

# Kerala's anticancer flora: A comprehensive review

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## ABSTRACT

This ethnobotanical investigation explored native healing herbs for anticancer efficacy in Kerala's Wayanad and Kozhikode districts. Insights were gathered from various stakeholders, including spice dealers, exporters, Ayurveda practitioners, tribal communities, and farmers through discussions, interviews, and questionnaires from February 2021 to August 2022. Field expeditions to tribal settlements yielded crucial data on botanical nomenclature, common identifiers, vernacular names, traditional applications, and anecdotal applications. Following PRISMA guidelines, a systematic review incorporated a meta-analysis of 311 articles from Ovid Medline, Scopus, Web of Science, and PubMed. Results showed a significant overall effect ( $p$ -value 0.001), variable subgroup effectiveness (RR = 0.4118,  $p$  0.009), and study-related impacts ( $p$  = 0.4837). Reliability was confirmed through sensitivity testing with negligible bias ( $p$  > 0.05). Despite notable unexplained heterogeneity ( $I^2$  = 87.82%,  $H^2$  = 8.21), the study emphasized the statistical significance of the selected medicinal plants. This investigation advances the ethnobotanical knowledge of Malabar's anticancer herbs, underscoring the imperative for future research to exploit their therapeutic potential. It serves as pivotal groundwork for future developments in herbal medicine.

## INTRODUCTION

Plants have played a significant role in human life, and their utilization for treating various diseases has a long history [1]. The earliest documented records of using medicinal plants date back to 2,600 BC, authored by the Sumerians and Akkadians. In ancient India, the knowledge of medicinal herbs and their application was described in the Rigveda and Atharvaveda (3,500–1,500 B.C.), paving the way for the alternative medical system of Ayurveda [2]. In the present era, over 70% of people worldwide rely on plant-derived medicines to treat various illnesses and health conditions [3]. India stands at the forefront of medicinal plant cultivation and is renowned as the “Botanical Garden of the World.” The medicinal plant

market in India is currently valued at 4.2 billion (56.6 million USD) and is projected to reach 14 billion (188.6 million USD) by 2026 [4]. According to a World Health Organization (WHO) estimate, approximately 75% of people all over the world incorporate herbal remedies as alternative or complementary medicine. Plant-derived drugs are enormously consumed, particularly in combating various types of malignancies, due to their antioxidant, immune-modulatory, and cancer-healing properties, which offer minimal side effects.

Each year, more people throughout the world succumb to cancer. According to the “Globocon 2022” survey conducted by the WHO, nearly 19,292,789 new cancer cases were reported worldwide in 2020, resulting in 9,958,133 deaths across genders [5,6]. Lung cancer remains the leading cause of death with 18.4% of cancer cases, followed by breast cancer in women at 11.6%, and stomach and liver cancer at 8.2% each. Nearly 7% of cancer-related deaths are attributable to prostate and colorectal cancers, respectively [7,8].

Three basic categories of etiological factors, namely chemical, physical, and environmental, are responsible for

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turning normal cells into cancerous cells. Chemical carcinogens such as benzopyrene, asbestos, and over 800 other chemical moieties; physical carcinogens, such as various forms of ionizing radiation; and biological carcinogens, including microorganisms, are to name a few [9,10]. In addition, environmental factors like pollution and lifestyle choices such as smoking, alcohol consumption, sedentary living, obesity, and the adoption of high-fat, high-calorie diets significantly contribute to the incidence of various malignancies [11]. In practical terms, identifying the precise etiology and genetic factors responsible for a specific form of cancer is a complex process with limited treatment options. Modern cancer treatment methods primarily involve chemotherapy, radiation therapy, and immunotherapy, accompanied by surgical tumor removal through different procedures. However, chemotherapeutic agents often produce multiple side effects and adverse drug events, affecting normal cells such as the bone marrow, gastrointestinal tract, and hair follicles. In addition, synthetic drugs face significant challenges, including drug resistance [4].

The utilization of plants by ancient individuals, driven by astute observation and inherited sagacity, holds historical significance. Phyto-origin drugs offer substantial advantages over synthetic medications, displaying minimal side effects, adverse events, cost-effectiveness, efficacy, and low toxicity. The anti-cancer mechanisms of phytoconstituents encompass modulation of cell growth, differentiation, induction of cell death, hindrance of angiogenesis, and obstruction of metastasis. Recently, research on phytodrugs has been escalating exponentially [12]. In addition, more than 50% of the approved new chemical entities registered with the USFDA in the last 15 years originate from phytoconstituents and their derivatives [13]. Phytopharmaceuticals and their derivatives, with their diversified structures and distinctive pharmacological and molecular characteristics, harness potential as chemotherapeutic agents. Alkaloids isolated from *Vinca rosea*, such as Vincristine, Vinblastine, Taxane diterpenoids (Paclitaxel and Docetaxel), Epipodophyllotoxin (Etoposide and Teniposide), and Camptothecin, have significantly contributed to cancer chemotherapy [14,15]. Drugs such as Paclitaxel and Camptothecin command over 30% of the world's anti-cancer drug market [16], accounting for nearly \$9 billion, underscoring the significance of plant-derived drugs [17,18]. Numerous plant-origin drugs, such as Betulinic acid, Combretastatin, Curcumin, Homoharringtonine, Indirubin, Flavopiridol, Roscovitine, Brucantine, Lycopodium, Resveratrol, and Silvestrol, are currently undergoing clinical or preclinical trials, showcasing their potential for future utilization [14,19]. Therefore, access to ethnobotanical information on medicinal plants from both traditional and folklore sources is indispensable for the scientific community to develop innovative drugs and drug delivery strategies. Kerala, renowned as "God's own country," is celebrated for its biodiversity and traditional Ayurvedic wisdom. The tribes of Kerala, comprising Malayans, Kurumbas, Karimpalans, Kattunaikans, Mullukkurumans, Malapanickars, Kadars, Koragas, and Cholanaikkans, possess extensive knowledge of medicinal plant usage for diverse ailments, spanning millennia [19]. The Wayanad and Kozhikode districts were chosen and surveyed for this review. This study approach

encompassed 50% survey data, 30% meta-analysis reports, 11% observational studies, and 9% interventional studies. The PRISMA web tool (<https://prisma-statement.org>) was used for the systematic review guidelines [20]. Subsequently, a flow chart was plotted for the review screening process using the Prisma flow chart 2020 protocol. Furthermore, the screening of 552 articles obtained from Medline, Web of Science, and PubMed was done using the Ovid web tool (<https://ovidsp.ovid.com/>) [21] for duplication removal. The filtered articles underwent manual screening with two reviewers, and the final check was enabled by the third reviewer. The shortlisted articles underwent meta-analysis using the Meta-Mar web tool (<https://meta-mar.shinyapps.io/>) [22], covering subgroup analysis, effect size analysis, publication bias, and publication correlation.

### The Wayanad and Kozhikode regions of Kerala

Kerala is situated on the south-western Malabar coast, with latitudes ranging from 8°18' N to 12° 48' N. The longitudes cover the span of 74° 52' E–77°24' E. The state is divided into three main regions, namely the eastern highlands, the central midlands, and the western lowlands. The selected territory falls between the eastern highlands and the central midlands, with latitudes ranging from 11°5' N to 11° N and longitudes spanning from 75°2' E to 76°5' E. This region is situated between the Sayadri mountains and the coastal lowlands [23]. The climate in this area experiences a significant variation in temperatures throughout the year, ranging from 17°C to 48°C. During the summer months, temperatures can soar up to 50°C. In contrast, during the winter, the average temperature ranges from 17°C to 21°C in the Wayanad region and slightly higher (around ±5°C) in Kozhikode. The ethnobotanical information for this region was meticulously collected during the period from February 2021 to August 2022. Ethnobotany involves the study of the intricate relationship between plants and people, including the traditional knowledge and uses of plants in local communities. The data gathered during this time frame is expected to encompass the plant usage and traditional knowledge of the local people during that specific period [24].

The selected districts of "Wayanad and Kozhikode" in Kerala are known as the "Malabar Hill regions." These areas are inhabited by various tribes, each with its own unique culture and practices. In the "Wayanad region," the tribes include Adiyans, Paniyars, Mullukkurumans, Kattunaikans, Kurichyars of Wayanad, Kanaladi, and Wayanad Kadars. On the other hand, the tribes found in the "Kozhikode district" are Malapanickars, Malayans, Paniyans, Kattunaikans, Karimpalans, and Kurichyars [25,26]. The "Kadars" are inhabitants of various districts, including Malappuram, Wayanad, Thrissur, Kannur, and Kozhikode. The selected Malabar regions are represented in Figure 1.

The "Kattunaikans" tribes reside in the Palakkad, Kannur, and Kozhikode districts of the Malabar hills, where they are primarily involved in the cultivation of food grains and fruits. The "Mullukkurumans" community in Wayanad district is known for their traditional hunting and food gathering practices. However, in modern times, they have also extensively engaged in agriculture, particularly in growing various spices,

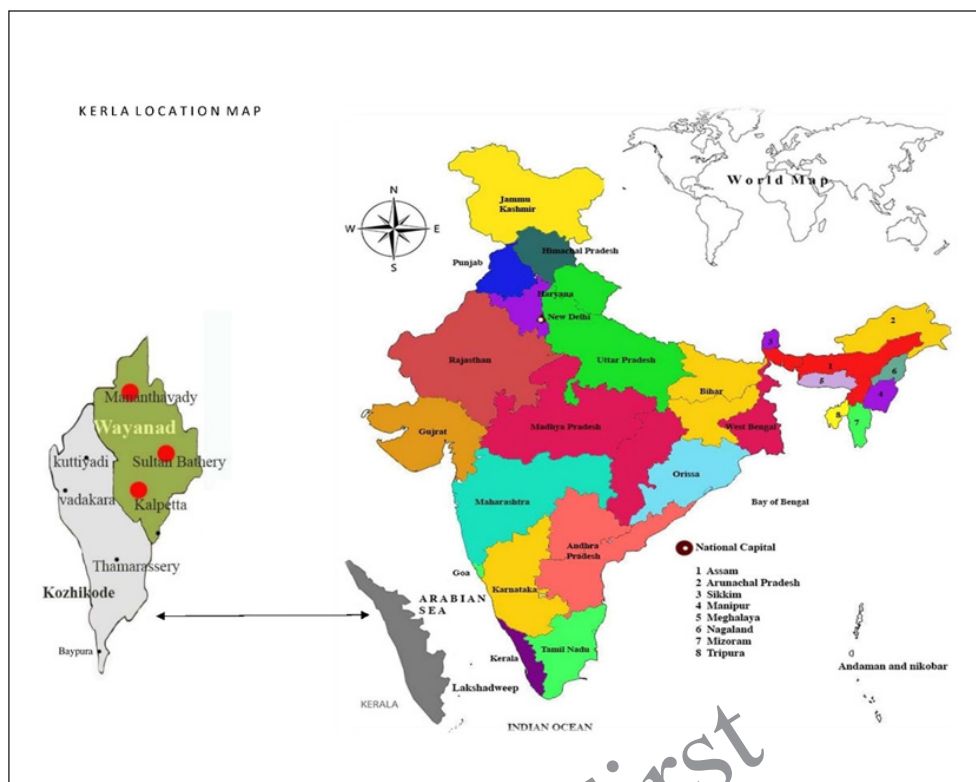


Figure 1. The selected Malabar regions (Wayanad and Kozhikode) of Kerala.

herbs, medicinal plants, and millets. The “Ayurveda” system of medicine is widely practiced and utilized by both experts and common people in the selected study regions. Moreover, the region is renowned for its enormous spice collection, trading, and exports, making it a significant hub for the spice industry [20,27].

