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Cytotoxic plants from the Indian subcontinent: promising reservoir of anticancer agents

Vipendra Kumar Singh[1], Vikas Kumar Singh[2], Urmilesh Singh[2,3], Aditya A. Singh[4], Ved Prakash[5], Rashmi P. Sharma[6], Ankit Kumar Singh[7]

[1]Department of Biochemistry and Molecular Medicine, George Washington University, Washington, D.C., United States

[2]Department of Chemistry, Supaul College of Engineering, Supaul, Bihar, India

[3]Department of Botany, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh, India

[4]Department of Botany, University of Lucknow, Lucknow, Uttar Pradesh, India

[5]Zebrafish Research Laboratory, Department of Life Sciences, Parul Institute of Applied Sciences, Research and Development Cell, Parul University, Vadodara, Gujarat, India

[6]School of Life Sciences, Swami Ramanand Teerth Marathwada University, Nanded, Maharashtra, India

[7]University Department of Botany, Lalit Narayan Mithila University, Darbhanga, Bihar, India

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Abstract

In recent decades, cancer has remained the leading cause of mortality globally. The increasing incidence of cancer and the rise in the mortality rate pose substantial challenges for effective management strategies. Currently, several chemotherapeutic agents, including cisplatin, doxorubicin, and gemcitabine, are routinely used as frontline treatment options for cancer. Although these agents exhibit initial efficacy during the early stages of tumor development, their widespread application in clinical settings is significantly limited by their lack of selectivity, high cost, and toxicity to normal tissues. Phytochemicals have been recognized as promising alternatives to address these limitations. Their remarkable anticancer efficacy is attributed to various distinct mechanisms. Additionally, they are cost-effective and relatively nontoxic, which represent a significant advantage over conventional treatment approaches. To date, only a few phytochemicals, including resveratrol, gingerol, curcumin, and epigallocatechin-3-gallate, have progressed to clinical application. However, the current array of these phytochemicals is inadequate to meet the increasing demand for novel medicines against cancer. Thus, ethnopharmacology has emerged as a promising avenue for discovering and developing novel anticancer drugs. Medicinal plants from the Indian subcontinent are a valuable resource of diverse phytochemicals, which have traditionally been used for treating several health conditions and diseases. However, the evaluation of potential of these phytochemicals as anticancer medicines has largely been limited to preliminary screening. Therefore, this review specifically explores potent anticancer plants native to the Indian subcontinent that are yet to undergo rigorous clinical validation. It includes 60 plants from 44 families and details their therapeutic targets in various malignant cancers. It also discusses the major challenges and potential prospects for their effective application in cancer treatment.

Key words: Indian subcontinent, cancer, anticancer drugs, medicinal plants, phytochemicals

Introduction

In recent decades, cancer has consistently ranked among the leading causes of death worldwide (Sung et al. 2020). The GLOBOCAN database (2020) reported 10 million cancer-related deaths and 19.3 million new cases of cancer globally, with a predicted increase to 28.4 million new cases in 2040 (Deo et al. 2022). Various emerging and complex challenges are contributing

Corresponding authors: Ankit Kumar Singh, University Department of Botany, Lalit Narayan Mithila University, Darbhanga, Bihar, India, e-mail: ankitbhu30@gmail.com; Rashmi P. Sharma, School of Life Sciences, Swami Ramanand Teerth Marathwada University, Nanded, Maharashtra, India, e-mail: sharmarashmi.p@gmail.com

to the cumulative risk of cancer and its related mortality worldwide. These include unhealthy lifestyle choices, exposure to pesticides through the food chain, premature aging, rapid population growth, and the emergence of new air pollutants, which significantly impact low socio-economic countries such as India (Cavalier et al. 2023). The alarming projection from the National Cancer Registry Programme 2020 highlights a critical public health crisis in India, with an estimated 2.08 million people expected to be diagnosed with cancer by 2040, marking an increase of 57.5% from the figures reported in 2020 (Ferlay et al. 2020). Additionally, in terms of cancer-related mortality, India ranks third, following China and the United States. The data also revealed that cancer remains the predominant cause of mortality in the 65+ age group globally, whereas it mostly affects the 40–64 age group in India (Ferlay et al. 2020; Sathishkumar et al. 2022). Many studies reported that the aggressive nature of cancer and its limited treatment choices, including radiation, chemotherapy, and surgery, have led to unsatisfactory outcomes (Anand et al. 2023). Currently, several chemotherapeutic agents, including anti-tubulin agents (taxanes), DNA interacting agents (such as doxorubicin and cisplatin), anti-metabolites such as methotrexate, hormones, and various other molecular targeting agents, are predominantly used in cancer treatment (Choudhari et al. 2020). However, resistance to chemotherapeutic agents, their severe side effects, tumor recurrence, and off-target efficiency pose significant challenges, which can negatively impact public health and socio-economic living standards (Wang et al. 2019). Thus, exploring new anticancer agents, particularly those derived from medicinal plants, is a promising avenue in cancer research because of their excellent therapeutic properties and minimal side effects (Tomar et al. 2024).

Phytochemicals, defined as compounds primarily derived from plants, are known for their therapeutic potential since ancient times (Dehelean et al. 2021). The unique characteristics of phytochemical compounds mostly rely on the diverse genetic constituents of plants and the distinct geographical environments in which they are grown (Moore et al. 2014). Moreover, several studies have reported that these phytochemicals can vary in chemical profile or quantity, even when extracted from the same plant species. Consequently, the development of new herbal medicines for cancer treatment has become a focus in all geographic areas (Lautié et al. 2020). To date, approximately 50,000 to 80,000 plant species have been explored for their potential medicinal applications (Chen et al. 2016). In this context, the National Cancer Institute (NCI) has undertaken substantial efforts to screen around 35,000 plant species to assess their viability for cancer treatment. The extensive screening yielded only 3,000 plant species that exhibited consistent anticancer activity (Desai et al. 2008). However, thus far, there are nearly 140 clinically approved antitumor drugs available for treating over 200 types of cancer. According to previous reports, almost 60% of widely prescribed plant-based anticancer medicines are derived from common sources, such as vincristine and vinblastine from *Catharanthus roseus*, paclitaxel from *Taxus brevifolia*, podophyllotoxin from *Podophyllum hexandrum*, and camptothecin from *Camptotheca acuminata* (Mazumder et al. 2020). Therefore, exploring untapped plant resources from various geographic locations for new anticancer compounds has been encouraged.

The Indian subcontinent is known for its biodiversity, encompassing four hotspots: the Indo-Burma region, the Western Ghats, the Himalayas, and the Sundalands. These regions host a rich array of medicinal plants, which have potential for contributing to the discovery of new anticancer agents (Regassa et al. 2022). Thus, the development of new anticancer therapeutics derived from medicinal plants, particularly those from the Indian subcontinent, has generated noteworthy interest within the field of contemporary cancer research. Despite the presence of several rich biodiversity hot spots and a blend of environments, phytochemical research in India remains in a nascent stage. Although various research groups are making valuable contributions to this field, there has been advancement only in few directions (Singh et al. 2023; Banerjee et al. 2016). Existing research is mostly conducted through *in vitro* experiments rather than through *in vivo* experiments. Therefore, extensive investigations into the pharmacokinetics and biodistribution of these molecules are necessary for validating their potential for cancer treatment.

Plant-derived drugs: the Indian research scenario

Ancient scripture Ayurveda highlights the importance of plants as a prominent source of effective remedies for both acute and chronic diseases (Raghuvanshi et al. 2021). Additionally, the entire plant or its

specific components, such as roots, stems, leaves, flowers, fruits, and seeds, are utilized in various forms, for example, dried powder, decoction, and herbal pastes, to treat a range of conditions, including infectious diseases, diabetes, neurological disorders, skin-related issues, and other health problems (Trivedi et al. 2024). This knowledge is extensively covered in textbooks such as *Ayurveda Materia Medica* and *Indian Materia Medica* (Gajarmal et al. 2020).

