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Ficus spp. (Figs) and their anticancer potential: A systematic review of laboratory studies and traditional uses in the Philippines

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ABSTRACT

Introduction: *Ficus* species (figs) have been traditionally utilized for managing various diseases, including cancer, a leading cause of global morbidity and mortality. Despite their widespread use, it remains an underexplored genus in modern pharmacognosy. This review documents species used as anticancer remedies in the Philippines and synthesizes global laboratory evidence supporting their anticancer properties. This approach bridges traditional knowledge with modern research, offering new insights into the therapeutic potential of the genus.

Methods: A systematic review was conducted following PRISMA guidelines. Relevant studies were retrieved from electronic databases (ScienceDirect, PubMed) and expanded search (Google Scholar). Database filters and keywords, such as "anticancer" and "*Ficus*", were optimized with Boolean operators and wildcards to refine search results. Study quality was evaluated using the Mixed Methods Appraisal Tool (MMAT).

Results: A total of 76 articles met the inclusion criteria, with 58 classified as high quality and 18 as moderate-high quality. Five key species, namely *Ficus septica, Ficus elastica, Ficus congesta, Ficus concinna,* and *Ficus botryocarpa,* were recorded for local traditional use, predominantly prepared as leaf decoctions. Laboratory evidence identified bioactive compounds such as terpenoids, flavonoids, alkaloids, phenolics, and species-specific compounds, exhibiting cytotoxic effects against multiple cancer types through mechanisms such as cell cycle arrest, apoptosis, antioxidant modulation, and metastasis inhibition.

Conclusion: This review highlights the potential of *Ficus* spp. as a source of anticancer agents, aligning traditional uses with laboratory evidence. Findings provide a foundation for further exploration of *Ficus*-based therapies in clinical applications.

Implication for health policy/practice/research/medical education:
This review provides information on the potential of *Ficus* species as anticancer agents, encouraging further research into their clinical use. Policymakers should support funding for research and collaborations between scientists and traditional healers to bridge ethnomedicine and modern medicine. In medical practice, *Ficus*-based medicines may serve as complementary cancer treatments, especially in resource-limited settings.

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Introduction

Cancer remains a leading cause of morbidity and mortality worldwide, with its prevalence steadily increasing in both developed and developing countries (1). Current estimates of approximately 20 million new cases annually are projected to double by 2070, driven by demographic shifts and rising cancer incidence across regions (2). This growing global burden accentuates the urgent need for effective prevention, treatment, and therapeutic strategies to combat this complex disease. However, traditional cancer treatments such as chemotherapy, radiation, and surgery, are often associated with significant side

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effects and limitations, prompting a growing interest in alternative and complementary therapies, particularly those derived from natural sources.

Throughout history, medicinal plants have been vital natural resources in improving health outcomes, forming the foundation of herbal therapy. As a biodiversity hotspot, the Philippines boasts a rich tradition of herbal medicine, making its local ethnobotanical knowledge particularly significant (3). These longstanding practices provide valuable ethnobotanical information that can guide scientific research. Medicinal claims rooted in tradition are often based on generations of empirical observation, offering a practical starting point for identifying plants with bioactive compounds and therapeutic potential. Investigating these claims presents an opportunity to uncover novel therapeutic agents and mechanisms, advancing the scientific understanding of natural products and their latent applications in modern medicine.

Ficus species, commonly known as figs, have nutritional value and diverse medicinal properties (4). *Ficus* species hold a unique place in Filipino culture, where their use is deeply intertwined with spiritual beliefs and healing rituals. They are often regarded as sacred, believing that they aid in healing. This belief is integral to the practices of traditional healers or shamans who emphasize the connection between spirituality and physical well-being (5,6).