## MATERIALS AND METHODS

### Data collection methods for the survey

The data collection of this survey enabled the “participatory rural appraisal method,” which proved to be a cost-effective and time-efficient approach. All the data for this study were gathered through structured interviews, semi-structured questionnaires, field surveys, sample collection, and note procurement. The study took place in the selected area of the Malabar Hills, which is inhabited by various tribal communities, including Mullukurumban, Kattunaikans, Karimpalans, Malapanickars, Malayans, Paniyans, Kurichyars, Kadars, and Koragas. Within these two districts, a total of 38 villages were included in the study, each hosting more than five types of indigenous tribes unique to that particular territory. Extensive interviews were conducted with the tribal people using different methods, predominantly semi-structured questionnaires and field surveys. In addition, traditional healers among the tribes were identified, and their knowledge of folklore-related ailments was documented. To ensure the reliability of the data, two separate visits were made to the tribal settlements, and the medicinal plant samples were locally identified. The samples were labeled with ethnobotanical

information, and all the acquired information was diligently recorded in field notebooks.

### Meta analysis

#### Literature search methods

The PRISMA systematic review guidelines were followed for this study, and the flow chart was plotted using the PRISMA web tool 2020 [20]. The article search was achieved using PubMed, Ovid/MEDLINE, Scopus, and Web of Science databases. The option for English abstracts from database inception to April 3, 2023, was enabled. The search strategy consisted of keywords related to phytochemicals, the English language, and cancer. Furthermore, screening of the 552 selected articles was carried out using the Ovid web tool (<https://ovidsp.ovid.com>) [21]. The Prisma flow chart for the screening process is illustrated in Figure 2.

#### Inclusion and exclusion criteria

The inclusion criteria encompassed full-text articles with phytoconstituents, anticancer activity, and pharmacological uses. The search was enabled using Boolean search terms such as “Phytoconstituents AND anticancer activity OR pharmacological uses” and “Phytochemicals OR plant constituents AND (Antitumor activity OR cytotoxicity) OR medicinal properties.” The articles that are phytoconstituent derivatives, incomplete data, duplicate articles, retracted articles, non-English articles, and articles not of interest were excluded. The inclusion and exclusion criteria were achieved with a manual review with two reviewers, followed by a final check

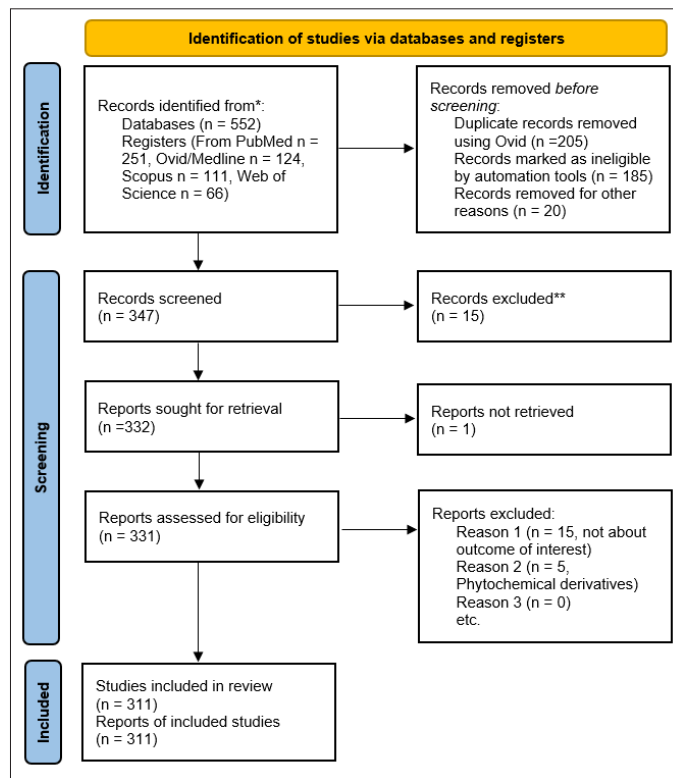


Figure 2. Prisma flow chart for the systematic review screening process.

by a third reviewer. The 347 shortlisted articles were screened for inclusion and exclusion criteria. Around 15 articles were excluded. The 331 original articles were subjected to the final screening process. Fifteen articles that were not the outcome of interest and five articles with phytochemical derivatives were excluded after screening, and the 311 articles were included for further analysis using the Meta-Mar web tool [22].

### Meta analysis

The meta-analysis of the included articles covering risk ratio (RR), publication bias, publication correlation, subgroup analysis, effect size prediction, sensitivity, and heterogeneity was performed using the Meta-Mar web tool. The 311 articles were thoroughly analyzed statistically using the Meta-Mar web tool (<https://meta-mar.com>) [22]. Effect sizes were determined after the articles were chosen based on their quality and relevancy. To evaluate the diversity of the study outcomes and pinpoint heterogeneity, statistical techniques like Cochran's  $Q$  and  $I^2$  were utilized. To investigate the probable cause of the discrepancy in results among selected articles, subgroup analyses were performed. To examine the potential impact of study-specific factors on the noted effects, a meta-regression analysis was conducted. Analyses using funnel plots and statistical tests were used to determine the likelihood of publication bias and publication correlation. A sensitivity analysis was carried out to guarantee the accuracy of the findings when particular articles were excluded.

## RESULTS

There are 4,600 native plants in Kerala, and 900 of them have potent therapeutic properties. More than 180

medicinal plants can be found in Kozhikode and Wayanad, the two districts that were chosen. Among these, 95 plant species from 46 plant families have demonstrated the possibility of possessing anticancer characteristics. The information was gathered and organized, and screening and meta-analysis were performed for phytoconstituents and pharmacological applications, including cancer (Table 1). The common names, vernacular names, folklore applications, and traditional usage were obtained from survey reports, observational, and interventional study data. The tribal communities have used medicinal plants for centuries. They prepare decoctions and pastes from plant parts, such as leaves, flowers, stems, barks, and roots. These preparations are ingested or applied externally for a variety of health conditions. The native tribal people have a deep knowledge of the medicinal properties of plants. They are able to identify the plants that are effective for specific conditions, and they know how to prepare the plants for optimal effectiveness.

The alternative medical science of "Ayurveda" is extensively practiced and embraced by the common people in the selected districts of Wayanad and Kozhikode. Despite this, it is essential to note that many of the selected medicinal plants remain unexplored or only partially explored in terms of their potential benefits and uses. Ayurvedic practitioners in the region have a long history, with records dating back 3,000 years detailing the usage of various medicinal plants found in the region. Some Ayurvedic preparations for the aforementioned medicinal herbs can be procured from Ayurvedic pharmacies. In Ayurveda, medicinal plants and their parts are formulated in different forms depending on the disease condition, need, and efficacy. These formulations include Choornams, Vati, Kashayams, Arishtams, Avaleha, and Tailams [27].

A comprehensive analysis was conducted utilizing 326 articles. In the context of a common effect model, the pooled RR exhibited a value of 0.6503 [95% confidence interval (CI): (0.6007; 0.7040)], indicating a statistically significant association ( $p < 0.0001$ ). The random effects model demonstrated an RR of 0.4894 [95% CI: (0.3301; 0.7257)], which was also statistically significant ( $p = 0.0019$ ). Heterogeneity within the study was substantial, with an  $I^2$  value of 92.1% [95% CI: (88.3%; 94.7%)] and a corresponding Tau<sup>2</sup> value of 0.3132 [95% CI: (0.1197; 1.1115)]. The Cochran's  $Q$  test supported the presence of significant heterogeneity [ $Q$ : 152.23, degrees of freedom (d.f.): 12,  $p < 0.0001$ ]. Subgroup analysis under the common effect model revealed varying RR values across different subgroups: subgroup 1 [RR = 0.2644, 95% CI: (0.1449; 0.4825)], subgroup 2 [RR = 0.4118, 95% CI: (0.3602; 0.4708)], subgroup 3 [RR = 0.9836, 95% CI: (0.8704; 1.1115)], and subgroup 4 [RR = 0.6563, 95% CI: (0.5519; 0.7805)]. Significant differences were identified among the subgroups ( $Q$  between groups: 97.32, d.f.: 3,  $p < 0.0001$ ;  $Q$  within groups: 54.91, d.f.: 9,  $p < 0.0001$ ). Similarly, the random effects model's subgroup analysis demonstrated varying RR values: subgroup 1 [RR = 0.2644, 95% CI: (0.1073; 0.6514)], subgroup 2 [RR = 0.4355, 95% CI: (0.0970; 1.9554)], subgroup 3 [RR = 0.4784, 95% CI: (0.0000; 1482.5025)], and subgroup 4 [RR = 0.6376, 95% CI: (0.3002; 1.3543)]. While the differences in subgroups were not statistically significant in the random effects model ( $Q$ : 6.87,