The Indian subcontinent has historically been a cultural and economic hub because of its favorable geographical characteristics. This has led to a rich heritage of plant-based traditional therapies, especially those rooted in Ayurveda and folk medicine (Jaiswal and Williams 2017). This proficiency arises from various factors, such as spiritual beliefs, easy accessibility, historical and cultural beliefs, and prevailing socioeconomic conditions. These practices thrived in remote areas due to a lack of modern medical facilities (Ravishankar and Shukla 2007). However, the practice of Ayurveda declined significantly during the medieval era due to political instability, external invasions, and the British colonial administration that focused on promoting allopathy through financial support (Jaiswal and Williams 2017). A renewed interest in Ayurveda emerged during India's independence movement, prompting the government to implemente several key initiatives to protect these traditional medicine systems (Jaiswal and Williams 2017). In the mid-20th century, research in plant-based therapeutics led to the discovery of vinblastine, vincristine, and podophyllotoxins, prompting the NCI to launch a plant collection program focused on temperate regions in 1960 (Kinghorn et al. 2016; Sak 2022). This initiative resulted in the discovery of various plant-derived compounds, including topotecan, irinotecan, navelbine, teniposide, etoposide, paclitaxel, and docetaxel, which are clinically approved as anticancer medications (Newman and Cragg 2020). Many herbs have been investigated for their ability to mitigate the side effects of cancer treatments and enhance immunity. These natural compounds often inhibit cancer cell growth by influencing cell proliferation, cell cycle regulation, apoptosis, angiogenesis, and metastasis (Dehelean et al. 2021). The commercial production of plant-based drugs has a slow pace of development with limited financial incentives, which hinders its progress. For instance, the development of effective clinical agents from camptothecins and taxanes spanned approximately 30 years, leading to a decline in pharmaceutical research interest (Li et al. 2017). However, the situation has changed significantly with the discovery of several new phytochemicals such as artemisinin, lupeol, curcumin, epigallocatechin-3-gallate, gingerol, resveratrol, and quercetin. Presently, these phytochemicals have reached the clinical application stage (Mazumder et al. 2020; Chandra et al. 2023). In 2015, the discovery of an artemisinin compound renewed hope regarding the potential of plant components to yield novel pharmaceutical drugs (Su and Miller 2015). A recent study showed significant progress in the past few years by examining new patents related to various polyphenols with anticancer properties (Gupta et al. 2023). Many plants used in ancient medicine have increasingly become an integral part of the modern healthcare system. Consequently, this traditional knowledge of medicinal plants has evolved into a highly profitable industry, with estimates suggesting that the global demand for therapeutic plants might reach $5 trillion by 2050 (Koul and Koul 2019). The Indian subcontinent is known for its safe and effective ethnomedical research practices (Shi et al. 2021). Ancient remedies were developed based on practical experience rather than in-depth scientific understanding of their effective ingredients (Pandey et al. 2013). Recently, Indian research groups have focused on exploring the anticancer potential of numerous plants, primarily through plant extracts rather than investigating isolated compounds (Reddy et al. 2023). Thus, this review aims to present information regarding cytotoxic plants from the Indian subcontinent, highlighting preclinical reports on their *in vitro* activity and tests on animal models for various cancers (Figure 1).

Potential cytotoxic plants from the Indian subcontinent

Ayurveda, the oldest medical system in India, continues to exert substantial influence on current medical practices and has contributed significantly to advancements in global healthcare (Fatima et al. 2021). Presently, the most commonly prescribed medications such as aspirin, morphine, digitoxin, artemisinin, and quinine are mainly derived from ethnomedicine practices. While numerous Indian plants are noted for their remarkable therapeutic benefits, their cytotoxic properties have often overlooked (Prasathkumar et al. 2021).

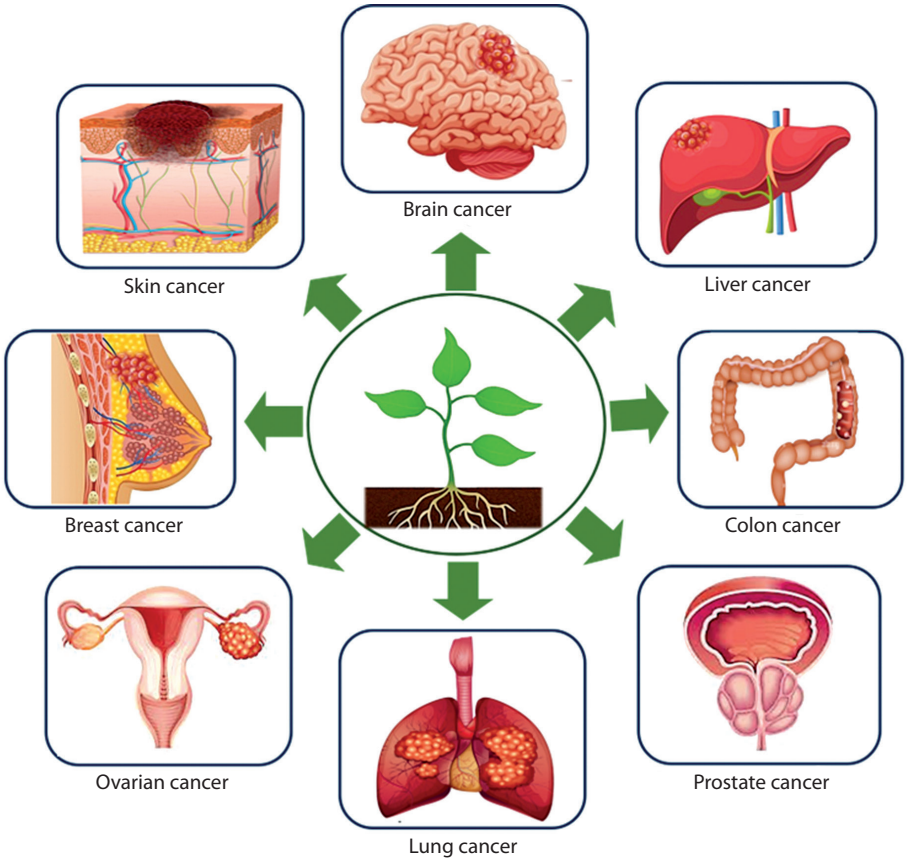

Figure 1. Cytotoxic plants showed anticancer potential in many types of cancers

Nevertheless, vital knowledge about Indian cytotoxic plants is preserved in sacred texts, awaiting further discovery. A narrow focus on known anticancer plants limits our understanding of less-studied species. Thus, this review examines lesser-known plants for their potential anticancer compounds. Some of the significant plant-based bioactive compounds with anticancer potential are summarized in Supplementary Table 1, with their possible effects illustrated in Figure 2 and succinctly reviewed below.

Abrus precatorius L.

Abrus precatorius L. is a tropical medicinal plant in the *Fabaceae* family. Generally, its seeds, roots, and leaves are used to treat various disorders such as parasitic worms, diarrhea, depression, cataract, allergies, cancer, and infertility. Recent studies have shown that its bioactive components, tannic acid and rutin, exhibit promising anticancer activity against cervical carcinoma Hep-2C and HeLa cells and act as cyclooxygenase-2 inhibitors (Kaur et al. 2024). Isoflavanquinones derived from the roots prevent inflammation by promoting phagocytosis and inhibiting the expression of the cytokine tumor necrosis factor-alpha (TNF-α). Additionally, abruquinones M and N exhibited cytotoxic effects against the human colorectal adenocarcinoma (Caco-2) and human tongue squamous cell carcinoma (CAL-27) cancer cell lines, with abruquinone M also suppressing the proliferation of the human non-small cell lung cancer cell line (NCI-H460) (Okoro et al. 2021).