Despite their rich traditional usage and cultural significance, *Ficus* species remain underexplored compared to other medicinal plants. Systematic evaluations of their anticancer potential are limited, which is likely due to the genus's vast biodiversity, fragmented ethnobotanical knowledge, and the chemical complexity of its secondary metabolites (7). Furthermore, research has historically prioritized plants with well-established pharmacological profiles, leaving *Ficus* spp. as an underutilized resource for drug discovery.

This study aimed to address this gap by systematically reviewing laboratory studies on the anticancer properties of *Ficus* spp., providing an inventory of the potential anticancer compounds identified in different parts of the plants, their mechanisms of action, and the types of cancer for which these compounds exhibit anticancer-related effects. The emphasis on plant parts is due to the understanding that different parts may contain distinct compounds, similar to traditional practices that use various parts of the plants. Additionally, the review provides an overview of the *Ficus* species used in the Philippines as traditional remedies for cancer and the methods employed to harness their perceived medicinal potential. Unlike previous reviews (8), this study provides a novel perspective by integrating global laboratory studies with local ethnobotanical knowledge from the Philippines, highlighting the therapeutic potential of *Ficus* spp. through a combined traditional and scientific lens (ethnobotany and herbal medicine pharmacology). Through this dual approach, patterns and correlations between traditional and scientific information can be deduced, unveiling the pharmacological activities of *Ficus* spp. while situating their anticancer properties within the broader context of traditional medicine. This perspective supports drug discovery efforts and validates and preserves traditional knowledge systems, which are at risk due to modernization and habitat destruction. Moreover, the review of available studies allows for noting research gaps, such as variability in experimental methods and challenges in translating findings into clinical applications. Ultimately, this comprehensive evaluation seeks to strengthen the foundation for future research, conservation efforts, and drug development pipelines, reinforcing *Ficus* species as promising candidates for novel anticancer therapies.

Review Methodology

Review team

One reviewer (KC), initially screened the titles and abstracts for relevance. Articles deemed potentially suitable were retrieved in full text and assessed independently by CD and MAT, with KC performing a subsequent re-assessment. In cases where there was disagreement on article inclusion, a consensus was made through a thorough and collaborative review by all evaluators. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were used to guide the process of record identification, screening, and inclusion (Figure 1).

Data sources and design

The electronic databases ScienceDirect and PubMed were systematically searched, with additional expanded searches, including forward and backward citations, conducted via Google Scholar. These databases were selected for their extensive coverage and strong reputation for reliability, which are commonly favored by other authors conducting literature reviews. Additionally, they were chosen for accessibility, given that other academic databases require institutional subscriptions that the authors' institute did not have. The systematic conduct of this review was referred from the PRISMA design (9) from inception to November 15, 2024.

Search strategy plan and optimization process

An iterative trial-and-error approach was used to refine search strategies and achieve ideal results. The titles and abstracts of five relevant studies were initially searched to identify potential search keywords. These keywords were added to the 'Advanced Search' fields in the databases and expanded the search. Relevant filters were applied to the fields such as titles, abstracts, and full texts. Wildcards were adjusted where necessary to improve search flexibility and accommodate different terminologies. Box 1 shows the final set of optimized keywords for these sources.

The eligibility criteria established were as follows:

Box 1. Optimized keywords

PubMed
(((Ficus) AND (cancer)) NOT (nanoparticle)) NOT (review)

NCBI filter
Text availability: Free full text

ScienceDirect
"Ficus", "anticancer" -review -nanoparticle

SD Filter
Article type: Research articles

Google Scholar
"Ficus", "anticancer" -review -nanoparticle

written in English; tested on a single *Ficus* species only (no herbal combinations); the genus of plant/s tested was/were *Ficus*; natural compounds from *Ficus* spp.; analysis focused on plant extract itself, not symbionts; and directly tested for anticancer activity. These criteria were initially established upon initial screening of articles for inclusion. However, in the course of extracting data, other reasons for exclusion were distinguished and presented in the PRISMA flow diagram (Figure 1).