**Table 1.** Significant anticancer medicinal plants from Wayanad and Kozhikode districts of Kerala.

Sr. No	Botanical name & family	Malayalam names and common names	Phyto constituents	Folklore/Tribal uses	Uses given by <i>in-vitro</i> , <i>in-vivo</i> studies	References
1.	<i>Abrus precatorious</i> L. <b>Family:</b> Fabaceae	English: Jequirity bean, rosary pea Malayalam: Kunnikuru	Lectins, Abrin-A to D, Abrus agglutinin	Treatment for ulcer, Boils, Paralysis, Alopecia and Mouth Ulcers	Anticancer (Lung, Stomach, Breast)	[2]
2.	<i>Acanthus illicifolius</i> L. <b>Family:</b> Acanthaceae	English: Mangrove, holy leaf acanthus Malayalam: Chulli, Chullikandal, Chakkaramulli, Payinachulli	Alkaloid - (Tri terpenoids alkaloids) Acanthicifoline, Acansifoliuside, Megastigmone, Flavone glycosides, triterpenoid saponins	Hepatoprotective, Antiulcer, Anti- microbial, Vermicidal, and Anti-rheumatic Properties.	Anticancer (Breast, Stomach, Colon)	[28,29]
3.	<i>Acorus Calamus</i> <b>Family:</b> Araceae	English: Sweet flag Malayalam: Vayambu, Vasampa	A-Asarone, $\beta$ -Asarone, aterpineol, Caracorene, Acorone, Acrenone, Calacorene	Use in Bronchitis, Sinusitis, Epilepsy, Dysmenorrhoea, Mental problems, Aphrodisiac, and as a Brain tonic	Anticancer (Prostate, Liver)	[30,31]
4.	<i>Acyranthes aspera</i> L. <b>Family:</b> Amaranthaceae	English: Chaff flower, Prickly Chaff flower Malayalam: Kadaladi	Alkaloids, Cardiac glycosides, tannins, Steroids, Flavonoids, terpenoids and proteins	Antiulcer, dropsy, Boil treatment, Dog bite, Snake bite and Scorpion bite ailments	Anticancer (Lung, Breast)	[2,32,33]
5.	<i>Adenanthera pavonia</i> L. <b>Family:</b> Fabaceae	English: Red lucky seed Malayalam: Manjadi, Maniadi	Triterpenoid Alkaloids, Flavonoids, Steroids	Asthma, Gout, Inflammation, Boils, Diarrhoea, Ulcer, Rheumatism	Anticancer (Oesophagus, Lung Stomach)	[34–36]
6.	<i>Adhatoda vasica</i> L. and <i>Adhatoda beddomei</i> <b>Family:</b> Acanthaceae	English: Malabar nut, Malayalam: Adolakam, Adalodakam	Quinazoline alkaloids, Vasicine, Peganine, Vasicinone	Fever, Cough, Cold, Respiratory tract infections, Asthma, Bronchitis, Diabetes, Skin infections, Depression and Cancer	Anticancer (Breast, Lungs, Colon)	[37,38]
7.	<i>Allamanda cathartica</i> L. <b>Family:</b> Apocynaceae	English: Golden trumpet Malayalam: Manjalolambi kolaambi	Hydrocarbons, aldehydes, flavonoids, Rutin, Plumieride,	Antiemetic, diuretic, Cathartic, Anti-colic, Anticancer and Laxative	Anticancer (Colon, Stomach)	[39]
8.	<i>Alstonia scholaris</i> <b>Family:</b> Apocynaceae	English: Devil's tree, Milk wood pine Malayalam: Ezhilam Pala	Alkaloids such as Alstonine, Echitamine, $\beta$ -Amyrine	Arthritis, Dog bites, Wounds, Jaundice, Hepatitis, Malaria and Impotency	Anticancer (Stomach, Colon, Leukaemia)	[40–42]
9.	<i>Alternanthera brasiliana</i> L. (Kuntze) <b>Family:</b> Amaranthaceae	English: Brazilian joy weed, Penicillin Malayalam: Chuvanna cheera	Phenols, flavonoids, Alkaloids, Phytosterols and Tannins	Cough, inflammation, Diarrhoea, wounds, viral infections, and Tumours	Anticancer (Stomach, Intestine, Liver)	[43,44]
10.	<i>Anacardium occidentale</i> <b>Family:</b> Anacardiaceae	English: Cashewnut tree, cashew apple Malayalam: Kappamavu, Kasumavu, Parangimavu	Poly phenols, Carotenoids, Anacardic acid, Cardol, Cardanol, Zoapatanolide-A, Agasthisflavone, Vitamins (B2, B3, C, E), Proanthocyanidins (Flavonoids)	Inflammation, Microbial infections, Herpes- simplex virus infections, Malaria, Fungal infections, Cancers, Tumours, Immuno modulatory and Dietary supplement,	Anticancer (Breast, Glioma, Cervical, Lung, Liver, Cervix)	[45–49]
11.	<i>Andrographis paniculata</i> (Burn F) Nees. <b>Family:</b> Acanthaceae	English: King of bitters Malayalam: Kaakanjiram, Kiriyaatu, Nilavepu	Diterpene lactones, Andrographolide, Neo-andrographolide	An Anti-Diabetic, Antiulcer, Anticancer, Hepato protective, Immunomodulatory, Antiarthritic, Anti-inflammatory, and Antipyretic	Anticancer (Lung, Breast, Cervix, Colon and Stomach)	[50,51]

(Continued))

Sr. No	Botanical name & family	Malayalam names and common names	Phyto constituents	Folklore/Tribal uses	Uses given by <i>in-vitro</i> , <i>in-vivo</i> studies	References
12.	<i>Annona squamosa</i> Linn. Family: Annonaceae	English: Sugar apple, Custard apple Malayalam: Seethapazam, Aathi, Aatha	Cinnamic acid derivatives (p-Coumaric acid, Ferulic acid), Tannins, Glycosides, Alkaloids, Saponins	Antitumor, Vermicide, Skin problems, Insect bites, Antiulcer and Hysteria treatment	Anticancer (Utrus, Ovary, Breast, Cervix and Intestine)	[52–55]
13.	<i>Aristolochia indica</i> L. Family: Aristolochiaceae	English: India birthwort Malayalam: Eshwaramulla, Karudakodi. Ishwaramooli	Sesquiterpene hydrocarbons (Ishwarane, Aristolochene), Aristolochic acid, $\beta$ -Sitosterol, Essential oils,	Malaria, Diarrhoea, Cholera, Leprosy, Ulcers, Tumours, Dermatological disorders, Spider and Insect bites	Anticancer (Breast)	[56,57]
14.	<i>Artemisia vulgaris</i> and <i>Artemisia nilagarica</i> Family: Asteraceae	English: Mug wort, St John's plant, Worm wood Malayalam: Thirunitripachcha, karpoora thulasi	Mono and Sesquiterpenes, Crys anthenone, Sabenene,	An Analgesic, Antispasmodic, Diuretic, Flavouring agent, Upper respiratory tract infections, Cardiotonic, Antitumor, Cough and Cold	Anticancer (Colon, Breast, Stomach, Intestine)	[58–60]
15.	<i>Asystasia gangetica</i> L. Family: Acanthaceae	English: Chinese violet, creeping foxglove Malayalam: Thuppalampotti	Poly Phenols, Flavonoids, Tannins (Proanthocyanins) and Polysaccharides	Tumour regression, Epilepsy, Fever, Stomach ache, Snake bite, Cough and Upper respiratory tract infections	Anticancer (Stomch, Lungs, Throat)	[61,62,25]
16.	<i>Azadirachta indica</i> A. Juss. Family: Meliaceae	English: Indian lilac, Margosa tree Malayalam: Ariyaveppu, Nimbam, Veppu	Azadirachtin, Nimbin, Nimbolinin, Nimbidol, Gedunin, Nimbidin Catechin, Gallic acid, Morgolone, Morgolonone and Quercetin	Chicken pox, Small pox, Tumours, Cancers, Inflammation, Skin disorders, Diabetes, Fungal and Bacterial infections	Anticancer (Lukemia, Stomach, Skin, Colon, Intestine, Breast)	[63,64]
17.	<i>Bauhinia variegata</i> L/ <i>Bauhinia tomentosa</i> L. Family: Fabaceae	English: Mountain ebony Malayalam: Chuvannamandaram, Malayakathi, Mandaram	Alkaloids, Flavonoids, Saponins, Quercetin, Rutin and Isoquercetin	Tumour regression, Leprosy, Worm infestation, antiseptic and Cervical lymphadenitis	Anticancer (Breast, Skin, Cervix, Ovary, Liver)	[65–67]
18.	<i>Berberis vulgaris</i> L. Family: Berberidaceae	English: Barberry Malayalam: Kastuimanja, Maradarisina	Benzylisoquinolines, Berberine, Berbamine, Berberubbine, Columbamine, Coumarin, Flavonoids and Tannins	Anti-tumour, Anti-inflammatory, Antibiotic, Antiseptic, Anti-microbial, Antidepressant, Hepatitis and Bilary fever treatment	Anticancer (Myeloid Leukaemia, Breast, Ovary, Lung)	[68–70]
19.	<i>Bidens Pilosa</i> var. minor. Family: Asteraceae.	English: Farmers friend, Black Jack Malayalam: kithachedi, Snehakoora	Polyacetylenes, Polyacetylene glycosides, Terpenes, Phyto sterols, Flavone glycosides	Ailment of Diabetes, Malaria, Hypertension, Tumours and Cancers	Anticancer (Adenocarcinoma)	[71–73]
20.	<i>Biophytum sensitivum</i> L. (D.C.). Family: Oxalidaceae	English: Life plant Malayalam: Mukkutti, Theendavadi	Steroids, Terpenes, Flavonoids, Tannins, Saponins, Polysaccharides and Pectin	Antitumor, Anticancer, Immunomodulatory, Antidiabetic, Anti-inflammatory and Anti-atherosclerotic	Anticancer (Lung, Liver, Breast, Cervix, Skin)	[74,75]
21.	<i>Blepharis maderaspatensis</i> L. Heyne ex Roth. Family: Acanthaceae	English: Creeping Blepharis Malayalam: Elumbotti, Hemakandi	Verbascoside, Vanillic acid, Apigenin, Coumoryl purine	Ailment of wounds, Skin burns, Stomach ache, Inflammation, Edema, Tumors regression, Bacterial and Fungal infections	Anticancer	[76,77]
22.	<i>Boerhavia diffusa</i> Family: Nyctaginaceae.	English: Hogweed, Pigweed Malayalam: Punarnava	Amino acids, Arachidic acid, Iso palmitic acid, Behenic acid, Calcium	Immunomodulatory, Hepatoprotective, Anti-tumour, Anti-oxidant, Gastro Intestinal disorders, Menstrual disorders, Diuretics, Cancer treatment	Anticancer (Lung, Liver, Ovary, Breast, Oesophagus, Glioma)	[78–80]

(Continued))