Adenanthera pavonina L.

Adenanthera pavonine possesses several therapeutic properties, including astringent, antioxidant, anti-inflammatory, and anticancer effects. It is used to treat gout, rheumatism, diarrhea, and hypertension (Krishnan et al. 2022). A previous study revealed that its seeds and leaf extracts are effective against various pathogens and cancer cells (Chauhan et al. 2015). Another study showed that the chloroform extract of the leaves significantly inhibited the growth of MCF-7 human breast adenocarcinoma cells (Sophy et al. 2016). Furthermore, Araujo et al. (2019) noted that enzymatic treatment with cellulase and protease enhanced the antiproliferative

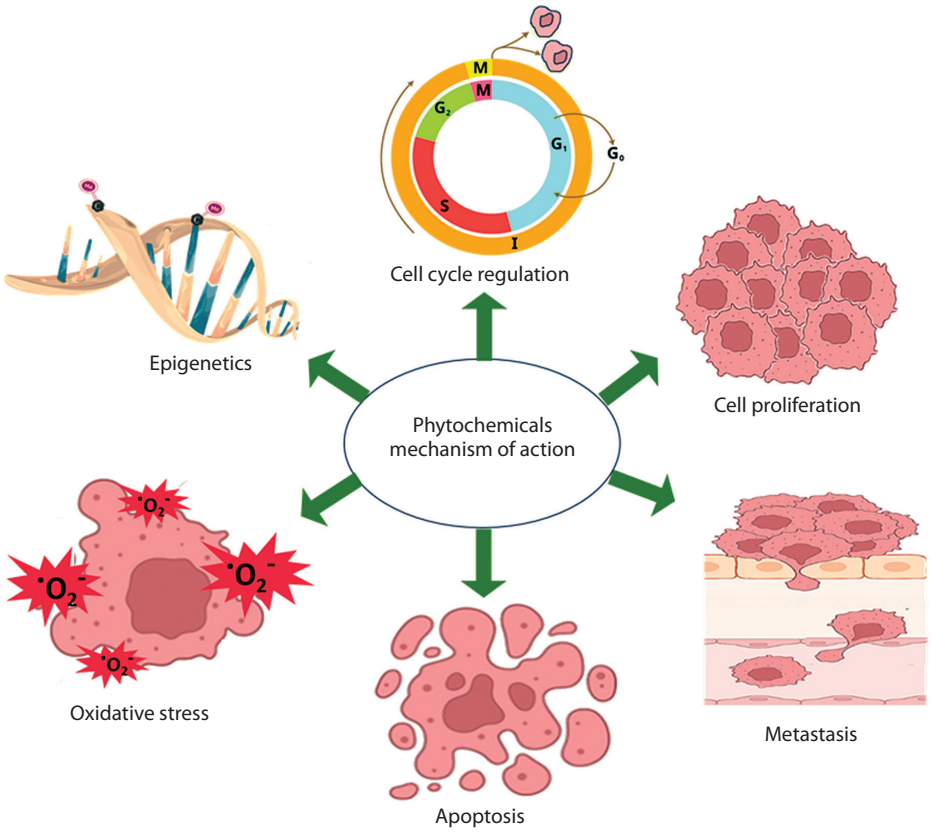

Figure 2. Phytochemicals and possible mode of action

effect of this plant extract against 786-O human renal carcinoma and PC-3 human prostate cancer cell lines.

Aloe vera L. Burm.f.

The anticancer activity of the herbal plant *Aloe vera* was assessed against the human hepatocellular carcinoma cell line Hep-G2. The results revealed a dose-dependent repression of cancer cells at the IC_{50} value of 10.5 μg/ml. This plant showed cytotoxic activity by initiating Hep-G2 cell apoptosis through reduced B-cell lymphoma 2 (Bcl-2) and enhanced p53 expression (Shalabi et al. 2015). Further studies indicate that aloin and emodin are effective anticancer agents present in this plant. Aloin inhibits growth and angiogenesis in cancer cells, while emodin exhibits antiproliferative effects (Radha and Laxmipriya 2015).

Annona muricata L.

Annona muricata, commonly known as Graviola, contains acetogenins in its seeds, leaves, and fruits, which block adenosine triphosphate synthesis and inhibit the transport of anticancer drugs outside the cell, thereby enhancing the effectiveness of chemotherapy. Previous studies indicate that acetogenins are effective against multidrug-resistant cancers. *In vitro* studies have revealed that the leaf extract of *A. muricata* exhibits antiproliferative effects on breast cancer cell lines, including malondialdehyde (MDA), SK-BR-3, and EACC (Gavamukulya et al. 2014) and the prostate cancer cell line BPH-1 by inducing apoptosis and reducing prostate size (Asare et al. 2015). The oral administration of an ethanolic extract of *A. muricata* to BALB/c mice implanted with 4T1 breast cancer cells demonstrated its anticancer efficacy, thus supporting its use in traditional Mexican medicine (Merlín-Lucas et al. 2021).

Annona squamosa L.

The *Annona squamosa* plant belongs to the family *Annonaceae*; it is extensively used for treat microbial infections, inflammation, and cancer (Shehata et al. 2021). Recent studies indicate that extracts from its seeds, peel, and pulp show significant anticancer efficacy against diverse cancer cell lines such as MCF-7, HepG-2, Caco-2, and PC3 (Shehata et al. 2021). The seed extract

of this plant demonstrated strong cytotoxicity and growth inhibition of various cancer cell lines, including asoral (KB), lung (A549), chronic myeloid leukemia (K-562), and MCF-7, without impairing normal lymphocytes (Vikas et al. 2019).

***Arbutus andrachne* L.**

Arbutus andrachne belongs to the *Ericaceae* family. Almost all parts of the *A. andrachne* plant, including roots, leaves, and fruits, have ethnomedical applications. The aerial parts of this plant exhibit strong anticancer effects on various cancer cell lines, including T-47D, MCF-7, HRT-18, Caco-2, A375.S2, and WM1361A. Substantial anticancer activity has been reported against MCF-7, A375.S2, and HRT-18 cell lines, whereas moderate cytotoxic effects were detected against Caco-2, T-47D, and WM1361A cell lines (Abu-rish et al. 2016).

***Aristolochia ringens* Vahl**

This plant, also known as *Howardia ringens*, is traditionally used for treating digestive issues, rheumatoid arthritis, piles, insomnia, and edema (Aigbe et al. 2019). The root extract of *A. ringens* exhibited anticancer activities against A431, A549, PC-3, HeLa, and the human acute monocytic leukemia cell line THP-1 (Akindele et al. 2015). *A. ringens* dose-dependently significantly inhibited tumor growth in S180 ascites and S180 solid tumor models. Moreover, it improved the average survival duration in *in vivo* models (L1210 lymphoid leukemia cells) (Daoudi et al. 2013).

***Asplenium nidus* L.**

Asplenium nidus, a medicinal fern, is a member of the *Aspleniaceae* family. A recent study extracted two bioactive flavonoids from *A. nidus*, including quercetin-7-O-rutinoside and gliricidin-7-O-hexoside. These compounds exhibited excellent anticancer effects against HeLa and Hep-G2 cells (Jarial et al. 2018).