The traditional anticancer use of *Ficus* spp. in the Philippines was taken from our previous results (10). Meanwhile, the group/class of compounds were mentioned in each article where they were cited. In a few cases where the compound class was not mentioned, other articles were referred for proper identification. Microsoft Excel was the spreadsheet tool used to tabulate, organize, and sort all the data, consequently transferred to be presented in tabular form using Microsoft Word. The R package and Shiny application (11) were used to generate the PRISMA flow diagram.

The initial data extraction from databases and search engines yielded 3,814 records, with 274 articles from ScienceDirect, 88 from PubMed, and 3452 from manual searches—including forward and backward citations—via Google Scholar. After removing duplicates, 3765 articles remained for further screening. Of these, 3524 were excluded for reasons outlined in Figure 1, leaving 241 articles for retrieval. Full-text availability allowed 202 articles to be assessed for eligibility, with 76 ultimately included in the review.

Quality assessment

The quality of the included studies was assessed independently by the reviewers using the Mixed Methods Appraisal Tool (MMAT) (12), specifically under the "quantitative non-randomized studies" category. This categorization was appropriate for this review as they typically report results such as IC_{50} values. However, to avoid bias, these values were not currently considered since

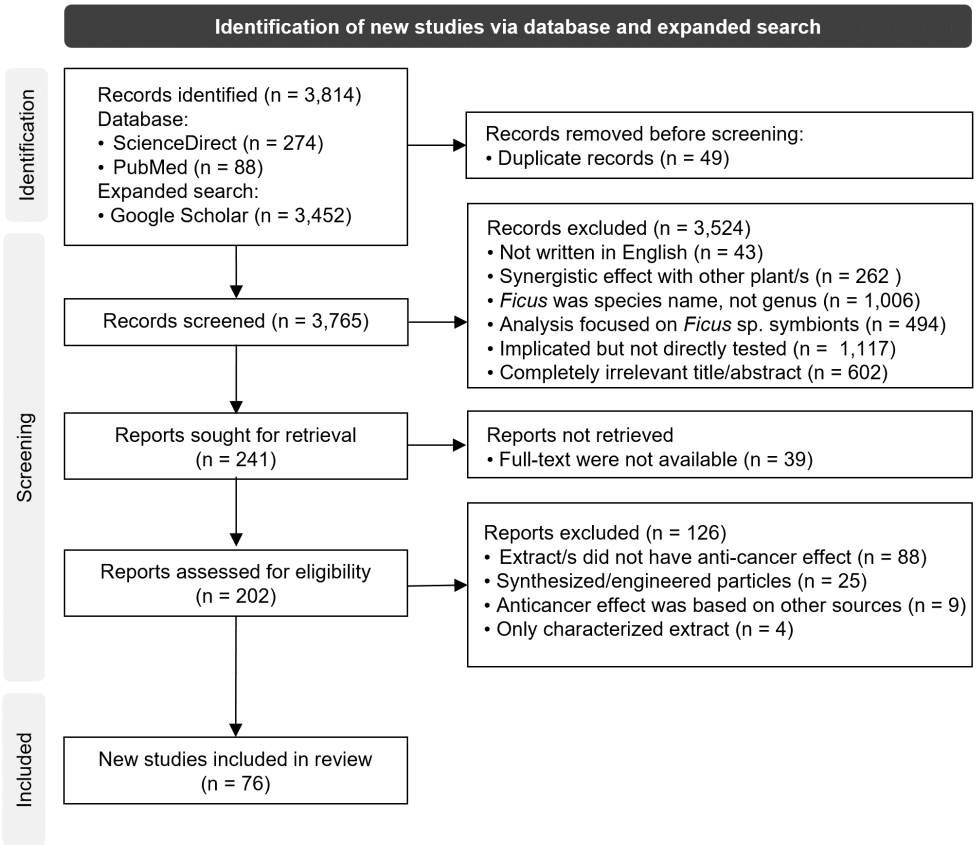

Figure 1. PRISMA flow diagram of the review on the ethnobotany and anticancer potential of *Ficus* spp.

