Madanakumar et al., 2018).

Carica papaya L. *(Caricaceae)*

Carica papaya is known as *'betik'* in Malay and papaya in English. The plant can be found in Malaysia and Philippines. Nguyen et al. (2015) examined four different types of *C. papaya* extract, which include basic ethanolic, acidic ethanolic, basic aqueous, and acidic aqueous. They found that all four extracts showed a significant effect on SCC-25 cancer cell viability, starting at different concentrations: 25 µg/mL for serial basic ethanol, 10 µg/mL for serial acidic ethanol (SAE), and 5 µg/mL for both serial acidic water (SAW) and serial basic water fractions. Two out of four extracts with acidic pH showed a significantly selective effect on the SCC-25 cells with an effective range of 25–100 µg/mL for SAE and 5–20 µg/mL for SAW fractions (Nguyen et al., 2015).

Clinacanthus nutans (Burm.f.) Lindau *(Acanthaceae)*

Clinacanthus nutans is recognized as '*dendang gendis*' or '*ki tajam*' in Indonesia, '*belalai gajah*' in Malaysia, and as '*phaya yo*' in Thailand. *C. nutans* itself has been reported to have antiproliferative effects on various cancer cell lines and exhibit apoptotic effects on liver cancer cell lines. However, a recent study reported the effect of silver nanoparticles *C. nutans* (AgNps-CN) on oral cancer cell lines (Yakop et al., 2018). The study showed a significant cytotoxic effect of AgNps-CN against the HSC-4 cell line, a subclass of oral squamous cell carcinoma cell line with IC_{50} of 1.61 ± 0.14 mg/mL. Compared to *C. nutans* extracts alone, the AgNps-CN showed better cytotoxic activity against the HSC-4 cell lines. Furthermore, AgNps-CN was tested against 3T3-L1, the normal fibroblasts isolated from the embryo of a mouse. The study showed that the combination was not cytotoxic toward normal cells, even at the highest tested concentration (3 µg/mL). Yakop et al. (2018) found that the AgNps-CN was also able to induce apoptosis, as evidenced by the presence of membrane blebbing, nuclear fragmentation, chromatin condensation, and an increase in the ratio of Bax/Bcl-2 protein. Bcl-2 family members are crucial in the regulation of apoptosis intrinsic pathways, comprising the pro- and anti-apoptotic proteins. Pro-apoptotic proteins caused increased permeability of the mitochondrial membrane, leading to the release of pro-apoptotic molecules such as cytochrome C, which resulted in cells undergoing apoptosis and vice versa for anti-apoptotic proteins. The imbalance between the ratio of pro- and anti-apoptotic protein leads to dysregulation of apoptosis. Thus, in this study, it was found that AgNps-CN induced apoptosis in HSC-4 cell lines through an intrinsic pathway by suppressing the release of Bcl-2 protein, which led to increased permeability of the mitochondrial membrane (Yakop et al., 2018). Despite the positive findings *in vitro*, no further study has confirmed these findings in an *in vivo* setting.

Cratoxylum formosum subsp. pruniflorum (Kurz) Gogelein *(Hypericaceae)*

Cratoxylum formosum subsp. pruniflorum is known as *'teawdang'* or *'derum'* or *'gerunggung'* or *'kemutun'* or *'mempitis ruku'* in Malaysia, *'kala-pi-sein'* or *'pin-sein-net'* in Myanmar and holy or sacred basil in English. It can be found in Indonesia, Malaysia, Thailand, Singapore, and Vietnam. Promraksa et al. (2015) tested HSC-2 cell lines derived from OSCC from the oral cavity and three types of extracts, including hexane, ethyl acetate, and methanol extracts. They found that both methanol and ethyl acetate extracts at 200 µg/mL were cytotoxic to HSC-2 cell lines. However, the methanol extract alone was also cytotoxic to Vero cells, a type of normal cells that originate from kidney epithelial cells of an African green monkey, whereas the ethyl acetate was not. Despite the positive findings, its anticancer mechanism was not explored further.

Curcuma longa L. *(Zingiberaceae)*

Curcuma longa, which is widely known as turmeric, can be found in Indonesia, Malaysia, Philippines, and Thailand. The buccal pouch of hamsters treated with a turmeric diet showed various anticancer activities. It decreased cell proliferation, shown by diminished PCNA and Bcl-2 expression, enhanced apoptosis, evidenced by increased expression of Bax, caspase-3, and apoptotic index, and decreased inflammation, as revealed by the reduced levels of COX-2, the downstream target of AP-1/NF-κB, and prostaglandin E2 (PGE2), and caused aberrant expression of differentiation markers, the cytokeratins (Garg et al., 2008). In addition, curcuminoid found in the plant exerted a cytotoxic effect on SAS cell lines (oral cancer cell line established from a tongue squamous cell carcinoma) by inducing apoptosis by reactive oxygen species (ROS) production, caspase-8, caspase-9, and caspase-3 activations, and decreased the levels of MMP and apoptosis-inducing factor (AIF) release. Curcuminoid also induced autophagy through EGFR, phosphoinositide 3-kinases (PI3K), Akt, NF-κB or AMP-activated protein kinase (AMPK)/MAPK to form Unc-51-like kinase (ULK) complex leading to autophagy (Hsiao et al., 2018).

Ficus deltoidea Jack (*Moraceae)*

Ficus deltoidea, known as '*tabat barito*' in Indonesia, '*mas cotek*' in Malay, and mistletoe fig in English, can

be found in Indonesia, Malaysia, and Thailand. *F. deltoidea* extract was found to exert chemo-preventive and chemotherapeutic activities in animal models for oral cancer, which was evidenced by the significant reduction in the expression of a key tumour marker, cyclin D1, and a significant increase in the expression of B-catenin and E-cadherin, which are associated with enhanced cellular adhesion (Al-Koshab et al., 2020). In addition, *F. deltoidea* extract reduced the expression of the twist-related protein 1 (TWIST1) and RAC1 genes associated with epithelial-mesenchymal transition and had significantly downregulated the COX-2 and EGFR genes associated with cancer angiogenesis, metastasis, and chemoresistance.