***Azadirachta indica* A. Juss.**

Azadirachta indica, belonging to the *Meliaceae* family, is primarily distributed throughout the Indian subcontinent and contains several active compounds, including nimbin, nimbidol, nimbidin, and nimbolide. It has around 40 active limonoids compounds, which exhibit antiulcer, antimicrobial, antiviral, and anticancer properties (Guchhait et al. 2022). Takagi et al. (2014) purified 17 limonoid compounds and tested their activity against breast (SK-BR-3), lung (A549), stomach (AZ-521), and leukemia (HL-60) cancer cell lines; of these, 7 compounds showed significant cytotoxic activity. Nimonol exhibits cytotoxicity by inducing apoptosis (Takagi et al. 2014). Kitdamrongtham et al. (2014) isolated flavonoids from *A. indica* and reported that these compounds showed cytotoxicity against HL-60, SK-BR-3, AZ-521, and A549 cancer cell lines. Nimbolide inhibited cancer cell autophagy and promoted apoptosis through the phosphoinositide 3-kinase (PI3K)/Akt/glycogen synthase kinase-3 beta (GSK-3β) signaling pathway (Kitdamrongtham et al. 2014). Kashif et al. (2019) found that nimbolide-treated cancer cells (A549, PC-3, and DU-145) exhibited a significantly higher number of apoptotic and necrotic cells compared to untreated cells, with no apparent effects on normal cells (NIH/3T3 and CCD-18Co). Nimbolide-treated cancer cells showed high expression of caspases 3, 8, and 9. Additionally**,** ethanolic foliar extract suppresses the growth of cancer cells, particularly breast and cervical cancer cells, through apoptosis (Kashif et al. 2019).

***Barleria grandiflora* Dalzell**

Barleria grandiflora belongs to the *Acanthaceae* family. It shows cytotoxic effects on Dalton's lymphoma ascites (DLA) and Vero cell lines. Manglani et al. (2014) demonstrated that the administration of *B. grandiflora* leaf extract to mice bearing DLA tumors reduced ascitic fluid and suppressed tumor growth, ultimately increasing the longevity of mice. A significant adverse effect associated with cancer chemotherapy often causes myelosuppression, leading to anemia. However, treatment with *B. grandiflora* leaf extract increased the hemoglobin level and red blood cell count and decreased white blood cell count, highlighting its anticancer potential (Manglani et al. 2014).

***Berberis aristata* DC.**

This shrub is also commonly known as Daru haldi or tree turmeric. The root extract of *Berberis aristata* showed cytotoxic activity toward A2780 (ovary), Hop-62 (lung), and DWD (oral) cancer cell lines (Gaidhani et al. 2013). Ethanol extract of *B. aristata* stem bark reduced weight gain due to tumor cell proliferation and increased the viability of Ehrlich ascites carcinoma (EAC)-bearing mice as compared to cisplatin reference

(Pai et al. 2012). A recent study revealed that the root extract of this plant contains three important alkaloids, namely thalifendine, jatrorrhizine, and berberrubine, and exhibits significant antioxidant and antiproliferative effects on MCF-7. The docking analysis also confirmed that these alkaloids target the epidermal growth factor receptor (EGFR) of breast cancer cells (Kumari 2022).

***Biancaea sappan* L. Tod**

Biancaea sappan, commonly known as sappan wood or Indian redwood, is a flowering tree. Its ethyl acetate extract contains brazilin A compounds, which inhibit tumor cell growth by causing DNA strand scission (Bukke et al. 2018). Leaf and heartwood extracts of *B. sappan* were evaluated for significant anticancer efficacy against MCF-7 and A549 cells. Additionally, a docking analysis established that brazilin A acts by inhibiting the anti-apoptotic gene *BCL2* (Widodo et al. 2022).

***Bidens pilosa* L.**

Bidens pilosa is native to South America and is frequently used in ancient remedies worldwide, particularly in herbal teas for various ailments, including inflammation, diabetes, pharyngitis, enteritis, and bacillary dysentery. Its hydroalcoholic root preparations are utilized for treating malaria and tumors in the Amazon and other southern Brazilian regions (Singh et al. 2017a). *B. pilosa* extracts demonstrate several beneficial effects such as anti-inflammatory, immunosuppressive, chemopreventive, hepatoprotective, antimalarial, antimicrobial, and anticancer effects (Shen et al. 2018). Specific isolated compounds, for example, phenyl-1,3,5-heptatriyne, have been identified for their anticancer and antimalarial effects. Notably, petroleum ether extracts of this plant show cytotoxic activity against A549 cells (Shen et al. 2018). Furthermore, tris (2,4-di-tert-butylphenyl) derived from this plant extract exhibited promising cytotoxicity toward A549, HeLa, and Hep-G2 cell lines. *In vivo* confirmation of these findings was obtained using *Artemia salina*, C*aenorhabditis elegans,* and *Danio rerio* (Zahara et al. 2022). However, despite these observations, more research is required to fully understand the antitumor efficiency and active compounds of *B. pilosa.*

***Calligonum comosum* L'Hér**

Calligonum comosum is a leafless perennial shrub that produces several phytoconstituents, including phenolics, flavonoids, alkaloids, and essential oils. *C. comosum* extract showed cytotoxicity toward Hep-G2 cells at an IC_{50} value of 9.60 μg/ml (Shalabi et al. 2015). It contains major phytoconstituents such as kaempferol, catechin, and derivatives of these compounds, which enhance cytotoxicity by inducing apoptosis. It also decreases Bcl-2 protein expression by increasing *TP53* gene expression (Shalabi et al. 2015; Alehaideb et al. 2020).

Carissa carandas

Carissa carandas, known as karonda in Asia, belongs to the *Apocynaceae* family and exhibits excellent antimicrobial, antioxidant, and anti-inflammatory potential (Saeed et al. 2024). Previous studies have indicated that its leaves as well as fully ripe and unripe fruits show significant cytotoxic effects against various cancers, including liver, lung, breast, cervical, bone, and ovarian cancers (Mishra et al. 2024). Bano et al. (2022) revealed three potent anticancer agents derived from the fresh leaves of this plant: uvaol, 23-hydroxy ursolic acid, and 27-O-Z-p-coumaroyl ursolic acid, which showed anticancer effects on NCI-H460 cancer cells. Additionally, carissic acid derived from *C. carandas* fruits showed potent anticancer acativity against HT-29 (colon), MCF-7, and A549 cancer cells by inducing apoptosis and inhibiting cell proliferation (Kour et al. 2024).

***Cedrus deodara* (Roxb. ex D. Don) G. Don**

Cedrus deodara is an evergreen coniferous tree known by its common name, Deodar cedar or Himalayan deodar or Himalayan cedar. Total lignans from *C. deodara* (CTL) needles were extracted and analyzed for anticancer activity against A549 cells. CTL exerted cytotoxic effects by inducing apoptosis (Shi et al. 2019). *C. deodara* bark extract also show cytotoxic effects on MCF-7 cells (Kumar et al. 2021). Furthermore, this plant extract demonstrated significant cytotoxicity against PC-3, A2780 (ovary), and Mia PaCa-2 cancer cell lines (Gaidhani et al. 2013).

***Cenchrus ciliaris* L.**

Cenchrus ciliaris is a herbaceous grass known by its common name, dhaman/anjan grass. Both aerial and root extract of *C. ciliaris* show cytotoxicity against Hep-G2, A549, MCF-7, and HeLa cells as well as against colon cell lines HCT-116 and Caco-2, with the highest efficacy toward Hep-G2 cells (Alothman et al. 2018).

***Centaurea antiochia* Boiss**

Centaurea antiochia is classified under the *Asteraceae* family (Bona 2013). Certain *Centaurea* species, such as *C. adjarica*, *C. bracteata*, *C. cataonica*, *C. cynaroides*, *C. dealbata*, *C. indurata*, *C. macrocephala*, *C. melitensis*, *C. nigrescens*, and *C. ruthenica*, have been documented to exhibit anti-inflammatory effects (Csupor et al. 2013). *C. antiochia* extract shows a dose-dependent anticancer effects on HeLa cells (Ozcan et al. 2016).