different *Ficus* species and cancer cell lines were tested. Hence, quantitative comparisons were unwarranted. In using MMAT, each criterion was equivalent to a score of 1 for yes, 0 for no, and CT for can't tell. In cases where confusion arised, a thorough discussion was made between the reviewers to reach a consensus. After consolidating input from the three reviewers, 58 articles (76.32%) were classified as high quality (≥0.80), while 18 articles (23.68%) fell into the moderate-high quality range (0.66–0.79), as evaluated using MMAT ver. 2018.

Results

Taxonomy

Modern taxonomy places *Ficus* spp. within the following classifications: Kingdom Plantae (all plants), Subkingdom Viridiplantae (green plants), Phylum Tracheophyta (vascular plants), Subphylum Spermatophytina (seed plants), Class Magnoliopsida (dicotyledons), Order Rosales (plants like roses, figs, and mulberries), Family Moraceae (mulberries), and Genus *Ficus* (figs) (13).

Botany

The genus *Ficus*, belonging to the Moraceae family, comprises more than 750 species classified into four subgenera and 20 sections (14), including well-known varieties such as the common fig (*Ficus carica*) and the rubber tree (*Ficus elastica*). These trees and shrubs are characterized by their large, often glossy leaves, which can be lobed or unlobed depending on the species. Their leaves produce a milky latex when damaged, which has traditional medicinal and adhesive properties (15,16). Many *Ficus* species also develop aerial roots, which, in species like the banyan tree (*Ficus benghalensis*), form massive and complex structures that provide additional support.

Ficus encompasses diverse growth forms, including trees, shrubs, epiphytes, and vines, easily recognized by their unique reproductive structure, the syconium. This enclosed inflorescence houses numerous small male and female flowers that, upon pollination, develop into multiple fruits known as figs (17,18). Each *Ficus* species is typically pollinated by a single species of wasp from the family Agaonidae (19), illustrating a mutualistic coevolutionary process. These fig wasps pollinate the flowers while simultaneously laying eggs inside the syconium, facilitating seed production for the *Ficus* and providing a protected environment for their larvae (20).

Traditional anticancer uses of *Ficus* spp. in the Philippines

Previous ethnobotanical studies have documented traditional uses of *Ficus* as an anticancer agent in the Philippines (Table 1).

While there was no direct counterpart to the biomedical concept of 'cancer' in local terminology, traditional healers and knowledge systems recognized it through distinct signs and symptoms. These include (1) bukol or 'lump,' which refers to any abnormal growth or swelling in the body, (2) sakit sa laman or 'disease of the flesh,' describing chronic and worsening pain in the body, and (3) pagpayat or 'wasting,' which signifies unexplained weight loss and general physical decline. These indicators help local healers identify potential cancer cases through observable

Table 1. Traditional use of *Ficus* species as potential anticancer agents in the Philippines based on local practices