Sr. No	Botanical name & family	Malayalam names and common names	Phyto constituents	Folklore/Tribal uses	Uses given by <i>in-vitro</i> , <i>in-vivo</i> studies	References
23.	<i>Capsicum annum</i> L. <b>Family:</b> Solanaceae.	English: Chilli pepper, Cayenne pepper Malayalam: Pacha mulaga	Capsaicinoids, Capsaicin, Capsiate, Dihydro capsaicin, Nondihydro capsaicin, Nor capsaicin	Analgesic, Anti-inflammatory, Anticholestrenemic, Anti-oxidant, Anti-tumour, Anticancer, Stimulant, Cardio diseases, Vaso dilator	Anticancer (Ovary, Breast, Liver, Oesophagus, Intestine, Lung)	[81–83]
24.	<i>Carica papaya</i> Linn. <b>Family:</b> Caricaceae	English: Papaya Malayalam: Boppayi	Alkaloids such as $\alpha$ -Carpaine, Suedo Carpaine, Dehydro Carpaine, Carposide	Ailment of Malaria, Platelet deficiency, Inflammation, Hypotension, Cancer, Obesity, Diabetes	Anticancer (Prostate, Ovary, Cervix, Breast)	[84–86]
25.	<i>Carallia brachiata</i> Lour. <b>Family:</b> Rhizophoraceae	English: fresh water mangrove Malayalam: Vallabham, Vankana, Varanga	Alkaloids, Hygroline, Di glycosyl megastigmane, megastigmanes, Phenolic compounds and Flavonoids.	Analgesic, Antipyretic, Cuts and Wounds healing, Anti-tumour	Anticancer	[87–89]
26.	<i>Cassia fistula</i> L. <b>Family:</b> Caesalpinioideae	English: Golden shower tree Malayalam: Kanikonna, Karnikaram	Flavonoids, Anthraquinones, Chromones, Coumarins, Alkaloids, Phytosterols, Triterpenes, Rhein,	Anti-microbial, Anti-fertility, Anti-oxidant, Anti-tumour, Anti-inflammatory, Anti-pyretic. Pulmonary protective and Hepatoprotective.	Anticancer (Uterine, Lung, Ovary)	[90–92]
27.	<i>Centratherum punctatum</i> Cass. <b>Family:</b> Asteraceae	English: Brazilian bachelor's button Malayalam: Keshavardhini	Sesquiterpenes, Centratherin, Isocentratherin	In Microbial infections, Cardiac diseases, Tumours regression, Hair fall, Alopecia	Anticancer	[93–95]
28.	<i>Cinnamomum Zeylanicum</i> CZ. <b>Family:</b> Lauraceae	English: Cinnamon, Cassia Malayalam: Elavangam	Cinnamon oil, Eugenol-Cinnamyl acetate, Trans- $\alpha$ -Benzoin ester, Caryophyllene	Antitussive, Cold, Influenza, Diarrhoea, Hair fall, Toothache, Tumors regression, Dementia, Insomnia, Arthritis	Anticancer	[96–98]
29.	<i>Clitorea ternatea</i> L. <b>Family:</b> Fabaceae	English: Butterfly pea Malayalam: Sankupushpum, Aaral, Malayamukki	Cyclotide peptides, Phlobatannins, tannins, Saponins, Phenols, triterpenoids, Anthraquinone	Anti-oxidant, Pesticidal, Anti-bacterial, Anti-malarial, Analgesic, Diuretic, Anti-pyretic	Anticancer (Breast, Thyroid, Medulla, Colon, Pancreas, Lung)	[99,100]
30.	<i>Corchorus olitorius</i> L. <b>Family:</b> Tiliaceae	English: Jute Malayalam: Chanacedi	Cardiac glycosides, B-Sitosterol, Riboflavin, Niacin, Flavonoids, Tannins, Alkaloids, Glycosides, Carbohydrates, Saponins	A Diuretic, Antioxidant, Purgative. Treatment of Gonorrhoea, Tumours, Headache, Chronic cystitis,	Anticancer	[101–103]
31.	<i>Coscinium fenestratum</i> <b>Family:</b> Menispermaceae	English: Yellow vine Malayalam: Maramanjil	Alkaloids, Glycosides, berberine, Sitosterol glucoside, Oleic acid, Saponin, Ceryl alcohol, Palmitic acid	Antiseptic, Tumours regression, Inflammation, Diabetes, Jaundice, Ulcers and Fever	Anticancer (Leukaemia, Head, Neck, Lung, Liver)	[104–106]
32.	<i>Crataeva magna</i> Lour. DC. <b>Family:</b> Capparaceae.	English: Three leaved caper, Garlic pear tree Malayalam: Neermanthalam, Neerval, Kili	Alkaloids, Flavonoids, Diterpenes, Saponins, Tannins, Diosgenin, Phytosterols	vermifuge, Laxative, Anti-inflammatory Treatment of Rheumatism, Spleen disorders, Liver disorders, Bronchitis, Bladder stones, Edema, Tumour and Cervical adenitis	Anticancer	[63,107]
33.	<i>Curcuma Zedoaria</i> <b>Family:</b> Zingiberaceae	English: White turmeric Malayalam: Manjakoova, Adavikachola, Kasturimanjal	Sesquiterpenes, Curcumin, $\beta$ -Turmerone, $\beta$ -Edusmol, Ethyl-p-methoxy cinnamate, Zingiberene, $\beta$ -Elemene	A Blood purifier, Antivenom for snake bites, Anti-colic. Ailment of Coronary heart disease, Liver cancer, Bronchitis, Inflammation, Leukoderma	Anticancer (Ovary, Leukaemia, Lung, Breast, Liver)	[108–110]

(Continued)

Sr. No	Botanical name & family	Malayalam names and common names	Phyto constituents	Folklore/Tribal uses	Uses given by <i>in-vitro</i> , <i>in-vivo</i> studies	References
34.	<i>Curcuma longa</i> <b>Family:</b> Zingiberaceae	English: Turmeric Malayalam: Manjal	Curcuminoids (Curcumin (I, II, III), De methoxy curcumin, Carotenoids, terpenoids, Poly Phenols, $\alpha$ -Turmerone, $\beta$ -Turmerone, Flavonoids	Leukoderma, Antiseptic, Inflammation, Tumour regression, Vaso constriction, Bronchitis, Pain, Hepatic disorders and as an Expectorant	Anticancer (Breast, Cervix, Ovary, Lung, Liver, Glioma, Head, Uterine, Mouth)	[111–114]
35.	<i>Cyathillium cinereum</i> (L) H Rob. <b>Family:</b> Asteraceae	English: Little iron weed Malayalam: Poovamkurunilla, Poovamkurunilla	Caryophyllene oxide, n-Hexa decanoic acid, Phytol, Cardiac glycosides, Tannins, Phenols, Flavonoids, Steroids, Saponins	In the ailment of Pain, Inflammation, Colic pain, Cholera, Asthma, Rheumatism, Asthma, Dysentery, Night blindness, Diarrhoea, Conjunctivitis, Arthritis and Cancers	Anticancer	[115,116]
36.	<i>Cyclea peltata</i> Hook F. Thoms. <b>Family:</b> Menispermaceae	English: Indian moon seed, Bicklered leaved moon seed Malayalam: Padakizhangu, Padathali, Padavalli	Fangchinoline, Cycleapeltine, Cycleacurine, Cycleonorine, Cycleadrine, Bisbenzyl isoquinoline alkaloids, Tetrandrine, Tropolo isoquinoline alkaloids, Parairubrine A, B	In the treatment of Fever, Nephrotic diseases, Cough, Malaria, Asthma, Diabetes, Tooth pain, Hypercholesterinaemia, Tumours. Useful as Blood purifier, Memory enhancer, Antioxidant	Anticancer (Leukaemia, Breast, Ovary, Kidney)	[117–119]
37.	<i>Cymbopogon citratus</i> <b>Family:</b> Poaceae/ Graminae	English: Lemon grass Malayalam: Chayapullu, Chenganampullu, Inchipullu	Essential oils, Quercetin, Apigenin, $\alpha$ -Citral, $\beta$ -Citral, Geraniol, Geranyl acetate, Citronellal, Terpinolen Myrcene, Terpinol methyl heptanone, Phenols, Alcohols, Flavonoids, Ketones	Spasms, Pain, Inflammation, Fever, Microbial infections, Bacterial infections, Tumours and Cancers	Anticancer (Lung, Liver, Thyroid, Breast, Cervix, Ovary)	[120–124]
38.	<i>Cyprus rotundus</i> SSP. <b>Family:</b> Cyperaceae	English: Nut grass, Purple flat sedge Malayalam: Muthinga	Flavonoids, Phenyl propanoids, Sesquiterpenes, Alkaloids, Saponins, Phenolic acids	Antiulcer, Inflammation, Rheumatism, Fever, Neuroleptic disorders, Tumours regression.	Anticancer (Breast, Cervix)	[125–129]
39.	<i>Desmodium triflorum</i> L. (DC) <b>Family:</b> Fabaceae	English: Creeping tick trefoil, Tick clover, Beggar lice Malayalam: Nilamparanda, Cherupulladi, Kunnappalai	Alkaloids, Terpenoids, Flavonoids, Steroids, Phenylpropanoids, Coumarins, Pterocarpan, 5-Methoxy-N, N, dimethyl tryptamine, N-methyl-H4-Harman, $\beta$ -Carbolinium cation, Rutin, Quercetin, $\beta$ -Sitosterol, Stigmasterol, Lupeol, $\alpha$ -Amyrone.	Anti-inflammatory, Bactericidal, Anti-diarrhoeal, Antioxidant, Anticonvulsant, Anti spasmodic, Anthelmintic, Anti-nociceptive, Treatment of Neurological disorders, Anxiety, Dysentery and Diarrhoea	Anticancer	[130–132]
40.	<i>Dodonea viscosa</i> L. Jack., Hook. <b>Family:</b> Sapindaceae	English: Hopspeed bush, switch sorrel Malayalam: Aattotta, Vrali, Krali,	Alkaloids, Saponins, Tannins, Flavonoids, Steroids, Phenols, Sapogenins	Tumours regression, Cold, Sore throat, Rheumatism, Inflammation, Spasms, Diarrhoea, antiulcer, Constipation	Anticancer (Breast, Ovary, Cervix, Uterus)	[133–136]
41.	<i>Elephantopus scaber</i> Linn. <b>Family:</b> Asteraceae	English: Prickly leaved elephant's foot Malayalam: Anayadi, Anachuvadi,	Sesquiterpene lactones, Scabertopin, Deoxyelephantopin, Iso-deoxyelephantopin, Isoscabertopin	Aphrodisiac, Astringent, Expectorant, Analgesic, Antipyretic, Anti-tumour. Anti-hepatitis, Bronchial spasms, Neoplasms, Pneumonia,	Anticancer (Breast, Skin)	[137–142]

(Continued))