***Cordia dichotoma* G. Forst**

In India, *Cordia dichotoma* is used by various ethnic groups for its medicinal properties, including anticancer, astringent, antihelmintic, analgesic, antimicrobial, hepatoprotective, and diuretic properties (Raghuvanshi et al. 2022). Hussain et al. (2020) demonstrated the antitumor potential of *C. dichotoma* extract on EAC in Swiss albino mice (Hussain et al. 2020). Raina et al. (2022) reported its cytotoxic effects on several cancer cell lines, including SH-SY5Y, N2A, U-251, MCF-7, MDA-MB-231, A549, SW-620, HCT-116, MIA PaCa-2, and PANC-1, which originate from central nervous system, breast, lung, colon, and pancreas cancer cells; the authors reported that the extract contains compounds such as caffeic acid, cis-vaccenic acid, ferulic acid, gallic acid, palmitic acid, and vanillic acid. Usmani et al. (2018) found that the seed extract exhibited significant cytotoxicity against A549 and HeLa cells by inducing apoptosis in a dose-dependent manner from 25 to 250 μg/ml (Usmani et al. 2018).

***Cotinus coggygria* Scop.**

Cotinus coggygria (family *Anacardiaceae*) is found across southern Europe and the eastern region of Central Asia, stretching from the Himalayas to northern China. Indigenous populations use extracts of this plant owing to its antiseptic, anti-inflammatory, and hepatoprotective properties. This plant shows anticancer potential by inhibiting fibroblast activation protein α, with no adverse effects on normal human cell lines MCF-10A and BJ (Iliev et al. 2020). Flavonoids from *C. coggygria* inhibited cell proliferation with IC_{50} values of 93.57, 107.62, and 128.49 μg/ml against DBTRG-05MG, U251, and U87 glioblastoma cells, respectively. The anticancer effect was exerted through apoptosis induction by modulating the PI3K/Akt-extracellular signal-regulated kinase (ERK) cascade pathway. *In vivo* tests using xenograft animal models of glioblastoma revealed significant antitumor activity (Wang et al. 2015). Furthermore, at 48 h after treatment with the leaf extract, *HDAC5* and *HDAC7* mRNA transcripts were decreased in MCF-7 cells. Additionally, *HDAC3* gene expression was suppressed after 72 h of treatment (Gospodinova et al. 2017a); the extract exerted significant antiproliferative effects on MCF-7, T47D, HeLa, and ovarian (A2780) cancer cells, while sparing non-cancerous MCF-10 cells (Gospodinova et al. 2017b). Gospodinova et al. (2021) also observed that this plant extract induces S-phase cell cycle arrest and apoptosis; reduces colony formation; alleviates DNA damage; alters cellular thermodynamic properties; and decreases the expression of several transcripts such as *p300*, *MBD3*, *DNMT1*, and *DNMT3a*.

***Croton caudatus* Geiseler**

Croton caudatus is a scandent shrub widely utilized as an ethnomedicinal plant by the "Kuki" Indian tribe. A recent study revealed that the phytochemicals β-sitosterol, *(E)*-dodec-3-en-1-ol, and tricosan-1-ol, octacosanoic acid derived from the *C. caudatus* extract exhibited promising anticancer effects on A549 cells (Neipihoi et al. 2021). Another study demonstrated cytotoxic activity of the plant extract toward MCF-7, HeLa, and DL cell lines, with potential cytotoxicity specifically against DL cells (Rosangkima and Jagetia 2015).

***Curcuma longa* L. and *Curcuma zedoaria* (Christm.) Roscoe**

Curcuma longa and *C. zedoaria* belong to the *Zingiberaceae* family and offer significant health benefits. *C. longa* rhizome extract is extensively used in polyherbal medicine, particularly for cancer treatment. Furthermore, *C. zedoaria* rhizome extract demonstrated significant cytotoxicity toward DLA, EAC, and A549 cell lines through apoptosis induction (Shehna et al. 2022). Curcumin, a polyphenolic compound from *C. longa* rhizome, shows strong anticancer effects against Hep-G2 cells at 1000 μg/ml concentration (Srivastava and Srivastava 2015); it also inhibits glioblastoma cell proliferation by altering various pathways and promoting the expression of several tumor suppressor proteins, including p16, p21, p53, caspase-3, caspase-8, caspase-9, Egr-1, c-Jun N-terminal kinase, Elk-1, ERK, and Bax. Additionally, curcumin reduces the expression of the

proteins Bcl-2, Bcl-xL, mechanistic target of rapamycin (mTOR), p65, nuclear factor-kappa B (NF-κB), EGFR, retinoblastoma protein, cyclin D1, cell division cycle protein 2, cell myelocytomatosis oncogenes, and Akt (Vallianou et al. 2015). Curcumin also suppresses breast cancer growth by reducing NF-κB expression and potentially affecting the EGFR signaling pathway (Starok et al. 2015).

Cyclea peltata

Cyclea peltata is a plant belonging to the *Menispermaceae* family and is commonly found across south and east India. *C. peltata* root extract is widely utilized in traditional remedies to treat certain health conditions such as jaundice, stomach pain, and smallpox. The root of this plant contains various bioactive compounds, primarily alkaloids, including fangchinoline and several forms of tetrandrine. Tetrandrine is known for its antioxidant, anti-inflammatory, antifibrotic, immunosuppressive, plasma glucose lowering, free radical scavenging, and anticancer properties (Shine et al. 2014). A recent study reported that tetrandrine derived from this plant exerts prominent cytotoxic effects on MDA-MB-231 and PANC-1 cancer cell lines by activating programmed cell death through reactive oxygen species generation (Chandrashekar et al. 2019).

***Delphinium staphisagria* L.**

Delphinium staphisagria (Entele grass) belongs to the *Ranunculaceae* family; it reaches a height of 1.5 m and contains essential oils and alkaloids (Bousfiha et al. 2016). Akgun et al. (2022) assessed the cytotoxic effects of this plant extracts on A549, MCF-7, HT-29, and HeLa cells in a dose- and time-dependent manner. The authors also assessed the cellular toxicity of these extracts on healthy BEAS 2B cells. Moreover, cell death mechanisms, through apoptosis or necrosis, were evaluated using markers such as activated caspase 3, caspase-cleaved cytokeratin-18, and cleaved poly(ADP-ribose) polymerase by fluorescent imaging (Akgun et al. 2022).

***Dillenia pentagyna* Roxb.**

Screening of the ethanolic leaf extract of *Dillenia pentagyna* revealed its cytotoxic efficacy against U2OS, A549, and HeLa cells, with A549 cells exhibiting higher sensitivity toward the treatment. The mechanism of action involves the induction of the fundamental pathways of apoptosis (De et al. 2023). The bark and stem extract also showed cytotoxicity toward DL, MCF-7, and HeLa cells at concentrations of 25.8, 41.6, and 76.8 μg/ml, respectively. Animals treated with *D. petnagyna* extract exhibited a significant reduction in glutathione level, which is directly associated with tumor proliferation initiation through protein kinase C regulation. Therefore, *D. petnagyna* has been proven to be beneficial for cancer treatment as it induces glutathione depletion (Rosangkima et al. 2008).