Ficus spp.	Common name	Local name	Plant part used	Mode of preparation	Administration	Claimants	Sources
botryocarpa	Cluster fig	Busyong	Bark	Decoction	Boil 10 inches long and 5 inches wide bark in an ample amount of water; drink 1/2 glass often.	Subanen tribe (Lapuyan, ZDS)	(21)
concinna	Elegant fig	Pulang balite	Leaves; bark; roots	Decoction	Drink the decoction once a day in thrice a week for 2 months (5-7 glasses)	Manobo tribe (Agusan del Sur)	(22)
congesta	Red-leaf fig	Kalfagang	Leaves	Poultice	Apply to the affected part	B'laan tribe (Mt. Matutum)	(23)
elastica	Rubber fig	Dakit	Leaves	Decoction	Drink the decoction	Locals of Catmon, Toledo, and Alcoy, Cebu	(24)
elastica	Rubber fig	Balite na dako; Goma	Leaves	Decoction	Drink the decoction	Pagadian City	(25)
elastica	Rubber fig	Balite na dako; Goma	Leaves	Poultice	Poultice	Tribes of the Zamboanga peninsula (Visayan)	(26)
septica	Hauili fig tree	Hawili	Leaves	Poultice	Apply as salve	Kanawan Aytas	(27)
septica	Hauili fig tree	Marabutan	Leaves; bark	Decoction	Drink the decoction	Subanen Tribe (Sindangan)	(28)
septica	Hauili fig tree	Hawili	Leaves; bark	Decoction	Drink the decoction	Maranao (Bubong, LDS)	(29)
septica	Hauili fig tree	Ikmo/Buyo	Leaves; bark	Decoction	Drink the decoction	Iligan City	(30)
septica	Hauili fig tree	Marabutan	Leaves; bark	Decoction	Drink the decoction	Higaonon (Rogongon, Iligan City)	(31)
septica	Hauili fig tree	Marabutan	Leaves	Decoction	Drink the decoction	Dinagat Islands	(32)

physical signs, relying on a symptom-based understanding rather than a specific term equivalent to 'cancer'.

In contrast to more common ethnobotanical uses for ailments like coughs, wounds, or headaches, these cancer-related symptoms are relatively few, resulting in fewer documented plants for anticancer use. Ethnobotanical surveys in the Philippines identified five *Ficus* species specifically noted for their anticancer uses: *Ficus septica* (Hauili), *Ficus elastica* (Rubber fig), *Ficus congesta* (Red-leaf fig), *Ficus concinna* (Elegant fig), and *Ficus botryocarpa* (Cluster fig), listed according to their frequency of occurrence.

Laboratory studies on phytochemical constituents of *Ficus* spp. with documented anticancer activity

Previous studies have identified several bioactive compounds in *Ficus* species with documented anticancer activity (Table 2). Reviewing these compounds is essential for identifying potential therapeutic agents, validating traditional medicinal practices, and understanding the

Table 2. Documented anticancer phytochemicals in *Ficus* spp.