Impatiens balsamina L. *(Balsaminaceae)*

Impatiens balsamina is known as '*bunga tabo*' or '*inai air*' or '*inai ayam*' in Malaysia, '*pancar banyu*' or '*paru inai*' in Indonesia and garden balsam and rose balsam in English. The plant can be found in Indonesia, Malaysia, and Myanmar. Shin et al. (2015) discovered that the methanol extracts of *I. balsamina* L. decreased cell viability and induced apoptosis in HSC-4 cells. Higher levels of phosphorylated Akt (p-Akt) expression were observed in OSCCs than in normal oral mucosa, and it correlated with poor survival of the patients. This plant extract could dephosphorylate p-Akt and decrease Akt expression through proteasome-dependent degradation and could downregulate the expression level of survivin protein at the transcriptional level. The plant extract also significantly increased Bax, thereby inducing conformational change, mitochondrial translocation, and oligomerization. In addition, the plant extract induced growth inhibition and apoptosis in OSC-20, another human OSCC cell line, mediated by regulating Akt and its downstream targets, survivin, and Bax (Shin et al., 2015).

Imperata cylindrica (L.) Raeusch. *(Poaceae)*

Imperata cylindrica is known as thatch grass or cogon grass in English and *'lalang'* in Malay. It can be found in Cambodia, Laos, Indonesia, Malaysia, Philippines, Singapore, Thailand and Vietnam. Keshava et al. (2016) examined the anticancer activities of *I. cylindrica* leaf extract towards the SCC-9 cell line. They found that the extract treatment caused cytotoxicity and induced cell death *in vitro* in SCC-9 cells in a dose-dependent manner. This treatment also significantly reduced the clonogenic potential and inhibited cell proliferation by arresting the cell cycle in the G_2/M phase. Furthermore, DNA fragmentation assays showed that the observed cell death was caused by apoptosis.

Momordica charantia L. *(Cucurbitaceae)*

Momordica charantia, also known as *bitter gourd,* or *bitter melon* or *'peria'* in Malay, can be found in Indonesia, Malaysia, Philippines, Thailand, and Vietnam. Treatment with bitter melon extract on oral cancer cell lines could significantly reduce the mRNA and protein expression levels of key glycolytic genes SLC2A1 (GLUT-1), PFKP, LDHA, PKM, and PDK3 (Sur et al., 2019). Pyruvate and lactate levels and glycolysis rate were reduced in oral cancer cells following the *M. charantia* extract treatment, which indicates its ability to inhibit the glycolysis pathway. In the lipogenesis pathway, a significant reduction was observed in genes involved in fatty acid biogenesis, ACLY, ACC1, and FASN, at the mRNA and protein levels following treatment with this plant extract. In addition, treatment with this plant extract significantly reduced phosphatidylcholine, phosphatidylethanolamine, and plasmenylethanolamine and reduced iPLA2 activity, which indicates the inhibition of the lipogenesis pathway (Sur et al., 2019). Additionally, it inhibited lipid raft marker flotillin expression and altered its subcellular localization. The plant extract also induced the expression of endoplasmic reticulum (ER)-stress-associated C/EBP homologous protein (CHOP) and the generation of mitochondrial reactive oxygen species, which facilitated apoptosis (Sur et al., 2019).

Moringa oleifera Lam. *(Moringaceae)*

Moringa oleifera is known as *'kelor'* in Indonesia, '*gemunggai*' or '*meringgai*' or '*muringa*' in Malaysia, *'dandalonbin'* in Myanmar, '*marum*' in Thailand and horse-radish tree or behen tree in English. It can be found in Indonesia, Malaysia, Myanmar, and Thailand. Vicenin-2 is a bioactive compound found in *M. oleifera* (Li et al., 2021). Vicenin-2 (30 mg/kg) treatment on DMBA-brushed hamsters prevented tumour incidence, improved the antioxidant status, and inhibited lipid peroxidation. Moreover, vicenin-2 could inhibit the expression of PCNA, cyclin-D1, and Bcl-2, and it significantly restored the apoptotic Bax levels. The vicenin-2 treatment also prevented the lesion formation in the oral epithelium of the DMBA-induced hamsters and potentially halted the production of proinflammatory cytokines (IL-6, IL-1β, and TNF-α) in OSCC hamsters.

Ocimum sanctum L. *(Lamiaceae)*

Ocimum sanctum is recognized by the locals as '*ruku*' in Malaysia, '*kala-pi-sein*' or '*pin-sein-net*' in Myanmar, and is also known as holy or sacred basil in English. It can be found in Malaysia and Myanmar. Extract of *O. sanctum* could prevent early events of carcinogenesis, as evidenced by the significant reduction of incidence of papilloma and squamous cell

carcinoma and the increased survival rate in DMBA-induced carcinomas (Karthikeyan et al., 1999). Moreover, vicenin- 2, a bioactive compound found in *O. sanctum* possessed anticancer activities by inhibiting inflammation and cell proliferation. These are evidenced by the reduction in inflammatory and cytokines markers (IL-6, TNF-α, and IL1-β) and proliferative cell nuclear markers (PCNA and cyclin D1) in DMBA-induced buccal carcinogenesis, respectively (Li et al., 2021).

Osbeckia octandra DC. *(Melastomataceae)*

Osbeckia octandra is known as *'heen bovitiya'*, derived from the Sinhala language of Sri Lanka, where it originated. The plant can also be found in Malaysia. Kim et al. (2022) found that the leaf extract of *O. octandra* reduced the viability of OSCC cells (YD10B and HSC-2) in a dose-dependent manner but was non-toxic to the normal human epidermal keratinocytes (HEK). It is also suggested that the leaf extract of *O. octandra* inhibited the cancer cell proliferation through G_1 phase arrest, thereby interrupting DNA replication. It also triggered the apoptotic response via caspase-3 activation in OSCC cells, evidenced by the increased expression of cleaved caspase-3 protein. Furthermore, the expression of anti-apoptotic protein (Bcl-2 and Bcl-xL) was decreased in *O. octandra*-treated OSCC cells.