Eclipta alba

Eclipta alba, also known as Bhringaraj in Ayurveda, belongs to the *Asteraceae* family and is recognized for its beneficial effects on liver and hair. Its well-documented medicinal properties include antimycotoxic, antibacterial, antioxidant, antihepatotoxic, anticancer, and rejuvenating effects. *E. alba* contains compounds such as coumestan, wedelolactone, and β-sitosterol, which contribute to liver protection and antioxidant and anticancer effects (Nelson et al. 2020; Arya et al. 2015). Furthermore, *E. alba* extracts exhibit dose-dependent anticancer activity against various cancer cell lines, including MCF-7, HCT-116, PC-3, and the renal cell carcinoma cell line RCC-45, with notably high efficacy observed in HCT-116 cells, without adverse effects on normal embryonic lung fibroblast WI-38 cells (Nelson et al. 2020; Arya et al. 2015). Significant anticancer effects were also observed against MDA-MB-231 and MCF-7 cells as well as in a 4T1 syngeneic mouse model through the activation of mitochondrial apoptotic pathways and significant upregulation Hsp60 localization (Arya et al. 2015). Recent studies have identified bioactive compounds in *E. alba*, including ecliptalbine, wedelolactone, ursolic acid, and β-amyrin. These compounds were evaluated with an *in silico* approach and showed a strong affinity for breast cancer target proteins such as matrix metalloproteinase, estrogen receptor, and progesterone receptor. This observation confirms their excellent antioxidant and anticancer efficacy against MDA-MB-231 cells (Mani et al. 2024).

***Euphorbia hirta* L.**

Euphorbia hirta, also known as Dugdhika in Ayurveda, shows antimicrobial, antimalarial, anti-inflammatory, antioxidant, and antidiarrheal effects and is often utilized

for treating gastrointestinal disorders, respiratory diseases, and conjunctivitis. The *E. hirta* plant includes various bioactive compounds such as β-amyrin; β-sitosterol; euphorbin A, B, C, and D; gallic acid; heptacosane; kaempferol; n-nonacosane; protocatechuic acid; quercetin; rutin; 1,3,4,6-tetra-O-galloyl-β-D-glucose; 2,4,6-tri-O-galloyl-β-D-glucose; and 24-methylene cycloartenol (Kumar et al. 2010). *E. hirta* plant extract shows promising antitumor effects on Hep-G2 cells by inhibiting cell proliferation and triggering apoptosis (Kalaivani et al. 2024). Another study investigated its dose-dependent anticancer effects using the EAC model in mice. The findings revealed that treatment with the *E. hirta* plant extract reduced both tumor volume and weight and increased lifespan when administered at a dose of 200 mg/kg (Sulaiman et al. 2023).

***Euphorbia tirucalli* L.**

Euphorbia tirucalli is a small tree whose latex contains bi- and tri-terpenoid, which exhibit anticancer activity. The leaf and stem extracts of this plant show cytotoxic effects on Mia PaCa-2 cells (pancreas cancer cell line) (Munro et al. 2015). Latex of *E. tirucalli* primarily contains the triterpenes euphol and tirucallol, which are mainly responsible for anticancer activity (De Souza et al. 2019). In another study, euphol exhibited significant anticancer effects on 73 cancer cell lines, originating from 15 different human tumor types, with IC_{50} values ranging from 1.4 to138.89 μM (Silva et al. 2018).

***Ficus beecheyana* Hook. & Am.**

Ficus beecheyana is a member of the *Moraceae* family. Its root extract inhibited the survival of HL-60 cells by triggering apoptosis. Moreover, it also increased the expression levels of Bad, Bak, and Bax while decreasing Bcl-2 protein levels. It exerts cytotoxic effects through Fas and mitochondrial-dependent pathways. Several bioactive phytochemicals, including caffeic acid, gallic acid, and rutin, are mainly responsible for this effect (Yen et al. 2018).

***Ficus carica* L.**

Ficus carica is a small deciduous tree with notable cytotoxic properties. Its leaf latex showed cytotoxicity toward MDA-MB-231 cells by reducing the expression of several proteins, including adenosine monophosphate-activated protein kinase alpha, cAMP response element-binding protein, ERK, and GSK-3α/β (Al Ghalban et al. 2021). Acetone-based leaf extract of *F. carica* exhibited promising cytotoxicity against Hep-G2 cells at 0.179 mg/ml concentration, while its latex containing ficin showed efficacy against HT-29 and PC-3 cancer cells (Mustafa et al. 2021). Additionally, *F. carica* leaf extract increased the expression of apoptosis-promoting genes and reduced cell mobility in MDA-MB-231 cells (Zhang et al. 2018).

Garcinia indica

Garcinia indica (family *Clusiaceae*), also known as kokum, is native to India and widely distributed in Africa, Asia, and western Polynesia. This plant is extensively utilized to treat dermatitis and diarrhea and improve digestion. *G. indica* contains several important bioactive compounds, including cyanidin-3-glucoside, cyanidin-3-sambubioside, garcinol, and hydroxy-citric acid (Lim et al. 2021). Garcinol derived from the fruit peel and leaves of *G. indica* exhibits remarkable anticancer properties against esophageal, gastric, colorectal, pancreatic, and liver cancers (Lim et al. 2021). Recent studies suggest that garcinol inhibits histone acetyltransferases and disrupts the regulation of microRNAs (miRNAs), which are primarily responsible for tumor expansion (Kopytko et al. 2021). Previous studies have also shown that garcinol inhibits cell growth and triggers programmed cell death in different cancer cells, particularly in DU145, MDA-MB-231, and BxPC-3 cancer cells. The efficacy of garcinol in reducing tumor growth was confirmed through *in vivo* assays using the MDA-MB-231 xenograft mice model (Ahmad et al. 2012).

***Helicteres isora* L.**

Helicteres isora is a shrub known by its vernacular name, East Indian screw tree. The acetone-based fruit extract of this plant showed cytotoxicity toward NCI-H460 cancer cells (Raaman and Balasbramanian 2012). The entire plant has been screened for cytotoxic activity against Hep-3B, HL-60, PN-15, and HeLa-B75 cells, and a moderate anticancer effect on these cell lines was observed. The major cytotoxic compounds of this plant are isocucurbitacin B and cucurbitacin B (Shaikh et al. 2014). Fruit extract of *H. isora* showed differentiation-inducing properties in the colon cancer cell line RCM-1 (Rattanamaneerusmee et al. 2018).

***Hibiscus rosa-sinensis* L.**

This is a small bushy shrub containing several bioactive molecules, including phenolics, flavonoids, anthocyanins, and organic acids. Plant extracts of *Hibiscus rosa-sinesis* are reported to show anticarcinogenic effects because of their antioxidant and hypolipidemic properties (Al-Saily et al. 2018; Rasul et al. 2023). A phenolic extract of *H. rosa-sinensis* showed cytotoxicity against a macrophage cancer cell line (RAW 264.7) and a testicular cell line (Tera-1). Tera 1 cells showed more sensitivity at an IC_{50} value of 23.496 mg/ml compared to RAW 264.7 cells (IC_{50} value: 31.841 mg/ml) (Al-Saily et al. 2018). A recent study investigated potent anticancer phytochemicals in *H. rosa-sinensis* flowers, specifically targeting the mammalian target of rapamycin (mTOR) through docking analysis. The results showed that stigmastadienol, lupeol, and taraxasterol acetate exhibited strong binding affinities to mTOR compared to the control group. Thus, these compounds could serve as effective mTOR inhibitors for breast cancer therapy (Rasul et al. 2023).

Hibiscus sabdariffa

In Ayurveda, the plant *Hibiscus sabdariffa* (family *Malvaceae*) has been utilized to treat conditions such as hypertension, hypercholesterolemia, hyperlipidemia, diarrhea, and other ailments. Recently, its anticancer activities as well as antiproliferative, antimutagenic, apoptotic, antiangiogenic, and antimetastatic properties have been widely investigated in both human cancer cells and animal studies (Laskar and Mazumder 2020). Moreover, the *in vivo* anticancer effects of the extract from *H. sabdariffa* calyxes was evaluated using Wistar rats. The results demonstrated that the extract significantly decreased tumor volume by increasing superoxide dismutase activity and decreasing MDA levels (Bassong et al. 2022).