Plant part	Compound class	*Ficus* spp.	Compound	References
Leaves	Alkaloid	*septica*	(+)-Isotylocrebrine; Tylocrebrine; (+)-tylophorine; Ficuseptine; 14R-hydroxyisocrebrine N-oxide; Tylophorine; Indole	(33-35)
		fistulosa	Fistulopsene B; Tengechlorenine; Tengerensine	(36,37)
		hispida	Hispiloscine	(38)
	Alkane	*crocata*	Hexatriacontane	(39)
	Carboxylic acid	*carica*	Benzoic acid	(40)
	Carotenoid	*virens*	Lycopersen	(41)
	Coumarin	*carica*	Bergapten; Psoralen	(42)
	Ester	*virens*	Dibutyl phthalate	(41)
	Fatty acid	*ovata*	Hexadecanoic acid	(43)
		crocata	10,13,13-trimethyl-11-tetradecen-1-ol acetate	(44)
	Flavonoid	*carica*	Apigenin; Luteolin, Lutin, Quercetin	(40)
		deltoidea	Isovitexin; Vitexin	(45)
		pseudopalma	Quercetin	(46)
	Glycolipid	*microcarpa*	Gingerglycolipid B; (2S)-2,3-O-dioctadeca-9Z,12Z,15Z-trienoylglyceryl-O-β-D-galactopyranoside; (2S)-2,3-O-dioctadeca-9Z,12Z-dienoylglyceryl-O-β-D-galactopyranoside; (2S)-3-O-octadeca-9Z,12Z,15Z-trienoylglyceryl-6'-O-(α-D-galactopyranosyl)-β-D-galactopyranoside; (2S)-2,3-O-dioctadeca-9Z,12Z,15Z-trienoylglyceryl-6'-O-(α-D-galactopyranosyl)-βD-galactopyranoside; (2S)-2,3-O-dioctadeca-9Z,12Z-dienoylglyceryl-6'-O-(α-D-galactopyranosyl)-β-D-galactopyranoside	(47)
	Ketone	*religiosa*	Benzophenone	(41)
		elasticoides	6,10,14-trimethyl-2-pentadecanone	(43)
		ovata	6,10,14-trimethyl-2-pentadecanone	(43)
		rumphii	3-(2-hydroxyphenyl)-1-(piperidin-1-yl) propan-1-one	(48)
	Phenolic	*crocata*	Vitamin E	(39)
		benghalensis	Carvacrol	(41)
		religiosa	Tocopherol	(41)
		rumphii	1-isopentyl-3,4-dioxomethylene-2-phenol	(48)
		auriculata	2,4-ditertiary-butyl-phenol	(49)
		carica	Protocatechuic acid; Gallic acid	(40,50)
	Sterol	*crocata*	β-sitosterol	(39,44)
		carica	β-sitosterol	(40,51)
		ingens	β-sitosterol	(51)
		hispida	β-sitosterol	(52)
	Terpenoid	*benghalensis*	Phytol	(41)
		elasticoides	(E)-phytol; β-carophyllene	(43)
		ovata	(E)-phytol; Carophyllene oxide	(43)
		natalensis	(E)-phytol	(43)
		crocata	Lup20(29)-en-3-ol acetate (3β); Phytol; Squalene; Lup-20(29)-en-3-ol-acetate; Lupeol	(39, 44)
		pseudopalma	Lupeol	(46)
		microcarpa	2(S)-3-O-octadeca-9Z,12Z,15Ztrienoylglyceryl-O-β-D-galactopyranoside	(47)
		hispida	Lup-20(29)-en-3-ol-acetate	(52)
		pomifera	3β-Acetoxyurs-3-ene; 3β-hydroxyurs-3-ene	(53)
		deltoidea	Ursolic acid	(54)