Pergularia daemia (Forssk.) Chiov. *(Apocynaceae)*

Pergularia daemia is known as trellis-vine in English and *'bunga siam'* in Malaysia. In the Southeast Asian region, the plant can be found in Indonesia, Malaysia, and Myanmar. Oral administration of *P. daemia* methanolic extract (200 mg/kg) significantly prevented the tumour incidence and burden in DMBA-induced hamsters (Mirunalini et al., 2013). This can be seen as a mild-to-moderate preneoplastic lesion in the DMBA-treated hamsters given with the extract, as opposed to the myriad of histopathological changes (severe hyperkeratosis, hyperplasia, dysplasia, and well-differentiated squamous cell carcinoma of the epithelium) seen in non-treated DMBA-induced hamsters. The extract was also shown to be downregulating the expression of the vascular endothelial growth factor (VGEF) marker, which indicates a lower angiogenesis activity. In addition, the level of activated NF-κB was found to be significantly low in the treated animals with this extract. This might be due to the influence of antioxidant phytochemicals present in this plant, as it has been previously reported that natural antioxidants can block the NF-κB activation process due to their free radical scavenging capacity. Furthermore, the extract enhanced the expression of the Bcl-2 gene, which encodes for the membrane protein that functions as a suppressor of apoptosis (Mirunalini et al., 2013).

Rauvolfia serpentina Benth. ex Kurz *(Apocynaceae)*

Rauvolfia serpentina is known as '*akar tikus'* or *'pulai pandak'* in Malaysia and Indian snakeroot or devil peppers in English. It can be found across Southeast Asian countries, including Cambodia, Laos, Indonesia, Malaysia, Myanmar, Thailand, and Vietnam. Reserpine compound, which is isolated from *R. serpentina,* was found to act against DMBA-induced hamster buccal pouch carcinogenesis by suppressing DNA repair, cell proliferation, and invasion, as well as by inducing apoptosis through inhibition of TGFβ-RII/RISmad2/Smad3/Smad4/Snail signalling (Ramu et al., 2021).

Toona sinensis (A.*Juss.*) M.Roem. *(Meliaceae)*

Toona sinensis, which is known as Chinese mahogany in English, can be found in Indonesia, Malaysia, and Thailand. Wang et al. (2016) revealed the antiproliferative and apoptosis-inducing ability of *T. sinensis* leaf extract toward DMBA-induced hamster buccal pouch carcinogenesis. This was evidenced by the downregulation of survivin, X chromosome-linked inhibitor of apoptosis, PCNA, inducible nitric oxide synthase, and COX-2 proteins, as well as the increased apoptotic activity.

Piper betle L. *(Piperaceae)*

Piper betle is recognised by the locals as '*sireh'* in Malaysia and betel in English. It can be found in Malaysia and Indonesia. Veettil et al. (2022) observed that *P. betle* leaf extract displayed cytotoxic activity on human epithelial carcinoma cells, which is the KB cell lines, *via* MTT assay. The study established an inverse relationship between the extract concentration and the percentage viability of the cancer cells.

Persicaria odorata (Lour.) Soják *(Polygonaceae)*

Persicaria odorata can be found in Cambodia, Indonesia, Laos, Malaysia, Singapore, Thailand, and Vietnam. It is also known as '*chi krasang tomhom'*, *'daunkesom'*, *'phak phaew'*, *'kesum'*, *'laksa plant'*, *'phak phai'*, and *'rau rdm'*. Khwairakpam et al. (2020) discovered that *P. odorata* exhibits its anticancer properties by inhibiting cell proliferation, survival, and migration through the downregulation of the Akt-mammalian target of rapamycin (mTOR) signalling pathway in a dose-dependent manner. They observed that the methanolic extract of *P. odorata* dose-dependently reduced the expression of key proteins involved in cancer metabolism, such as survivin, cyclin-D1, COX-2, VEGF-A, and matrix metallopeptidase-9 (MMP-9). Survivin is known to be involved in

tumour cell survival, COX-2 and cyclin-D1 are important for cell proliferation, VEGF-A plays a role in angiogenesis, and MMP-9 is crucial for the metastasis of tumour cells.

Soliera robusta (*Greville*) Kylin 1932 (*Solieriaceae*)

Soliera robusta is known as red algae in English and can be found in Indonesia and Malaysia. The methanolic extract of *S. robusta* was found to exert its antiproliferative effect against oral cancer Ca9-22 cells, and this was coupled with apoptosis, ROS overexpression, and mitochondrial dysfunction effects. The extract-induced cell death of Ca9-22 was displayed by physiological biomarkers of apoptosis, including membrane blebbing, cell rounding, and the formation of apoptotic bodies as evaluated under the microscope (Yen et al., 2014).

Zingiber officinale Roscoe (*Zingiberaceae*)

Zingiber officinale is recognised by the locals as '*halia*' in Malaysia and ginger in English. [6]-Shogaol, which is the bioactive compound of the plant, possessed anticancer activities by inhibiting the phase I enzymes, and it increased phase II enzymes, which in turn enhanced detoxification, thereby eliminating the carcinogen. Antioxidant properties of [6]-shogaol were found to play a vital role in suppressing tumour development and inducing apoptosis by modulating the p53 and Bcl-2 family proteins (Annamalai and Suresh, 2018).

Bioactive phytochemical compounds from Southeast Asian medicinal plants with activities against oral cancer

In this systematic review of Southeast Asian medicinal plants with promising activities against oral cancer, we found a total of 15 bioactive compounds from various phytochemical classes, which were investigated and discussed in these studies. Phytochemical compounds are substances that can be found in plants and are produced via primary or secondary metabolism. A wide array of phytochemicals has been pharmacologically evaluated for their chemopreventive and chemotherapeutic potential for several decades (Akhtar et al., 2020).