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42.	<i>Elettaria cardamomum</i> <b>Family:</b> Zingiberaceae	English: Cardamom Malayalam: Bavula, Ealakkaya, Eallam	Essential oils, Pinene, methyl Eugenol, Myrcene, Sabinene, Phellandrene, Geraniol, Citronellol, Nerol, Linalyl acetatae	Flavouring agent, Condiment, Immune protective, Hepato protective, Carminative, Stimulant, and Antiulcer. Pulmonary infections, Teeth, Throat infections, Bronchial spasms, Pulmonary tuberculosis	Anticancer (Breast, Ovary, Rectum, Gastro intestine)	[143–146]
43.	<i>Embilica officinalis</i> <b>Family:</b> Euphorbiaceae	English: Amla Malayalam: Nelligaram, Nellikka	Flavonoids Quercetin, Rutin, PolyPhenols, Gallic acid, Ellagic acid, Vitamin C, D, Amino acids, tannins,	Cardioprotective, Immuno modulatory, Anticholestrnemic, Antilipidemic, Antidiabetic, Antioxidant, Anticancer, Antiulcer	Anticancer	[147–149]
44.	<i>Erigeron Karvinskianus L.</i> <b>Family:</b> Asteraceae	English: Daisy fleabane Malayalam: Pottu poovu	Mono terpenoids, Sesquiterpenoids, Diterpenoids, Triterpenoids, Phenolic derivatives	Anti- hepatitis, Dermatological disorders, Haematuria, Indigestion and Tumours regression.	Anticancer	[150,151]
45.	<i>Euphorbia heterophylla L.</i> <b>Family:</b> Euphorbiaceae	English: Painted leaf poinsettia, green poinsettia, Milk weed, Mexican fire Plant, Malayalam: Upila, Nelapalai	Diterpenoids, Terpenoid coumarins, Quercetin, Lignin, Quinin, Flavonoids, Phenols, Essential oils, saponins, Glycosides, Sitosterol, Tannins	Purgative, Anthelmintic, Hair tonic, Anti-bacterial, Anti-septic, Anticoagulant, Antitumor	Anticancer (Gastric, Intestine, Ovary, Breast)	[152–155]
46.	<i>Eurycoma longifolia</i> Jack. <b>Family:</b> Simaroubaceae	English: Long Jack, Malaysian Ginseng Malayalam: Nedu pazha	Quassinoids, Alkaloid-9-methoxy canthine, Terpenoids	Tonic during childbirth. Malaria, Diarrhoea, Fatigue, Inflammation, Ulcer, Elevated Blood pressure, Dropsy, Fever, Cough, Hypogonadism, Male- infertility, Osteoporosis	Anticancer (Breast, Ovary, Lung, Cervix, Melanoma, Fibrosarcoma)	[156–159]
47.	<i>Garcinia gummi-gutta</i> Linn. Robs. Or <i>Garcinia cambogia</i> <b>Family:</b> Clusiaceae/ Guttiferae	English: Malabar tamarind, Goraka, Malayalam: Pinampuli, Kadampuli	Hydroxy citric acid, Garcinol, Garbogiol, Isogarcinol, Tartaric acid, Citric acid, Guttiferone, Iso-guttiferone, Proteins, Pectins, Tannins, fat, Alkaloids, Polysaccharides,	Rheumatism, Bleeding piles, Wounds, Ulcers, Inflammatory bowel disease, Edema, Menstrual disorders, Obesity, Diabetes, Immune disorders	Anticancer	[160–162]
48.	<i>Garcinia indica</i> Choisy. <b>Family:</b> Clusiaceae/ Guttiferae	English: Wild mangosteen, Goa butter tree, Malayalam: Punampuli	Garcinol, Isoxanthochymol, Xanthochymol, Isogarcinol, Citric acid, tartaric acid, Malic acid	To heal Piles, Dysentery, Ulcers, Wounds, Inflammations, Cardiac diseases and as a Diuretic	Anticancer	[163–166]
49.	<i>Gaultheria fragrantissima</i> Wall. <b>Family:</b> Ericaceae	English: Fragrant winter green Malayalam: Kolakatta chedi, Kolgate chedi	B-Thujone, Camphor, Crysanthenone, Borneol, Germacrene, Sabinene, Methyl salicylate (Oil of wintergreen), Asarone, Flavonoids, Rutin, Morin, Luteolin,	Cough, Cold, Inflammation, Tumour, Bacterial and Fungal infections. Insecticidal activity	Anticancer Breast, Cervix, Ovary)	[167–171]
50.	<i>Gloriosa superba</i> <b>Family:</b> Liliaceae	English: Climbing Lily, Malabar Glory Lily Malayalam: Kanthel, Kariyilanchi, Karthika poovu	Tropalane alkaloids, Gloriosine, Colchicine, Isoperlolyrine, Trioxsalen, Caffeic acid, $\beta$ -Sitsterol, $\beta$ -Lumi colchicine, Colchicoside	Rheumatic disorders, Arthritis, Gout, Leprosy, Ulcers, Skin diseases, Tumours, Inflammation, Pain, Bacterial infections	Anticancer (Liver, Intestine, Breast, Ovary)	[172–175]

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51.	<i>Glycosmis mauritiana</i> Lam. <b>Family:</b> Rutaceae	English: Ash sheora, Gin berry, Rum berry Malayalam: Panal, Pooni Patty	Quinolinone alkaloids, Acridone alkaloids, Flavone glycosides, 7,8 -Di methoxy 2-2-6 -tri methyl pyranoquinoline-5-one,	Jaundice, Anaemia, Inflammation, Skin diseases, Eczema, Helminthiasis, Ascariasis, Snake bites	Anticancer (Breast, Cervix, Skin, Hepatocellular carcinoma)	[176–178]
52.	<i>Gymnema silvestre</i> R. Br. <b>Family:</b> Asclepiadaceae	English: Small Indian Ipecac, Australian cow plant Malayalam: Chakkaraikolli, Madhunaasini	Anthraquinone derivatives, Butyric acid, Gymnemic acids, d-Quercitol, Inositol, Hentriacontane, Formic acid, tartaric acid, Pentriacontane, Phytin	Diabetes, Inflammation, Cancers, Bone deformities, Atherosclerosis, Hepatic disorders. Larvicidal and Fungicidal activities	Anticancer (Melanoma, Osteosarcoma, Breast, Colon, Cervix)	[179–183]
53.	<i>Hemidesmus indicus</i> L. R. Br. <b>Family:</b> Apocynaceae	English: Indian sarsaparilla, Malayalam: Kappikodi, Nannari,	Triterpenoids, Flavonoids, Phenols, Saponins, Catechin, $\beta$ -Erythroidine, Butorphanol, Sinomanine, Methyl daphnetin	Diabetes, Cancer, Ulcer, Inflammation Neuroprotective, Cardioprotective, Hepatoprotective, Nephroprotective	Anticancer (Liver, Colon, Breast, Leukaemia, Skin)	[184–188]
54.	<i>Habenaria longicorniculata</i> J graham. <b>Family:</b> Orchidaceae	English: Long-tailed Habenaria Malayalam: Riddhi	Dendrobine type alkaloids, Bibenzyls, Stilbenoids, Terpenoids, Flavonoids, Phenanthrenes, Gigantol, Batatasin III	Haemorrhage, Blood disorders, Inflammation, Tumours	Anticancer (Liver, Breast, Cervix)	[189,190]
55.	<i>Hemigraphis colorata</i> Blume. <b>Family:</b> Acanthaceae	English: Red ivy, Red flame ivy, Waffle plant Malayalam: Murikooti	Alkaloids, Anthraquinones, Flavonoids, Glycosides, Anthocyanin, Carbohydrate, Coumarins, Phenols, Tannins, proteins, Terpenoids, Saponins, Steroids	Wounds, Cuts, Ulcers, Inflammation, Vitiated Pitta, Excessive menstruation, Gall bladder stones, Piles, Bloody dysentery, Anaemia, Skin diseases	Anticancer (Skin)	[191–193]
56.	<i>Holarrhena pubescens</i> Wall ex D. Gon. <b>Family:</b> Apocynaceae	English: Conessi bark, Ester tree, Ivory tree Malayalam: Kada mpala, Kudagapala	Pregnane alkaloids, Muklaangin D, Steroidal alkaloids, Triterpenoids, Coumarins, Ergosterols, Flavonoids, Saponins, Phenols, Carbohydrates, Tannins	Diarrhoea, Amoebic dysentery, Piles, Inflammatory bowel disease, Ulcer, Skin disorders, Diabetes, Hyperlipidaemia, Blood infections,	Anticancer (Oral, Tongue, Buccal, Squamous cell carcinoma, Liver, Breast, Ovary, Colon, Neuroblastoma,)	[194–196]
57.	<i>Holigarna arnottiana</i> Wall. <b>Family:</b> Anacardiaceae	English: Black varnish tree Malayalam: Charu, Cheru, Kattu chera	Tetramethyl-2-hexadecan, Squalene, 1-Iodo-2methylundecane	Antimicrobial, Antifungal, Obesity, Arthritis, Anti-inflammatory, Antitumour, Haemorrhoids, Cancers	Anticancer	[197–199]
58.	<i>Hybanthus enneaspermus</i> (Linn) F. Muell. <b>Family:</b> Violaceae	English: Spade flower Malayalam: Orilathamara, Kalthamara	Triterpenoids, Anthraquinones, Alkaloids, Flavonoids, Saponins, Sterols, Amino acids, Carbohydrates, Phenols, Phytosterols, Cyclotides, Cycloviolacin O2	Nephroprotective, Anticonvulsant, Anti-diabetic, Larvicidal, Anti-arthritis, Hepato protective, Anti-oxidant, Anti-tumour	Anticancer (Breast, Liver, Colon, Lung, Kidney, Cervix)	[200–203]
59.	<i>Ipomoea batata</i> <b>Family:</b> Convolvulaceae	English: Sweet potato, Purple sweet potato Malayalam: Cheeni kizhangu, Chakkara kizhangu, Madura kizhangu	Amino acid peptides, Phenolic compounds, Carbolines, Chlorogenic acid, Anthocyanins, Citrus nine- I, Poly phenols, Sterols, Caffeic acids,	Anti-stress, Anti-oxidant, Anti-inflammatory, Antitumour, Anticancer	Anticancer (Cervix, Ovary, Breast, Colon, Colorectum, Gastric cancers)	[204–210]
60.	<i>Ipomoea pestigridis</i> L. <b>Family:</b> Convolvulaceae	English: Bind weed, Cupid's flower, Tiger's foot Malayalam: Naripadam, Pulichuvadi, Poochakkal Valli	Alkaloids, Flavonoids, Tannins, Saponins, Terpenoids, Sterols, Chlorogenic acid, Polyphenols	Ailment of Boils, Sores, Eczema, Skin disorders, Dog bites, Microbial infections, Constipation, Tumours, Inflammation	Anticancer (Liver, Lung)	[211–214]