Table 2. Continued

Plant part	Compound class	*Ficus* spp.	Compound	References
Fruit	Amide	*carica*	(2-benzhydrylsulfnyl)-N-hydroxyacetamide)-Na	(55)
	Flavonoid	*hispida*	3'-formyl-5,7-dihydroxy-4'-methoxyisoflavone; Alpinumisoflavone; Isowigtheone hydrate; β-sitosterol 3-O-β-D-glucopyranoside	(56)
		bubu	Biochanin A	(57)
		carica	Cyanidin 3-O-glucoside; Quercetin; Quercetin 3-ß-glucoside; Rutin	(58)
		altissima	Isoflavone 2; Isoflavone 3; Isolupalbigenin; Isowigtheone; Lupinalbin; Luteolin	(59)
		vasta	Quercetin	(60)
		sycomorus	Quercetin-3-rutinoside	(61)
	Phenolic	*hispida*	Gallic acid; Chlorogenic acid; Chlorogenic acid methyl ester	(56)
		carica	Ellagic acid; Ferulic acid; Trans-cinnamic acid	(58)
		vasta	Gallic acid	(60)
		palmata	Caffeic acid; Catechin; Coumaric acid; Gallic acid	(62)
	Stilbene	*bubu*	Trans-resveratrol; Piceid	(57)
	Terpenoid	*hispida*	Betulinic acid	(56)
		carica	Ficutirucin A; Ficutirucin B; Ficutirucin C; Ficutirucin F; Ficutirucin G; Ficutirucin I	(63)
Roots	Alkaloid	*septica*	10S,13aR-tylocrebrine N-oxide; 13aR-isotylocrebrine; 13aR-tylocrebrine; 13aR-tylophorine; Ficuseptine A	(64,65)
	Amide	*elastica*	Elasticamide	(65)
	Flavonoid	*elastica*	Ficusoside B; Ficusoside B (peracetylated); Biochanin A	(65,66)
		beecheyana	Epicatechin; Rutin	(64,66)
	Lignin derivative	*hirta*	Ficuslignin B	(67)
	Phenolic	*beecheyana*	Caffeic acid; Chlorogenic acid; Gallic acid; p-coumaric acid; p-hydroxybenzoic acid; Protocatechuic acid	(66)
	Quinone	*elastica*	Elastiquinone	(65)
	Terpenoid	*microcarpa*	Plectranthoic acid	(68)
Stem	Alkaloid	*septica*	10S,13aR-isotylocrebrine N-oxide; 10S,13aR-tylocrebrine N-oxide; Tylophorine	(69)
	Terpenoid	*foveolata*	Foveolide A; Foveolide B	(70)
Bark	Alkaloid	*fistulosa*	Fistulopsine A	(35)
	Flavonoid	*drupacea*	5-O-methyllatifolin	(71)
		glumosa	6-prenylapigenin; Luteolin	(72)
	Phenolic	*religiosa*	Phenolic acid	(73)
	Saponin	*glumosa*	Dongnoside E	(72)
	Terpenoid	*drupacea*	Epifriedelanol; Epilupeol acetate; Friedelin; Oleanolic acid	(71)
		glumosa	β-amyrine; Lanosta-7,24-dien-3-one; Lupeol	(72)
		exasperata	Ursolic acid	(74)
Latex	Flavonoid	*carica*	Quercetin	(75,76)
	Phenolic	*carica*	Caffeic acid; Ferulic acid; p-coumaric acid; Protocatechuic acid	(75,76)
		dubia	Chlorogenic acid; Quinic acid; Syringoylquinic acid	(77)