The first two were alkaloidal compounds, namely the dehydroandrographolide (DA) from *A. paniculata* and reserpine from *R. serpentina.* Hsieh et al. (2017) found that DA from *A. paniculata* displayed anticancer effects by inhibiting oral cancer cell invasion and migration through inhibition of the phosphorylation of ERK ½, resulting in the downregulation of MMP-2 expression and inhibition of metastasis. In agreement with that, DA was previously reported to have anticancer activity towards colorectal cancer cells, osteosarcoma, and glioblastoma multiforme cells (Liu et al., 2019; Yang et al., 2017; Zhang et al., 2020).

The other alkaloidal compound is reserpine from *R. serpentina*. Reserpine was shown to exert its anticancer activities by inhibiting cell proliferation and invasion, inhibiting DNA repair, and inducing apoptosis (Ramu et al., 2021). Previously, reserpine also showed anticancer activity on lung cancer cells through ROS-mediated apoptosis (Senthamizh et al., 2020). Ramamoorthy et al. (2018) also found that reserpine, when tested on a prostate cancer cell line, resulted in apoptotic induction. Despite the applications of DA and reserpine on different types of cancer cells, there are not many studies on oral cancer cells.

S-allylcysteine is a bioactive organosulphur compound isolated from *A. sativum,* known as garlic. S-allylcysteine was shown to enhance antioxidant levels by enhancing the level of glutathione, glutathione peroxidase, and glutathione S-transferase (Balasenthil and Nagini, 2000). Al-Dabbagh et al. (2018) mentioned that by decreasing free radicals and oxidative stress, antioxidants play a role in ameliorating DNA damage, reducing the rate of abnormal cell division, and decreasing mutagenesis. Thus, many antioxidant-rich plants have also been shown to possess anticancer activity.

Other than alkaloids, many *in vitro* and *in vivo* studies have shown that flavonoids could exert anticancer activity (Kopustinskiene et al., 2020), and this is possible by various mechanisms, which include modulating ROS-scavenging enzyme activities, causing cell-cycle arrest, inducing apoptosis, autophagy, and suppressing cancer cell proliferation and invasiveness (Stabrauskiene et al., 2022). In the present review, a prior study by Li et al. (2021) discovered that vicenin-2, a flavonoid that was isolated from *O. sanctum* and *M. oleifera*, showed various anticancer activities, which include improving the antioxidant status, inhibiting lipid peroxidation, restricting inflammation, inhibiting cell proliferation, and enhancing apoptosis. Vicenin-2 enhanced apoptosis and declined cell proliferation by deregulating cytokines, interleukins (IL), and tumour necrosis factor-alpha (TNF-α). These influential sets of proteins are involved in promoting carcinogenesis and angiogenesis. In addition, vicenin-2 restricted the unusual cellular proliferation and growth of oral tumour by inhibiting the cyclin-D1 and PCNA in the OSCC hamsters. Vicenin-2 also significantly improved enzymatic/nonenzymatic antioxidant status, which advocates an antioxidant potential and free radical scavenging capability during buccal carcinogenesis, thereby suppressing lipid peroxidation. The anti-inflammatory property of vicenin-2 was evidenced by the reduced

levels of cytokines and interleukins in the serum of the DMBA-treated OSCC.

In addition, two flavonoid compounds, catechin and quercetin, were detected in areca nut extract from *Areca catechu*. Previous studies on catechins demonstrated that they could promote anticancer effects by modulating multiple processes, including inhibition of carcinogen activity, tumourigenesis, proliferation, apoptotic induction, cell-cycle arrest, metastasis, and angiogenesis. Besides catechin, quercetin was reported to have a strong antioxidant activity and could induce apoptosis and inhibit proliferation in gastric, breast, oesophageal, and ovarian cancer cells (Sari et al., 2020). Other than that, the *B. retusa* anthocyanin displayed the ability to inhibit the growth of oral cancer cell lines by inducing apoptosis (Madanakumar et al., 2018).

The next bioactive compounds with anticancer properties are nimbolide and azadirachtin (Sophia et al., 2018). Azadirachtin, isolated from seed kernels, and nimbolide present in leaves and flowers are potent neem limonoids that exhibit cytotoxic effects against various cancer cell lines *in vitro* (Harish Kumar et al., 2010). Nimbolide and azadirachtin were previously reported to have anticancer activities through anti-proliferative effects and apoptotic effects. Both nimbolide and azadirachtin transduce apoptosis by the mitochondrial pathway by increasing the Bax/Bcl-2 ratio, releasing the cytochrome C from mitochondria to the cytosol, forming apoptosome complex, and activating caspase (Ashok and Upadhyaya, 2012; Sophia et al., 2018). They also inhibit IκB degradation and nuclear translocation of p50-p65 nuclear factor (NF)-κB heterodimers, causing cell-cycle arrest by downregulating various genes involved in cell proliferation. Other than that, they enhanced apoptotic function by enforcing nuclear translocation of the survivin gene. Furthermore, azadirachtin also exerted an anticancer effect on oral cancer cells *via* poly [ADP-ribose] polymerase (PARP) cleavage (Sophia et al., 2018).

The next compound is [6]-shogaol, which is one of the main bioactive compounds in the rhizomes of dried *Z. officinale* (Bischoff-Kont and Fürst, 2021). The anticancer activity of [6]-shogaol has been extensively documented in a wide array of cancer cells *in vitro,* such as cervical carcinoma, colon cancer, breast cancer, and OSCCs (Annamalai and Suresh, 2018; Bawadood et al., 2020; Hafuth and Randhawa, 2022; Pei et al., 2021). In the present review, [6]-shogaol isolated from *Z. officinale* presented its anticancer properties against oral cancer through its antioxidant property, apoptotic induction, and enhanced detoxification, thereby eliminating carcinogens. [6]-shogaol is also shown to induce apoptosis by modulating the p53 and Bcl-2 family proteins (Annamalai and Suresh, 2018).