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61.	<i>Justica adhatoda</i> <b>Family:</b> Acanthaceae	English: Vasa, Malabar nut, Vasaka Malayalam: Adalodakam, Vasika of Malabar	Pyroquinazolidine alkaloids, Vasicol, Vasinone, Preganine, Vasicine, Alkaloids, saponins, Tannins	Cough, Bronchitis, Inflammation, Tuberculosis, Upper respiratory tract infections, Hepatic diseases, Rheumatism, Joint pain, Sprains, Tumours	Anticancer (Breast, Cervix, Lymphoma)	[215–218]
62.	<i>Justica gendarussa</i> Linn. <b>Family:</b> Acanthaceae	English: Willow leaved Justica, Warer willow Malayalam: Karunochi, Vathakodi	Alkaloids, Phenols, Flavonoids, Triterpenoidal Saponins, Lupeol, Stigmasterol, Naringenin, Kaempferol, Amino acids, Aromatic amines	Rheumatism, Fever, Bronchitis, Lumbago, Injuries, Inflammations, Ear and Headache, Eye infections	Anticancer (Liver, Breast, Cervix)	[219–221]
63.	<i>Justica simplex</i> <b>Family:</b> Acanthaceae	English: Water willow, Shrimp Plant Malayalam: Vathakodi	Alkaloids, Flavonoids, Phenols, Amino acids, $\alpha$ -Sitosterol, $\beta$ - Sitosterol	Inflammation, Chronic rheumatism, Bronchitis, Tumours	Anticancer	[222,223]
64.	<i>Lantana camara</i> L. <b>Family:</b> Verbenaceae	English: Lantana, Shrub Verbana, Wild sage Malayalam: Aripoochedi, Konda, Kongini, Njandukali	Sesquiterpenoids, $\beta$ -Gurgunene, Spatulanol, Essential oils, $\beta$ -Caryophyllene, Spathulenol, Sabinene, Limonene,	Bronchitis, Cough, Tumours, Inflammation, Cancers. Useful as Vermifuge	Anticancer (Liver, Lung, Breast)	[224–227]
65.	<i>Leucas aspera</i> (Wild.) Link. <b>Family:</b> Lamiaceae	English: Common Leucas Malayalam: Thumba, Chiruthumba	Triterpenoids, Oleanolic acid, Ursolic acid, Nicotine, B-Sitosterol, Poly phenols, Di-terpenes,	Anti-microbial, Anti-fungal, Anti-oxidant, Antihistaminic, Antipyretic, Anticancer, Antinociceptive	Anticancer (Liver, Prostate, Cervix)	[228–230]
66.	<i>Mangifera indica</i> <b>Family:</b> Anacardiaceae	English: Mango tree, Cuckoo's joy Malayalam: Amaram, Manga, Mampazham	Poly Phenols, Carotenoids, Tocopherol, Manganiferin, Benzoquinone, Ascorbic acid, Flavonoids, Anthocyanins	Ailment of Immune disorders, Microbial infections, Anticancer	Anticancer (Breast, Cervix, Oesophagus, Liver)	[231–235]
67.	<i>Mahonia leschenaultii</i> <b>Family:</b> Berberidaceae	English: Toda plant, Holy leaved berry Malayalam: Mullukadambu, Manjanathi	Isoquinoline alkaloids, Berberine, Palmatine, Barbamine, Neprotine, Oxycanthine, Columbamine, Palmatine, Coptisine	Dermatitis, Skin diseases, Psoriasis, Inflammation, Neoplasms, Melanoma, Tumours, Fungal infections	Anticancer (Skin, Melanoma, Breast, Lung, Gastric, Colorectum, Ovary, Endometrium)	[236–239]
68.	<i>Melastoma malabathricum</i> <b>Family:</b> Melastomataceae	English: Indian Rhododendron, Senduduk Malayalam: Athirani	Ursolic acid, Asiatic acid, $2\alpha$ -Hydroxy Ursolic acid, Phyto sterols, Saponins	Injuries, Wounds, Cuts, Inflammation, Tumours	Anticancer (Skin, Cervix, Uterus, Breast)	[240–242]
69.	<i>Mesua ferrea</i> Linn. <b>Family:</b> Clusiaceae/Guttiferae	English: Indian rose chesnut, Cobra's saffron, Nagas's tree Malayalam: Churuli, Naga champakam, Nagakesaram, Nagapoovu	Alkaloids, Coumarins, Xanthenes, Triterpenoids, saponins, Flavones, Terpenes, Mesuaxanthone-A and B, M-ferrone-b, $\beta$ -Sitosterol	Inflammation, Tumour, Scabies, Piles, Burning feet, Sores, Wounds, Ulcers, Rheumatic pain.	Anticancer (Pancreas, Breast, Liver)	[243–245]
70.	<i>Michelia champaca</i> Linn. <b>Family:</b> Magnoliaceae	English: Joy perfume tree Malayalam: Champakam	Aporpine alkaloid, Liriodenine, 4-o- $\beta$ -D-Gluco pyranoside aldehyde, Magnograndiolide, Michampanolide, Parthenolide, Anolobine, Champacaine, Quercetin, Syringaresinol, Vanillic acid, Vanillin, Michelia-A, Scopoletin	Inflammation, Arthritis, Hyperlipidaemia, Cancer, Muscle spasms, Helminthiasis, Rheumatism, Dyspepsia, Nausea, Vomiting, Fever	Anticancer (Nasopharynx)	[246–248]

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71.	<i>Myristica fragrans</i> <b>Family:</b> Myristicaceae	English: Nutmeg tree, Mace tree Malayalam: Jathikka, Jathi	Volatile oils, Myristicine, Elemicin, Iso-eugenol, Eugenol, Lignan, Neo lignan, Camphene, 4-Terpineol	Anti-oxidant, Anti-tumour, Condiment, Food spice, Carminative, Stimulant	Anticancer (Breast, Ovary, Liver, Lung, Cervix, Prostate, Colon)	[249–253]
72.	<i>Naringi crenulata</i> <b>Family:</b> Rutaceae	English: Toothed leaf limonia Malayalam: Dadhiphala, Kattunarakam, Narinarakam	Terpenoids, Steroids, Quinones, Alkaloids, Flavonoids, Naringin, Hesperetin, Hesperetin-7-rhamnoglucoside, Tanakamine	Antioxidant, Hepatoprotective, Anti-inflammatory, Larvicidal, Anti-microbial, Fungicidal, Anti-emetic, Anti-malarial. Mitigation of Dysentery	Anticancer	[254–256]
73.	<i>Nerium oleander</i> <b>Family:</b> Apocynaceae	English: Indian oleander, Rose Bay Malayalam: Chuvanna arali, Arali	Cardiac glycosides, Steroids, Terpenoids, Flavonoids, Oleandrin, Odoroside-A, H, Neritaloside,	Antidepressant, Inflammation, Antihyperlipidemic agent, Cancers, Ulcer, Hepatic disorders	Anticancer (Breast, Ovary, cervix)	[257–259]
74.	<i>Oroxylum indicum</i> (L.) Benth. <b>Family:</b> Bignoniaceae	English: Indian trumpet flower, Broken bones plant Malayalam: Aralu, Veluthapathiri	Iso-flavonoids, triterpenoids, Steroids, Anthraquinone, Aloe-emodin, Baicalein, Baicalin, Oroxin-A, B, Oroxilin-A, Scutellarin	Immunomodulatory, Antitumour, Antioxidant, Anti-inflammatory	Anticancer (Lung, Liver, Breast)	[260–264]
75.	<i>Phyllanthus amrus</i> <b>Family:</b> Euphorbiaceae/ Phyllanthaceae	English: Phyllanthus Malayalam: Keezhanelli, Kiruthnelli	Gallic acid, Phyllaemblic acid, Phyllanthine, Hypopyllanthine, Quercetin, Galloyl gluco pyranoside, Rutin, Corilagen,	Antiviral, Jaundice, Hepatic infections, Inflammation, Cancer	Anticancer (Prostate, Liver, Kidney)	[265–269]
76.	<i>Piper nigrum</i> L. <b>Family:</b> Piperaceae	English: Black Pepper, Common Pepper Malayalm: Kurumulaku	Alkaloids, Piperine, Piperolein, Piperinamide, Dihydro-piperonaline, Iso piperolein, Retrofractamide, 3,4-Methylene-di-oxy-cinnamaldehyde, Chabamide	Gastro intestinal disorders, Diarrhoea, Depression, Inflammations, Spasms, Asthma, Microbial infections, Tumours, Nasal decongestion, Upper respiratory infections	Anticancer (Leukaemia, Cervix, Ovary, Breast, Prostate, Lung, Colon, Gastro intestinal tract)	[270–274]
77.	<i>Polyalthia longifolia</i> <b>Family:</b> Annonaceae	English: Cemetery tree, Mast tree Malayalam: Aranamaram, Ashokam	Flavonoids, Sterols, Lignans, Diterpenes, Organic acids, Tannins	Fungal, Bacterial, Plasmodial infections, Tumours, Inflammations, Ulcer, Diabetes, Cancers	Anticancer (Cervix, Liver, Lung, Breast, Prostate)	[275–277]
78.	<i>Quisqualis indica</i> <b>Family:</b> Combretaceae	English: Burma creeper Malayalam: Kulamarinji, Thookuchethi	Alkaloids, Flavonoids, Trigonelline, Rutin, Quisqualic acid, Amino acids, L-Proline, L-Asparagine	To circumvent Skin diseases, Piles, Boils, Fever, Diarrhoea	Anticancer (Skin, Melanoma, Ovary, Colorectum)	[278–280]
79.	<i>Rauvolfia tetraphylla</i> <b>Family:</b> Apocynaceae	English: Devil Pepper, Garden Rauvolfia Malayalam: Pambumkolli	Alkaloids, Flavonoids, Steroids, Terpenoids, Reserpine, Canescine, Yohimbine, Rauvolscine, Ajmaliscine, Ajmaline, Carbohydrates, Amino acids, Phenols, saponins,	Anti-microbial, Anticancer, Anti-diabetic, Anti-HIV Cough, Cold, Stomach-ache, Anxiety, Nervous disorders, Convulsions	Anticancer (Breast, Ovary, Cervix, Rectum)	[281–284]
80.	<i>Sarcostemma viminalis</i> (L.) R. BR. <b>Family:</b> Asclepiadaceae	English: Moon creeper, Caustic bush, Milk bush Malayalam: Somam, Somavalli	Alkaloids, Saponins, Triterpenes, Flavonoids, Glycosides	Dermatological disorders, Skin cancers, Tumours	Anticancer (Skin, Cervix)	[285–288]
81.	<i>Semecarpus anacardium</i> Linn., f. <b>Family:</b> Anacardiaceae	English: Marking nut tree, Oriental Cashew Malayalam: Cherkuru, Cherumaram	Anacardic acid, Bilawanol, Cardol, Anacardol, Semecarpol,	Central nervous system stimulant, Anti-inflammatory, Hypoglycaemic, Anti-tumour. Ailment of Blood diseases, Skin diseases	Anticancer (Cervix, Lung, Blood, Breast, Liver)	[289–291]