***Hymenodictyon excelsum* (Roxb.) Wall.**

Hymenodictyon excelsum, belonging to the *Rubiaceae* family, has been studied for its cytotoxic and apoptotic activities. The methanolic extract from *H. excelsum* bark demonstrated cytotoxic activity against L-929 cells in a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and significantly inhibited the growth of DLA cells in a trypan blue dye exclusion assay. The apoptotic and cytotoxic effects are attributable to morphological changes such as cell shrinkage, chromatin condensation, and nuclear membrane blebbing (Khairunnisa and Karthik 2014). Studies have also demonstrated the anticancer potential of *H. excelsum* against HT-29 and Hep-G2 cells based on the presence of anthraquinone and coumarin compounds (Chakraborty et al. 2017). A molecular docking study identified several phytochemicals, including damnacanthal, esculin, lucidin, morindone, and soranjidiol, with promising binding affinity to the androgen receptor, similar to dihydrotestosterone, highlighting their potential for further research (Rahman 2015).

***Hypericum kotschyanum* Boiss.**

The genus *Hypericum* is known worldwide for its medicinal benefits. Aerial parts of this plant showed moderate cytotoxicity toward HeLa and Vero cell lines at 507 and 367 μg/ml concentrations, respectively (Artun et al. 2016).

***Inula viscosa* L. Aiton**

Inula viscosa, a therapeutic herb from the *Compositae* family, shows anticancer activity against human malignant melanoma cells, particularly A2058 and MeWo. Its methanolic extract induces cell death in these cells in a dose- and time-dependent manner by substantially altering miRNA expression. It downregulates oncogenic miR-191 and miR-193 and upregulates onco-suppressive miR-524 and miR-579 (Colak et al. 2022). Additionally, it repressed the development of 7,12-dimethylbenz(a) anthracene-induced skin carcinoma in mice (El Yaagoubi et al. 2021). Tomentosin, a phytochemical derived from this plant, exhibits antiproliferative effects on human Burkitt's lymphoma cancer cells by activating apoptosis and suppressing the cell cycle process. It inhibits growth-related genes such as *JAK/STAT* and *PI3K/AKT*, downregulates the antiapoptotic gene *CDKN1A* and *BCL2A1*, and upregulates the proapoptotic gene *PMAIP1* (Virdis et al. 2021). Tomentosin also exhibits cytotoxicity towards MOLT-4 cells by preventing NF-κB activation through the mTOR/PI3K/AKT pathway (Yang et al. 2021).

***Lagenaria siceraria* (Molina) Standl.**

This plant, classified under the *Cucurbitaceae* family, shows a wide range of medicinal benefits, including antioxidant, antibacterial, antituberculosis, antihelmintic, antidiarrheal, antidiabetic, antihypertensive,

analgesic, laxative, hepatoprotective, cardioprotective, and immunosuppressive effects. According to a recent study, *L. siceraria* fruit extract exhibits promising dose-dependent cytotoxicity toward HT-29 and MCF-7 cells (Attar and Ghane 2019). Cucurbitacin I, a crucial component of this plant, inhibits tumor growth by affecting apoptosis and targeting tumor blood vessel formation (Attar and Ghane 2018; Attar and Ghane 2019).

***Lannea coromandelica* (Houtt.) Merr.**

Lannea coromandelica, also known as the Indian ash tree, grows in south and southeast Asia. The bark and foliage extracts of this plant are highly cytotoxic. An *in vivo* study examined the influence of chloroform-based bark extract on mice seeded with EAC. After 7 days of treatment, the life span of treated mice increased by 33.3% (Hossain et al. 2018). Another study reported that the ethanolic extracts of twigs from *L. coromandelica* induced apoptosis in Hep-G2 cells. A gas chromatography–mass spectrometry analysis revealed that 2-palmitoylglycerol, hexadecanoic acid, and octadecenoic acid are the primary bioactive components in crude extracts (Weerapreeyakul et al. 2016). However, there are fewer positive reports describing the presence of anticancer components in *L. coromandelica*, indicating a significant scope for further research on potential pharmaceutical compounds in this species.

***Leea indica* (Burm.f.) Merr**

Leea indica, belonging to the *Leeaceae* family, originates from the tropical areas of India, Bangladesh, China, Bhutan, and Malaysia. The leaf of *L. indica* provides several therapeutic benefits in treating diabetes, diarrhea, and dysentery (Ghagane et al. 2017; Neo et al. 2023). The plant-derived leaf extract exhibited excellent anticancer efficacy against DU-145 and PC-3 cells (Ghagane et al. 2017). Another study demonstrated the significant cytotoxic properties of this plant extract (leaf) and its phytochemical methyl gallate when combined with oxaliplatin and natural killer (NK) cells. The findings suggest that ovarian cancer cells, including SK-OV-3 and OVCAR-5, became more susceptible to NK cells. Additionally, the plant extract reduced the production of proinflammatory cytokines TNF-α and interleukin-1 beta (Neo et al. 2023).

***Moullava digyna* (Rottler) Gagnon & G.P.Lewis**

This plant, generally named Vakul Mul, is categorized in the *Leguminosae* family. It contains homoisoflavonoids, commonly present in many fruits, beverages, vegetables, etc. Intricatinol, isolated from this plant, shows anticancer effects on A549 lung cancer cells. This compound enhances caspase-dependent apoptosis in A-549 cells when combined with a well-known anticancer drug, i.e., cisplatin. Furthermore, intricatinol activates the p38 mitogen-initiated protein kinases/p53 signaling pathway and damages DNA in A549 cells (Singh et al. 2017b).

***Myristica fragrans* Houtt.**

Myristica fragrans is an aromatic tree, commonly known as the nutmeg plant, and is recognized for its spicy products and essential oil, which is mostly used in fragrance, flavor, and pharmaceutical industries. This plant is native to Indonesia and primarily occurs in tropical regions and coastal areas (Ibrahim et al. 2020). Rengasamy et al. (2018) assessed the anticancer efficacy of this plant extract by the MTT assay against KB cell lines and demonstrated its ability to inhibit cancer cell growth. *M. fragrans* contains the bioactive compound myristicin, which is responsible for its significant cytotoxic effect (Rengasamy et al. 2018). Ginting et al. (2021) also identified anticancer properties of the root extract of *M. fragrans* against MCF-7 cells and discovered a lignan compound (6′-methyl-(7-hydroxy-8-methylbut-9-en)-3,2′-dimethoxybiphenyl-4,5-diol)) as an antitumor agent.

***Ocimum sanctum* L.**

Ocimum sanctum, also known by its common name "Tulsi," is the holy herb of India and belongs to the *Lamiaceae* family. *O. sanctum* exhibits several therapeutic properties and has been widely utilized in medical practice since ancient times. Essential oil from *O. sanctum* leaves demonstrated dose-dependent anticancer effects on MCF-7 cells by inducing apoptosis at an IC_{50} value of 170 μg/ml. Moreover, its leaf extracts increase the gene expression of *Bid*, *Bax, Bcl-2*, and *p53*, thereby confirming apoptosis induction (Manaharan et al. 2016). Another study revealed that the plant extract promotes apoptosis and suppresses PC-3 cell proliferation *in vitro* by downregulating genes such as *p65*, *FAK*, and activated *ERK-1/2*, while its intra-

peritoneal administration significantly hinders tumor growth *in vivo* (Shimizu et al. 2013). *O. sanctum* contains vicenin-2, which induces G2/M phase cell cycle arrest in HT-29 cells, triggers apoptosis, increases pro-apoptotic gene expression, and decreases *BCL2* gene transcription (Yang et al. 2018).