In the present review, there were three curcuminoid compounds that exhibit anticancer activities against oral cancer: Curcumin (CUR), dimethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC) (Hsiao et al., 2018). Curcumin is one of the polyphenols extracted from *C. longa* and has a wide range of biological activities, including antioxidant, anti-inflammatory, antimicrobial, and antiviral properties (Giordano and Tommonaro, 2019). Curcumin, the active ingredient of the *C. longa* plant, has received great attention over the past two decades as an antioxidant, anti-inflammatory, and anticancer agent (Tomeh et al., 2019). Several studies in the literature survey revealed the anticancer properties of curcumin against prostate cancer, cervical cancer, colorectal carcinoma, leukaemia, and human breast cancer cells (Gupta et al., 2017). DMC and BDMC are the analogues of curcumin. DMC has been shown to have anticancer activity *in vitro* against LN229 and GBM8401 glioma cancer cell lines via induction of apoptosis, autophagy, ROS production, suppression of cell viability, and proliferation (Luo et al., 2021). CUR, DMD, and BDMC were also revealed to act against osteosarcoma, breast cancer, and melanoma cell lines by inducing apoptosis through the activation of Smad 2/3 and repression of the Akt signalling pathway (Huang et al., 2020). In the latest study, CUR, DMC, and BDMC were found to possess *in vitro* anticancer activity towards SAS cell line by inducing apoptosis through ROS production, caspase-8, caspase-9, and caspase-3 activations, decreased the levels of MMP, AIF release for induced cell apoptosis (Hsiao et al., 2018).

The chemical structures of these 13 phytochemicals were illustrated in Fig. 4, and their brief anticancer activities are summarized in Table 4.

Mechanisms of actions against oral cancer

In the present review, we have summarized the multiple anticancer mechanisms by the plants found across Southeast Asia with remarkable activities for the prevention and treatment of oral cancer. The mechanisms include inducing and enhancing apoptosis, antiproliferative effect, inhibiting cell invasion and migration, improving antioxidant effect, enhancing carcinogen detoxification and anti-inflammatory properties, inhibiting DNA repair, and impairment of angiogenesis.

So far, it is noteworthy to mention that apoptosis is the most common anticancer mechanism found in the majority of plants in this review, i.e., *C. nutans,*

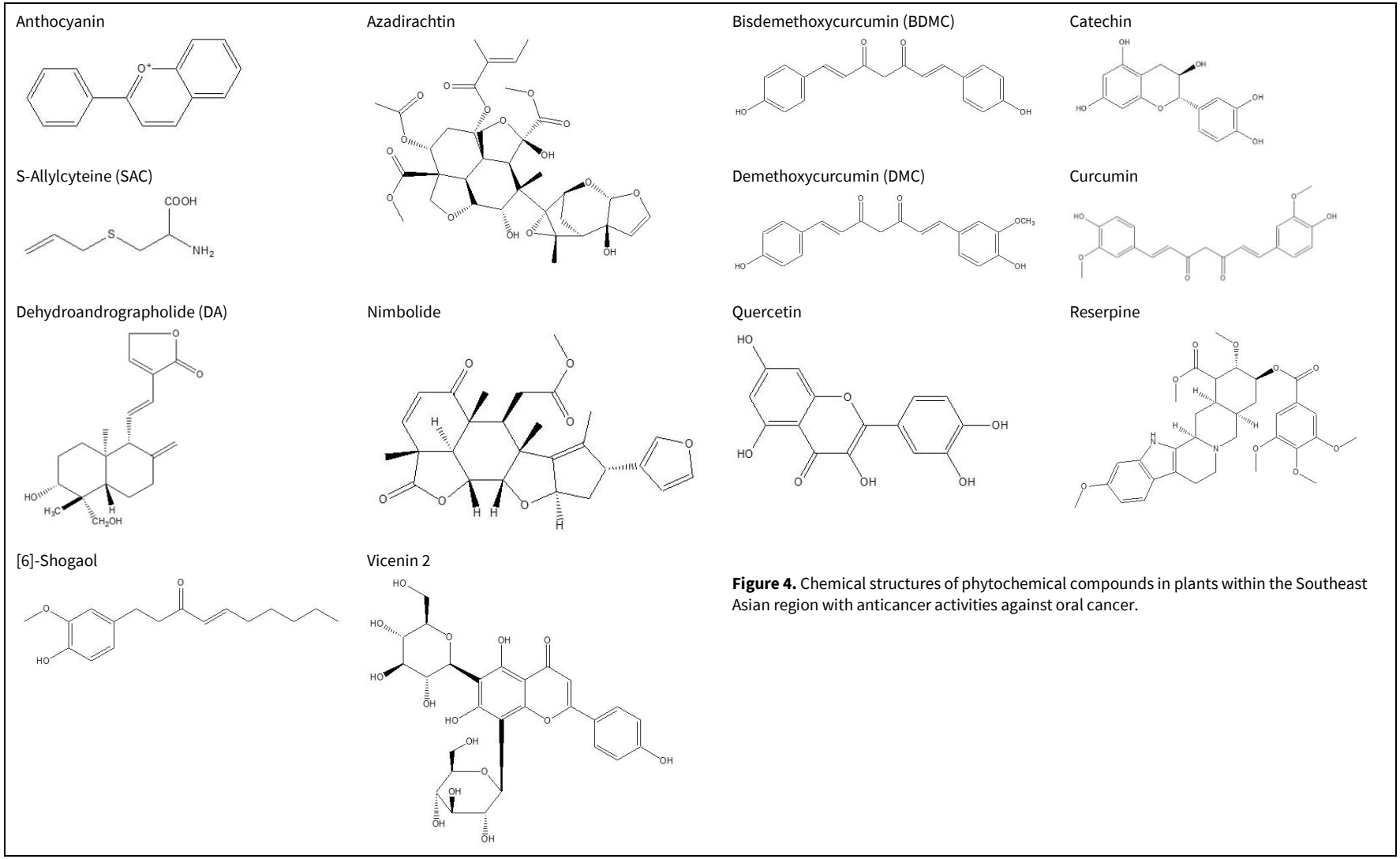

Figure 4. Chemical structures of phytochemical compounds in plants within the Southeast Asian region with anticancer activities against oral cancer.

Table 4. Phytochemical compounds from Southeast Asian medicinal plants with activities against oral cancer.