(Continued)

Sr. No	Botanical name & family	Malayalam names and common names	Phyto constituents	Folklore/Tribal uses	Uses given by <i>in-vitro, in-vivo</i> studies	References
82.	<i>Solanum torvum</i> <b>Family:</b> Solanaceae.	English: Devil's fig, Turkey berry Malayalam: Anachunda, Chunda	Flavonoids, Alkaloids, Steroids, Terpenoids, Saponins, Neochlorogenin-6-o-β-D-quinovic pyranoside, 3-o-acetyl-stigmasta-5,25-diene-2,3-diol, Quercetin, Iso-quercetin, Kaempferol	Rheumatism, Inflammation, Tumour, Hepatic disorders, Liver Cirrhosis	Anticancer (Breast, Ovary, Liver, Cervix)	[292–295]
83.	<i>Spondias pinnata</i> <b>Family:</b> Anacardiaceae	English: Hog plum, Indian Hog plum Malayalam: Ambazham, Mampuli, Kattambazham	Aliphatic alcohols, Monoterpene hydrocarbon, α-Terpeneoil, furfural, Benzoic acid, Methyl salicylate, Iso prophyll myristinate, Limonene, Isophorone, n-Nonacosane	Whooping cough, Diarrhoea, Indigestion, Inflammation, Pain, Detoxification, Tumours.	Anticancer (Glioblastoma)	[296–298]
84.	<i>Strobilanthes ciliatus</i> (Nees) Bremek. <b>Family:</b> Acanthaceae	English: Lesser Kurinji Malayalam: Cherukurinji, Karimkurinji	Triterpenoids, Betulin, Lupeol, Stigmasterol, Phenols, Flavones, Steroids, Glycosides, Tannins,	Inflammation, Pain, Diabetes, Immune disorders, Tumours, CNS disorders, Cancers	Anticancer (Cervical, Breast, Ovary)	[299–301]
85.	<i>Tabernaemontana divaricate</i> R. Br. <b>Family:</b> Apocynaceae	English: east India Rose bay Malayalam: Nandiyar vattom, Kattampale	Bis-indole alkaloids, 19,20, Dihydro-ervatanine-A, Alkaloids, Voacristine, Voacamine, Flavonoids, Diterpenoids, Phenolic acids, Vanillic acid, salicylic acid, Gentisic acid, Benzoic acid	Anti-asthmatic, Anti-epilepsy, Anti-diarrhoeal, Anti-tumour, Anti-leprotic, Anti-ulcer, Anti-emetic. Ailment of Eye infections, Arthralgia, Myalgia, Ecema, Fractures	Anticancer (Liver, Bladder, Breast)	[302–305]
86.	<i>Thunberiga fragrans</i> Roxb. <b>Family:</b> Acanthaceae	English: White Thunberiga Malayalam: Noorvan valli	Glycosides, Phenols, Sterol, Cis-9-Hexadecenol, Campesterol, Phytic acid,	Diabetes, Gout, Bloody dysentery, Inflammation, Tumours, Cancers	Anticancer (Colorectal, Cervical, Ovary)	[306–308]
87.	<i>Vanilla planifolia</i> <b>Family:</b> Orchidaceae	English: Vanila, Vanilla orchid Malayalam: Vanila	Essential oils: Vanillin, Naphthalene, caproic acid, Methyleneicosane, Trimethylacetophenone,	Carminative, Stimulant, Flavouring agent, Aphrodisiac, Anticancer. Hepato protective, Immune booster, Larvicidal, Antimalarial, Antispasmodic, Anti-dysmenorrhoea. Ailment of Skin disease	Anticancer (Breast, Skin, Liver)	[309–311]
88.	<i>Vateria indica</i> Linn. <b>Family:</b> Dipterocarpaceae	English: Indian copal tree, Piney varnish tree Malayalam: Pandam Payin, Vellappayin	Poly phenols, Azulenes, Epi-Catechin, Fisitinedol, Bergenin, Pzelechin, tri terpene hydro carbons, ketones, Oleo resins, Alcohols	Diarrhoea, Dysentery, Bronchitis, Piles, Skin eruptions, Gonorrhoea, Syphilis, Tumours, Microbial infections, Helminthiasis, Cancer, Ulcer	Anticancer (Sarcoma, Breast)	[312–314]
89.	<i>Veronica cinerea</i> <b>Family:</b> Asteraceae/Compositae	English: Ash coloured fleabane, purple fleabane Malayalam: Pirina, Puvankurunal	Flavonoids, Sesquiterpene lactones, Terpenoids, Sterols, terpenoid, Lupeol acetate	Anti-asthmatic, Anti-arthritis, Anti-rheumatism, Anti-inflammatory, Anticancer, Anti-diabetic, Anti-viral, Treatment of Urinary calculi, Cough, Malaria.	Anticancer (Breast, Colorectum, Lung)	[315–318]
90.	<i>Vitex negundo</i> <b>Family:</b> Lamiaceae	English: Chaste tree Malayalam: Indrani, Karunochi	Flavonoids, Phenolic compounds, Artemetin, Penduletin, Vitexicarpin, Tannins, Glycosides, Alkaloids	Leukoderma, Skin diseases, Spleen enlargement, Inflammations	Anticancer (Liver, Breast, Colorectum)	[319–322]

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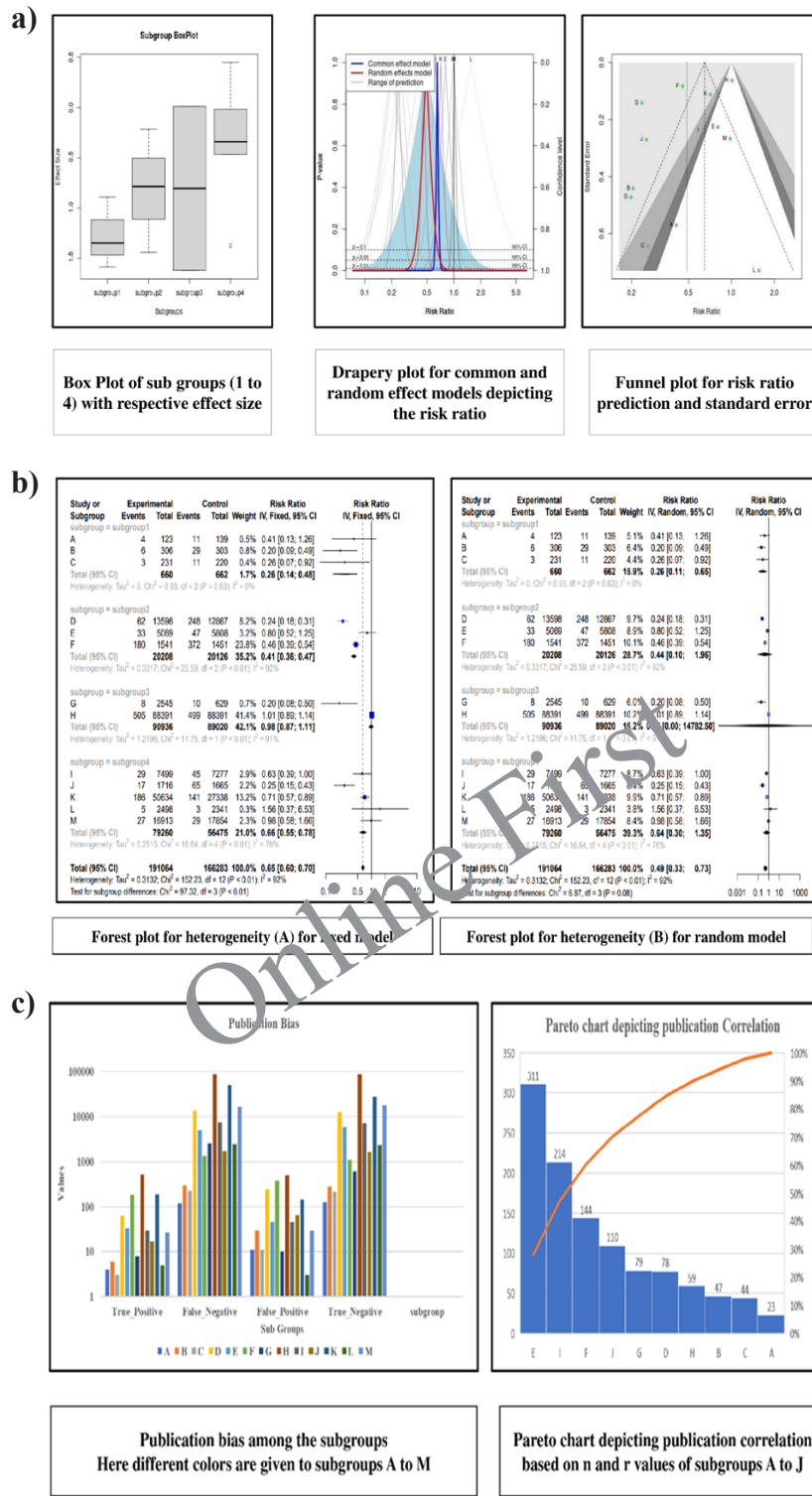
Sr. No	Botanical name & family	Malayalam names and common names	Phyto constituents	Folklore/Tribal uses	Uses given by <i>in-vitro</i> , <i>in-vivo</i> studies	References
91.	<i>Withania somnifera</i> <b>Family:</b> Solanaceae.	English: Winter cherry Malayalam: Amukkuram	Steroidal lactones, Steroids, flavonoids, Alkaloids, Phenols, saponins, Withanolides, Withaferin-A, Somniferine, Somnine, Withamine, Withamine, Somniferinine	Benign tumours, Inflammation, Arthritis, Diabetes, Depression, Fungal and Bacterial infections, Hepatic disorders, Ulcer, Alzheimer's disease, Cancers	Anticancer (Breast, Lung, Liver, Colorectal, Intestine, Cervix, Glioblastoma, Glioma, Leukaemia)	[323–326]
92.	<i>Woodfordia fruticosa</i> Kurz. <b>Family:</b> Lythraceae	English: Fire flame bush Malayalam: Thathiri poovu, Thathiri	Poly phenols, Anthraquinones, Flavonoids, Triterpenoids, Glycosides, Betulin, Betulinic acid, Lupeol, Ursolic acid, Oleanolic acid	Homeothermia, Dysentery, Ulcers, Fever, Boils, Inflammation, Hepatic disorders, cardiac diseases, Microbial infections	Anticancer (Liver)	[327–329]
93.	<i>Wrightia tinctoria</i> Roxb. (R.Br.) <b>Family:</b> Apocynaceae	English: Pala indigo, Sweet indrajao Malayalam: Aiyappala, Adukomba, Neelappala	Alkaloids, terpenoids, Flavonoids, Phenols, Steroids, Betulin, Lupeol, $\alpha$ -Amyrin, $\beta$ -Amyrin, Campesterol, Tocopherol, Squalene, Lupenone	Cancers, Bacterial infections, Scabies, Psoriasis, Skin infections	Anticancer (Breast, Liver)	[330–332]
94.	<i>Zingiber officinale</i> Var. <b>Family:</b> Zingiberaceae	English: Ginger, Canton ginger, Spice ginger Malayalam: Andrakam, Chukku, Inchi	Phenolic compounds, Gingerol, Shogaol, Paradol, Terpenes, $\alpha$ -Terpineol, $\alpha$ -Terpinene, Diaryl heptanoids, Volatile oils	Inflammation, Nerve disorders, Cough, Cold, Haemorrhoids, Edema, Indigestion, osteoarthritis, Chronic fever, Rheumatoid arthritis Useful as Carminative, Anti-tumour, Immuno modulatory, Anticancer, Anti-microbial, Larvicidal	Anticancer (Colon, Pancreas, Gastro intestinal, Prostate, Breast)	[333–339]
95.	<i>Ziziphus mauritiana</i> <b>Family:</b> Rhamnaceae	English: Jujube tree Malayalam: Badari, Lanthapazam	Phenolic compounds, Caffeic acid, Ferulic acid, P-Coumaric acid, 4-Hydroxy-benzoic acid	Anti-asthma, Anti-allergy, Anti-depressant, Analgesic, Anti-tumour, Anti-ulcer	Anticancer (Breast, Lung, Ovary, Cervix, Colorectum)	[340–342]