***Opuntia ficus-indica* L. Mill**

This plant is classified into the *Cactaceae* family. Its various components, including roots, stems, cladodes, fruits, peels, and seeds, were shown to exert anticancer effects in cellular experiments. Multiple studies reported the presence of various medicinally important compounds in this plant, including betanin, catechin, gallic acid, naringenin, naringin, protocatechuic acid, quercetin, and quinic acid (Wang et al. 2023). Another study emphasized the influence of the components of this plant on the anti-oncogene p16INK4a through the demethylation of its promoter and increased gene expression (Naselli et al. 2014).

***Phyllanthus emblica* L.**

Phyllanthus emblica, or Indian gooseberry, is a medicinal plant renowned for the widespread utilization of its fruit extract in traditional remedies for liver issues, constipation, diabetes, anemia, and tumors (Liu et al. 2012; Liu et al. 2024; Chekdaengphanao et al. 2022). Recent studies have highlighted the immune-enhancing and anticancer effects of various compounds derived from *P. emblica,* including geraniin, glucopyranoside, isocorilagin, kaempferol, kaempferol 3-β-d-glucopyranoside, quercetin, and rutin, on human embryonic lung fibroblast (HELF) and MCF-7 cells. The results of this study revealed that isocorilagin and geraniin exhibited higher cytotoxicity toward MCF-7 cells compared to the other compounds, influencing both cytotoxicity and inhibition of splenocyte proliferation in HELF and MCF-7 cells (Liu et al. 2012). Myricetin has also been reported to target carbonic anhydrase II in cancer pathways (Liu et al. 2024). Additionally, *P. emblica* herbal extract emonstrated anticancer effects on cholangiocarcinoma cell lines by promoting apoptosis and regulating the expression of key proteins caspase-3, caspase-9, Bax, and p53, while reducing Bcl-2 transcription (Chekdaengphanao et al. 2022). The plant has also shown potential against human papillomavirus-associated cervical cancers by suppressing the expression of oncogenes linked to cancer progression (Mahata et al. 2013).

The cytotoxic properties of *Piper betle, Portulaca oleracea* L., *Ricinus communis* L., *Saraca asoca* (Roxb.) Willd., *Saurauia roxburghii* Wall., *Tabernaemontana divaricata* (L.) R.Br. ex Roem. & Schult., *Teucrium polium* L., *Thymus vulgaris* carvacrol L., *Tillandsia recurvata* L., *Tribulus terrestris, Vitis vinifera* L., *Withania coagulans* (Stocks) Dunal, *Withania somnifera* L. Dunal, *Zea mays* L., and *Zingiber officinale* Roscoe are described in Supplementary Table 2.

Recent advances and opportunities in the discovery of novel anticancer drugs

Recent advancements in analytical chemistry, bioinformatics tools, and computational analysis have significantly improved our capability to investigate plant species that have been traditionally used across different cultures worldwide. By precisely characterizing their chemical compositions and evaluating their therapeutic activities, researchers are a step closer to establish important relationships between the two (Zhang et al. 2017). In recent years, there has been a global trend to create digital databases and resources that systematically catalog the active ingredients found in various herbs and herbal preparations, together with pertinent data (Ingle et al. 2024). In this context, Indian scientists have made significant achievements in creating digital databases for plant-based medicinal properties, including Phytochemica (Pathania et al. 2015), NeMed Plant (Meetei et al. 2012), MedPServer (Potshangbam et al. 2019), IMPPAT 2.0 (Vivek-Ananth et al. 2023), SuperNatural 3.0 (Gallo et al. 2023), and HIT 2.0 (Yan et al. 2022). However, many studies tend to address only the superficial aspect of the vast diversity of medicinal plants Repositories such as CancerResource and NPACT link cancer-related compounds to their targets, NPACT in particular, highlighting the anticancer activities of phytochemicals derived from *in vitro* and *in vivo* research studies (Ahmed et al. 2011; Mangal et al. 2013). These repositories serve as a crucial resource underscoring the significant potential of Indian herbs in the realm of future drug discovery. However, it is important to clearly differentiate between pharmacological properties observed in wet laboratories and those predicted through *in silico* methods.

Advancements in molecular modeling techniques, such as molecular docking and molecular dynamics, play

a crucial role in preclinical drug discovery. These techniques are essential for understanding how phytochemical analogs interact with their target proteins (Ferreira et al. 2015). Successful applications of computer-aided drug design are exemplified by several clinically approved drugs such as imatinib, dasatinib, and ponatinib. Nevertheless, these techniques encounter several challenges owing to the unavailability of three-dimensional structures of lesser-known anticancer compounds (Yi et al. 2018). Recent years have witnessed significant advancements in phytochemical extraction methods to address the environmental concerns associated with harvesting large quantities of plant materials (Liu et al. 2016). Therefore, the biosynthesis of natural medicines has garnered considerable interest, exemplified by success stories for artemisinin, paclitaxel, tanshinone, breviscapine, noscapine, and thebaine (Li et al. 2021). Unfortunately, almost 40% of natural bioactive components cannot be chemically synthesized (Potshangbam et al. 2019). Recent advances in biotechnology and metabolic engineering, particularly through heterologous expression systems and the use of elicitors in plant tissue culture, have facilitated increased production of anticancer compounds (Singh et al. 2020). In this regard, Indian research groups have worked diligently to improve extraction methods for anticancer phytochemicals such as camptothecin and tetrandrine (Srivastava et al. 2005). For example, *C. acuminata* Decaisne is a primary source of camptothecin worldwide; however, overharvesting of this plant has endangered its survival in many countries, particularly in China. As a solution, Indian researchers have shifted their focus to the plant *Nothapodytes foetida* for extracting camptothecin. Unfortunately, this plant produces camptothecin in considerably smaller quantities. Therefore, to improve the yield, a new method was developed to isolate camptothecin from the twigs and stems of *N. foetida*, which achieved a 36% increase in yield compared to that using previous methods (Srivastava et al. 2005). Thus, it is crucial to conduct more research on the diverse plant species from the Indian subcontinent to obtain specific phytochemicals and conserve endangered plants.

Recent studies have demonstrated that various phytochemicals show promising anticancer properties without damaging normal cells. However, their poor absorption and low bioavailability restrict their medicinal use. Therefore, strategies such as liposomal formulations, nanoformulations, and development of structural analogs of these phytochemicals are highly effective to overcome these issues (Lagoa et al. 2020). Consequently, more research in this direction is needed to improve the understanding of their bioavailability, bioactivity, and metabolism.

Conclusions

Medicinal plants indigenous to the Indian subcontinent have a key role in the advancement of novel pharmacological anticancer therapies. The overall progress in this field suggests that discovering new plant-derived anticancer drugs requires comprehensive *in silico* virtual screenings, preclinical studies, and pharmacokinetic evaluations of lesser-known plants and their phytochemicals in the Indian subcontinent. These strategies can enhance our understanding of novel plant-based anticancer medications and facilitate their discovery and development. Nonetheless, accurately predicting the roles of lesser-known phytochemicals in addition to traditional active compounds remains a significant challenge. Most studies often show methodological inadequacies, including the absence of control groups, small sample sizes, and short trial durations, which demand comprehensive clinical trials to assess toxicity and therapeutic potential. Combining modern advanced techniques and traditional medicines could enhance the introduction of novel phytochemicals into the market.

Author Contributions

Conceptualization and study design: V.K.S. and A.K.S. Data collection and assembly: V.K.S., U.S., and A.A.S. Data analysis and interpretation: V.K.S., V.P., R.P.S., A.K.S., U.S., and A.A.S. Writing-original draft: V.K.S., R.P.S., and A.K.S. Writing-review and editing: R.P.S., V.K.S., and A.K.S. Final approval of the article: V.K.S., R.P.S., and A.K.S. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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