Compound	Class	Plant name	Family	Plant part	Anticancer activity and mechanism	Reference
Dehydroandrographolide (DA)	Alkaloids	*Andrographis paniculata* (Burm.f.) Wall. ex Nees	*Acanthaceae*	-	Inhibit cell invasion and migration	(Hsieh et al., 2017)
S-allylcysteine	Organosulfur	*Allium sativum* L.	*Amaryllidaceae*	Bulb	Enhanced antioxidant status	(Balasenthil et al., 1999)
Reserpine	Alkaloids	*Rauvolfia serpentina* Benth. ex Kurz	*Apocynaceae*	-	Inhibit DNA repair, cell proliferation and invasion Induce apoptosis	(Ramu et al., 2021)
Catechin	Flavonoid	*Areca catechu* L.	*Arecaceae*	Seed	-	(Sari et al., 2020)
Quercetin						
Anthocyanin	Flavonoid	*Bridelia retusa (*L.) A.Juss.	*Phyllanthaceae*	Leaves, shoot tips	Induce apoptosis	(Madanakumar et al., 2018)
Vicenin-2	Flavonoid	*Ocimum sanctum* L., *Moringa oleifera* Lam.	*Lamiaceae, Moringaceae*	-	Improved antioxidant status Inhibit lipid peroxidation Restrict inflammation Restrict cell proliferation	(Li et al., 2021)
Nimbolide	Limonoid	*Azadirachta indica* A. Juss.	*Meliaceae*	-	Antiproliferative effect Apoptotic effect	(Sophia et al., 2018)
Azadirachtine Nimbolide	Limonoid			Seed kernels Leaves and flowers	Antiproliferative effect Apoptotic effect	(Harish Kumar et al., 2010)
[6]-Shogaol	Shogaol	*Zingiber officinale* Roscoe	*Zingiberaceae*	-	Antioxidant properties Induce apoptosis Enhance detoxification, thereby eliminating carcinogen	(Annamalai and Suresh, 2018)
Curcumin (CUR) Dimethoxy curcumin (DMC) Bisdemethoxycurcumin (BDMC)	Curcuminoids	*Curcuma longa* L.		Rhizome	Inducing apoptosis Reducing cell proliferation Reducing inflammation	(Hsiao et al., 2018)

R. serpentina, P. daemia, I. balsamina, M. charantia, B. retusa, I. cylindrica, C. formosum subsp. pruniflorum, O. octandra, A. indica, T. sinensis, S. robusta, Z. officinale, and *C. longa.* Apoptosis is a programmed cell death that occurs physiologically and pathologically. Thus, it is one of the areas most studied in developing anticancer drugs. When there is a defect in the apoptosis mechanism, it allows neoplastic cells to avoid cell-cycle arrest and cause the cells to survive over the intended lifespans (Yakop et al., 2018). Other than inducing apoptosis, another common anticancer property is having an antiproliferative effect, as there is usually an overexpression of protein involved in proliferation in malignant cells compared to normal cells. This property was shown by *R. serpentina, O. sanctum, M. oleifera, A. indica, F. deltoidea, P. betle, P. odorata, S. robusta,* and *C. longa*.

Furthermore, four plants were found to act against oral cancer by inhibiting cell invasion and migration, including *A. paniculata, R. serpentina,* and *P. odorata*. Cell invasion and migration are important in cancer development and progression in which the cancer cell disseminates from the primary tumour spreading through the circulatory and lymphatic and eventually distant organs, causing destruction (Pijuan et al., 2019). Thus, inhibition of cell invasion and migration of cancer cells is one of the strategies to fight against oral cancer.

Some plants such as *A. sativum, A. catechu, O. sanctum, M. oleifera*, *A. indica,* and *Z. officinale* were found to possess antioxidant activities, and by having this effect, they exert the anticancer and chemo-preventive effect. Antioxidants may suppress carcinogenesis through multiple mechanisms, which include prevention of pro-carcinogen activation, inhibition of cell proliferation, invasion and angiogenesis, and stimulation of apoptosis (Manikandan et al., 2008). Other than that, plants can also exert their anticancer activities by enhancing the detoxification of carcinogens, as shown by *A. indica* and *Z. officinale*. This enhanced detoxification could be via inhibition of phase I enzymes as well as by increasing the phase II detoxification enzymes, GST, glutathione reductase (GR), GSH, thereby eliminating the carcinogen.

The anti-cancer properties of plants can also be attributed to their anti-inflammatory properties, as shown by *O. sanctum, M. oleifera,* and *C. longa*. Chronic inflammation often precedes tumour development. Therefore, the anti-inflammatory effect could be very important in decreasing inflammation and enhancing the anti-tumour activity of immune cells (Kopustinskiene et al., 2020). Thus, the progression of carcinogenesis can be inhibited by suppressing inflammation. Usual indicators include attenuating the inflammatory and cytokine markers (IL-6, TNF-α, and IL-1β) (Li et al., 2021) and reducing the level of COX-2 and PGE2 (Garg et al., 2008).

A plant may also have its anticancer activities by causing impairment in the angiogenetic properties of oral cancer cells. This property is exhibited by *A. indica,* and *P. odorata*. Angiogenesis is a process of blood vessel formation in which new vessels are formed from pre-existing blood vessels. To grow or locally metastasise, tumour tissue also needs oxygen and nutrients transported by the blood vessels. Endothelial cells in growing cancers are also vigorously active (Rajabi and Mousa, 2017). Thus, the progression of carcinogenesis can be suppressed by stopping the oxygen supply to the cancer cell *via* inhibition of angiogenesis.

Another means of exerting anticancer effects is by inhibiting the DNA repair of cancer cells. This type of anticancer activity was only shown by reserpine found in *R. serpentina*. Recent scientific reports stated that OSCCs had high refractory effects on any treatment due to their overactive DNA repair factors, which increase genomic instability to tolerate DNA damage that brings the cancer cell back to its usual state with enhanced chemotherapy resistance. Therefore, resistance to chemotherapy by oral cancer cells can be reduced by inhibiting its DNA repair, which indirectly acts as an anticancer effect (Ramu et al., 2021).