d.f.:3,  $p = 0.0763$ ), a potential publication bias was assessed through Egger's regression, yielding a nonsignificant result ( $t = -1.40$ , d.f.: 11,  $p = 0.1887$ ). Subgroup meta-regression was carried out, indicating that the intercept was  $-1.2958$  [standard error (SE): 0.4565,  $t$ -value:  $-2.8384$ , d.f.: 9,  $p = 0.0195$ ], subgroup2 had a coefficient of 0.4650 (SE:0.5725,  $t$ -value: 0.8123, d.f.: 9,  $p = 0.4376$ ), subgroup3 had a coefficient of 0.6880 (SE: 0.6462,  $t$ -value: 1.0646, d.f.: 9,  $p = 0.3148$ ), and subgroup 4 had a coefficient of 0.8558 (SE: 0.5428,  $t$ -value: 1.5766, d.f.: 9,  $p = 0.1493$ ). This comprehensive analysis underscores the complex interplay of factors influencing the observed outcomes. The relevant data are listed in [Supplementary Tables S1–S6](#). The graphical visualization of the stated data as box plots, drapery plots, funnel plots, and forest plots is depicted in [Figure 3a](#) and [b](#). A need for increased sensitivity is indicated by subgroup 1, which displays apparent imbalances between true positives (ranging from 3 to 6) and false negatives (ranging from 119 to 300). From ranges 11 to 29, false positives exist with a control strategy. True negatives exhibit rather an evenly distributed dispersion. The greater true positives (ranging from 33 to 180) and significant false negatives (ranging from 1,361 to 13,536) in subgroup 2 suggest that recall has to be improved. In addition, noteworthy are false positives, which range from

47 to 372. Subgroup 3 has a balanced performance with low false positives and high true negatives, along with respectable true positives and false negatives (between 1,699 and 50,448) in subgroup 4, which highlights the need to improve sensitivity. True negatives and false positives can be controlled. Improved sensitivity in subgroups 1, 2, and 4 while preserving precision is necessary to maximize model performance. Already, subgroup 3 performs in a more even manner ([Fig. 3c](#)). The numerical values are categorized and illustrated in [Supplementary Table S7](#). The average " $n$ " value and average " $r$ " value for subgroup 1 are 38 and 0.44, respectively. Similarly, the " $n$ " and " $r$ " values of subgroup 2 are 144 and 0.18. The average " $n$ " for subgroup 3 is 115, while the average " $r$ " is 0.70. The data distribution is depicted as a Pareto chart ([Fig. 3c](#)), and the details are listed in [Supplementary Table S8](#).

## DISCUSSION

This review dives into 4,600 native plants in Kerala's botanical treasure trove, 900 of which have therapeutic promise. The districts of Wayanad and Kozhikode stand out since they are home to more than 180 medicinal plants, 95 of which may have anticancer qualities. India is a significant exporter of almost 960 medicinal herbs to different regions of the globe, with 178



**Figure 3.** (a). Box plot (effect size), Drapery (risk ratio), Funnel plot (standard error and risk ratio), (b). Forest plots for heterogeneity (A) fixed model, (B) random model, (c). Publication bias depicted as bar plot and publication correlation depicted as pareto chart.

plant species being traded for more than 100 metric tons. The global market has a significant demand for medicinal herbs such as barberry, senna, isabgol, chandan, long pepper, brahmi, kalmegh, satavari, madhunashini, ashwagandha, sankhpushpi,

kokum, and guggal, which are highly sought after. The Malabar Hill region, in particular, plays a crucial role, contributing more than 60% to the trade of medicinal plants [19]. Inspired by folklore origins, several drugs have been adapted for pilot

studies to address chronic conditions such as psoriasis, leprosy, HIV infections, cancer, arthritis, tuberculosis, and asthma [23]. Some of these drugs are currently in clinical use, while others are undergoing various stages of clinical trials. In a collaborative effort with India, the WHO established the “Global Centre for Traditional Medicine” in 2022, with a significant contribution of 250 million USD from the Indian government (gctm@who.int). This initiative aims to promote traditional medicine and explore its potential benefits further. In this study, 552 articles were carefully examined, and the results revealed a statistically significant relationship between specific plants and their anticancer potential. However, the studies’ notable variation highlights the complexity of this topic. Finally, Kerala’s plant diversity offers hope for both conventional and cutting-edge medicine.

## CONCLUSION

The study’s findings emphasized Kerala’s enormous potential for using its rich botanical resources, with an emphasis on the Kozhikode and Wayanad districts. There are 4,600 native species in the area, and 900 of them have plausible therapeutic benefits. The ongoing practice of Ayurveda, a science rooted in history, adds to this treasure. The examination of 552 articles along with the survey emphasized the complexity of this topic and the necessity for careful analysis. Hence, in the existing conditions, the exploration of more medicinal plants with extraordinary phytoconstituents for cancer therapy is crucial. In addition, it is imperative to focus on reinstating medicinal herbs that are on the verge of extinction, utilizing modern, sophisticated methods and tissue culture techniques. The selected region along with the entire Malabar Mountains, has an abundance of medicinal plants that remain unexplored or only partially studied. Therefore, scrutinizing these untapped medicinal plants is essential to addressing rare, chronic diseases, including cancer.

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The authors declare that there is no conflict of interest in this research.

## ETHICAL APPROVAL

This study does not involve experiments on animals or human subjects.

## DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

## USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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## DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the author(s) used Chat-GPT for writing assistance. After using this tool or service, the author(s) reviewed and edited the content as needed and took full responsibility for the content of the publication.

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**SUPPLEMENTARY MATERIALS****Supplementary Table S1.** RR for common effect and random effect models.

Model	RR	95%-CI	<i>p</i> -value
Common effect	0.6503	[0.6007; 0.7040]	<0.0001
Random effects	0.4894	[0.3301; 0.7257]	0.0019

**Supplementary Table S2.** Test of heterogeneity.

Measure	Value	95%-CI
Tau <sup>2</sup>	0.3132	[0.1197; 1.1115]
I <sup>2</sup>	92.1%	[88.3%; 94.7%]
H	3.56	[2.93; 4.34]

Here, *Q*: 152.23, d.f.: 12, *p*-value: < 0.0001.

**Supplementary Table S3.** Subgroup analysis (Common effects model).

Subgroup	<i>k</i>	RR	95%-CI
Subgroup 1	3	0.2644	[0.1449; 0.4825]
Subgroup 2	3	0.4118	[0.3602; 0.4708]
Subgroup 3	2	0.9836	[0.8704; 1.1115]
Subgroup 4	5	0.6563	[0.5519; 0.7805]

Here, test for subgroup differences (Common Effect Model): *Q* (Between groups): 97.32, d.f.: 3, *p*-value: <0.0001, *Q* (Within groups): 54.91, d.f.: 9, *p*-value: < 0.0001.

**Supplementary Table S4.** Subgroup analysis (Random effects model).

Subgroup	<i>k</i>	RR	95%-CI
Subgroup 1	3	0.2644	[0.1073; 0.6514]
Subgroup 2	3	0.4355	[0.0970; 1.9554]
Subgroup 3	2	0.4784	[0.0000; 14782.502]
Subgroup 4	5	0.6376	[0.3002; 1.3543]

Test for subgroup differences (Random Effects Model): *Q*: 6.87, d.f.: 3, *p*-value: 0.0763.

**Supplementary Table S5.** Publication bias analysis.

Test	<i>t</i> -value	df	<i>p</i> -value
Egger's regression	-1.40	11	0.1887

**Supplementary Table S6.** Meta regression analysis of subgroups.

Coefficient	Estimate	SE	<i>t</i> -value	df	<i>p</i> -value
Intcpt	-1.2958	0.4565	-2.8384	9	0.0195
Subgroupsubgroup 2	0.4650	0.5725	0.8123	9	0.4376
Subgroupsubgroup 3	0.6880	0.6462	1.0646	9	0.3148
Subgroupsubgroup 4	0.8558	0.5428	1.5766	9	0.1493

**Supplementary Table S7.** Publication bias analysis.

Study	True_ Positive	False_ Negative	False_ Positive	True_ Negative	Subgroup
A	4	119	11	128	Subgroup 1
B	6	300	29	274	Subgroup 1
C	3	228	11	209	Subgroup 1
D	62	13,536	248	12,619	Subgroup 2
E	33	5,036	47	5,761	Subgroup 2
F	180	1,361	372	1,079	Subgroup 2
G	8	2,537	10	619	Subgroup 3
H	505	87,886	499	87,892	Subgroup 3
I	29	7,470	45	7,232	Subgroup 4
J	17	1,699	65	1,600	Subgroup 4
K	186	30,448	141	27,197	Subgroup 4

**Supplementary Table S8.** Publication correlation analysis.

Study	<i>n</i>	<i>r</i>	Subgroup
A	23	0.33	Subgroup 1
B	47	0.44	Subgroup 1
C	44	0.55	Subgroup 1
D	78	0.22	Subgroup 2
E	311	0.11	Subgroup 2
F	144	0.23	Subgroup 2
G	79	0.88	Subgroup 3
H	59	0.66	Subgroup 3
I	214	0.55	Subgroup 3
J	110	0.73	Subgroup 3