M. charantia is the only plant that has demonstrated anticancer effects by inhibiting glycolysis and lipid metabolism. Glycolysis and lipogenesis are enhanced in cancer cells compared to normal cells, and these two pathways are linked. Glycolysis is elevated due to the Warburg effect, in which cancer cells undergo glycolysis by converting glucose to lactate even in the presence of adequate oxygen, resulting in the accumulation of lactic acid in the tumour microenvironment. Accumulation of lactic acid maintains a relatively low pH in the microenvironment, thus helping the cancer cells to escape immune destruction. Lipogenesis is enhanced in cancer cells to form phospholipid bilayers, and protection against oxidative damage and stress-induced cell death. Cancer cells also generally prefer lipogenesis to avoid the electron transport chain (ETC). Avoiding ETC is advantageous for regulating ROS generation in cancer cells (Sur et al., 2019). Thus, cancer progression can be halted by targeting glycolysis and lipogenesis pathways of cancer cells.

The anticancer mechanisms of Southeast Asian medicinal plants are hereby summarized in Table 5 and Fig. 5.

Table 5. Summary of anticancer mechanisms for Southeast Asia medicinal plants against oral cancer.

Family	Plant name	Induced and enhanced apoptosis	Anti-proliferative	Inhibited cell invasion and migration	Improved antioxidant effect	Enhanced detoxification of carcinogen	Anti-inflammatory	Impairment in angiogenetic property	Others	References
Acanthaceae	*Andrographis paniculata* (Burm.f.) Wall. ex Nees			✓						(Hsieh et al., 2017)
Acanthaceae	*Clinacanthus nutans* (Burm.f.) Lindau	✓								(Yakop et al., 2018)
Amaryllidaceae	*Allium sativum* L.				✓					(Balasenthil and Nagini, 2000)
Apocynaceae	*Pergularia daemia* (Forssk.) Chiov.	✓								(Mirunalini et al., 2013)
	Rauvolfia serpentina Benth. ex Kurz	✓	✓	✓					Inhibit DNA repair	(Ramu et al., 2021)
Arecaceae	*Areca catechu* L.				✓					(Sari et al., 2020)
Balsaminaceae	*Impatiens balsamina* L.	✓								(Shin et al., 2015)
Cucurbitaceae	*Momordica charantia* L.	✓							Inhibit glycolysis and lipid metabolism	(Sur et al., 2019)
Hypericaceae	*Cratoxylum formosum subsp. pruniflorum* (Kurz) Gogelein	✓								(Promraksa et al., 2015)
Lamiaceae	*Ocimum sanctum* L.	✓	✓		✓		✓			(Karthikeyan et al., 1999)
Moringaceae	*Moringa oleifera* Lam.	✓	✓		✓		✓			(Li et al., 2021)
Melastomataceae	*Osbeckia octandra* DC.	✓								(Kim et al., 2022)

Table 5. Summary of anticancer mechanisms for Southeast Asia medicinal plants against oral cancer (continued...)

Family	Plant name	Induced and enhanced apoptosis	Anti-proliferative	Inhibited cell invasion and migration	Improved antioxidant effect	Enhanced detoxification of carcinogen	Anti-inflammatory	Impairment in angiogenetic property	Others	References
Meliaceae	*Azadirachta indica* A. Juss.	✓	✓		✓	✓		✓		(Harish Kumar et al., 2010; Manikandan et al., 2008; Sophia et al., 2018; Subapriya et al., 2006)
Meliaceae	*Toona sinensis* (A.Juss.) M.Roem.	✓								(Wang et al., 2016)
Moraceae	*Ficus deltoidea* Jack		✓							(Al-Koshab et al., 2020)
Phyllanthaceae	*Bridelia retusa* (L.) A.Juss.	✓								(Madanakumar et al., 2018)
Piperaceae	*Piper betle* L.		✓							(Veettil et al., 2022)
Poaceae	*Imperata cylindrica* (L.) Raeusch.	✓								(Keshava et al., 2016)
Polygonaceae	*Persicaria odorata* (Lour.) Soják		✓	✓				✓		(Khwairakpam et al., 2020)
Solieriaceae	*Soliera robusta* (Greville) Kylin 1932	✓	✓							(Yen et al., 2014)
Zingiberaceae	*Zingiber officinale* Roscoe	✓			✓	✓				(Annamalai and Suresh, 2018)

Source of scientific names of species were obtained from https://www.worldfloraonline.org/

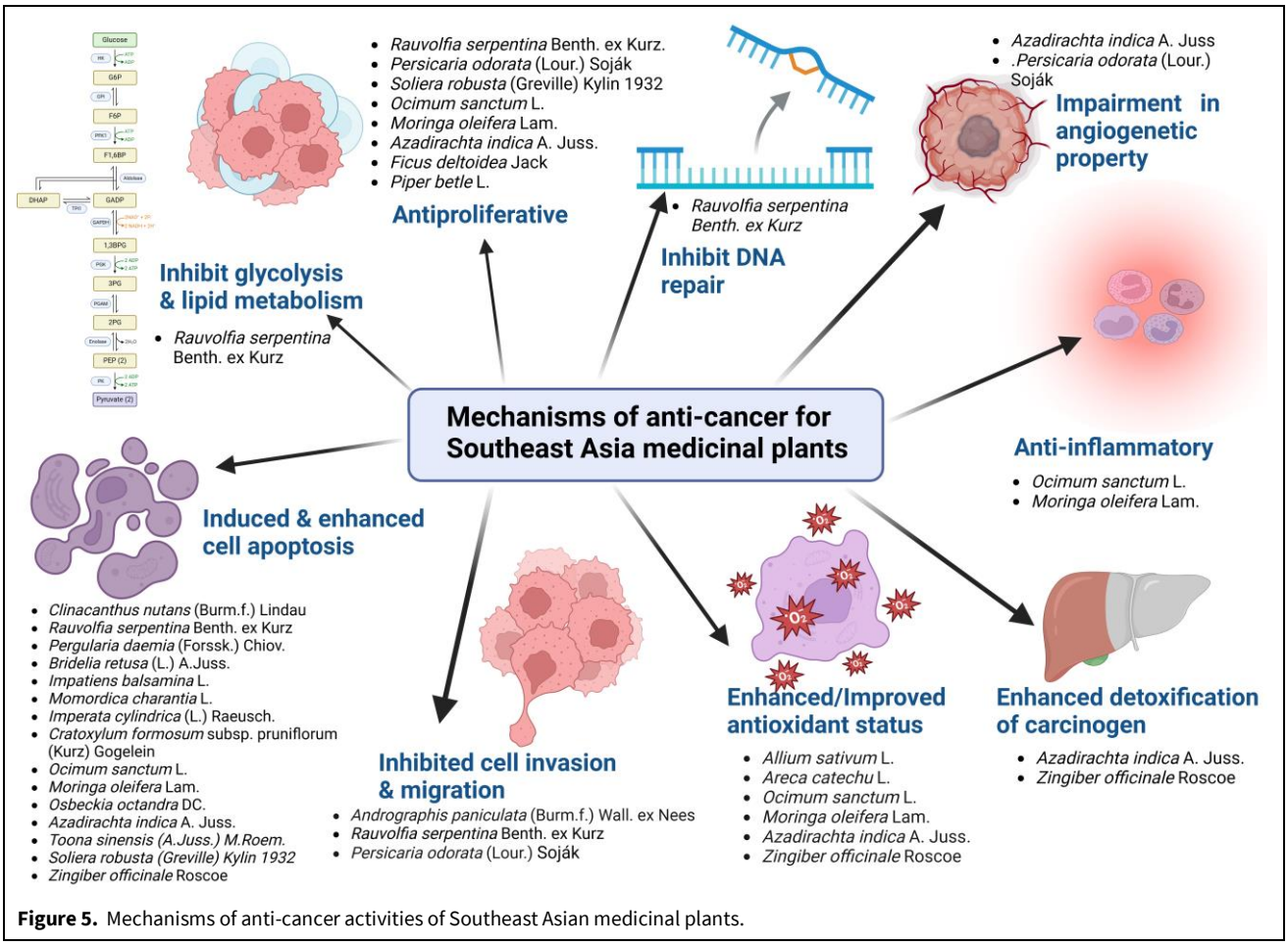

Figure 5. Mechanisms of anti-cancer activities of Southeast Asian medicinal plants.

Promising plants as preventive and treatment of oral cancer

Among the plants included in the present review, *A. indica* has been the most extensively studied. *A. indica,* when tested *in vitro*, shows a very low IC_{50}, in general indicating its high potency in comparison to other plants with a higher IC_{50}. *A. indica,* when tested *in vivo,* has also shown promising results whereby there was no tumour formation upon treatment with the extract. Furthermore, the anticancer mechanism of this plant has been widely investigated. *A. indica* was shown to be involved in regulating apoptosis, cell proliferation, antioxidant level, carcinogen detoxification, and angiogenesis (Harish Kumar et al., 2010; Manikandan et al., 2008; Sophia et al., 2018; Subapriya et al., 2006). Considering the extensive studies and promising findings for *A. indica*, the plant, and its bioactive compounds have the most promising potential to be considered in the future development of chemotherapeutic agents for oral cancer. Other than that, it is also noteworthy that there are three commonly edible plants that are frequently used in cooking that may be able to provide potential prophylactic activity against oral cancer, these include *A. sativum*, *Z. officinale*, and *C. longa*.

Limitations of study

There are some notable limitations pertaining to the scope of studies that are included in this review. Many studies were still limited to *in vitro* experiments without *in vivo* validation, which restricts the ability to validate the anti-cancer effects in more complex biological systems. The majority of studies did not report important parameters such as IC_{50} and selectivity index, which are highly relevant to suggest the potential promising plant to be researched further in the future. Additionally, only a few plants had been characterised for their respective bioactive compounds, making it difficult for standardisation for in-future product/drug development.

In terms of the review process itself, the search was limited to English-language publications, potentially omitting relevant non-English studies from countries that frequently publish in their native language such as Indonesia. Moreover, the use of the AXIS appraisal tool introduced subjectivity, as the assessment of study quality was performed manually, making it susceptible to reviewer bias despite efforts to reach a consensus.

Gap of studies, challenges, and future recommendations

Despite huge investments and efforts in cancer research, it still takes time for natural product-research advancements to be translated into drugs that significantly improve the treatment of many cancers. There are gaps and challenges in the studies that must be addressed in the future. It has been found that the majority of research is still at a very early stage of drug development; some plants have been examined only at the *in-vitro* level without further *in-vivo* validation, and only some plants have known bioactive compounds. The process of developing anticancer drugs generally begins with the identification of a prospective drug target. However, the role of drug targets in the development of certain cancers, including OSCCs, may not be fully understood. Another challenge in the area of research is that natural products are generally isolated in inadequate quantities to support subsequent drug discovery procedures such as lead optimization, lead development, and clinical trials. Thus, it is suggested that plants with promising results must be further investigated in the future development of oral cancer chemotherapy agents by scaling up bioactive leads and performing high-throughput screening bioassays. Furthermore, it is strongly recommended that the use of *in silico* analysis of bioactive chemicals be increased prior to validating *in vitro* and *in vivo* research. Last but not least, since medicinal plants also do not guarantee the safety of consumption, extensive toxicological studies are highly recommended.

CONCLUSION

This review showed some medicinal plants in the Southeast Asia region with remarkable potential for the prevention and treatment of oral cancer. From the perspective of this review, the findings of these studies imply the potential of these plants to be considered for the preventive and treatment measures for oral cancer.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Contribution	Ahmad Rokis AQ	Hanafi MF	Ismail CMKH	Haris MS	Lestari W	Ichwan SJA	Ismail A
Concepts or ideas				x	x		x
Design				x		x	x
Definition of intellectual content						x	x
Literature search	x	x					
Experimental studies	x	x					
Data acquisition	x	x	x				
Data analysis							
Statistical analysis							
Manuscript preparation	x	x	x				
Manuscript editing	x					x	x
Manuscript review	x	x	x	x	x	x	x

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