mechanisms through which these compounds exert their effects on cancer cells. This exploration can lead to the discovery of novel drug leads and highlight the ecological and cultural significance of *Ficus* species. Additionally, understanding their phytochemical diversity can inspire the development of synergistic therapies that enhance the efficacy of conventional treatments while potentially reducing side effects.

The leaves contained a wide variety of compounds, with terpenoids being the most abundant (18 occurrences), followed by alkaloids (11), flavonoids (7), and phenolics (7) (Figure 2). Other compounds belonging to classes of glycosides (6), ketones (5), sterols (5), coumarins (2), fatty acids (2), alkane (1), carboxylic acid (1), carotenoid (1), and ester (1) were also reported.

The most common compounds in fruits were flavonoids (14 occurrences), mainly from *Ficus altissima* and *Ficus carica*, alongside phenolics (11) and terpenoids (7). In the

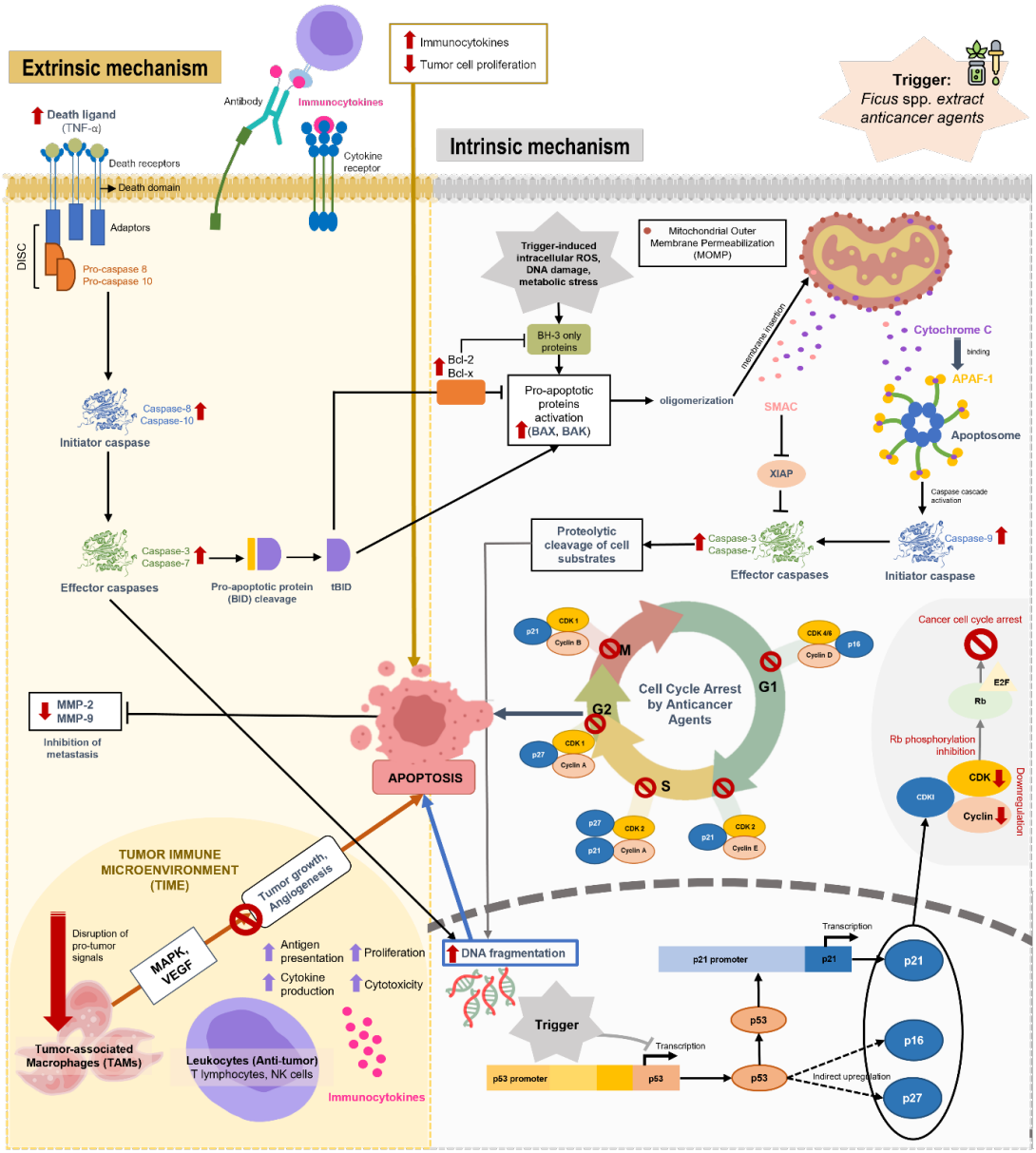

Figure 2. Mechanisms of actions of *Ficus* spp. extracts against cancer cells, synthesized from previous studies included in this review. DISC: Death-inducing signaling complex; BID: BH3 interacting-domain death antagonist; tBID: Truncated BID; MMP: Matrix metalloproteinase; MAPK: Mitogen-activated protein kinase; VEGF: Vascular endothelial growth factor NK Cells: Natural killer cells; Bcl-2/x: B cell lymphoma/leukemia type 2/x; BAX: Bcl-2-associated X protein; BAK: Bcl-2 homologous antagonist/killer; SMAC: Second mitochondria-derived activator of caspases; XIAP: X-linked inhibitor of apoptosis protein; APAF-1: Apoptosis protease–activating factor 1; CDK: Cyclin-dependent kinase; E2F: transcription factor; Rb: Retinoblastoma protein.

roots, alkaloids (5 occurrences) were prevalent, especially from *Ficus septica,* and phenolics (6), notably from *Ficus beecheyana*. The bark was reported to be rich in terpenoids (7 occurrences), with additional findings of flavonoids and alkaloids. The latex mainly contained phenolics (8 occurrences) and flavonoids (2), with most compounds isolated from *Ficus carica*. In the stem, previous studies reported the presence of alkaloids (3) and terpenoids (2).

The most commonly identified compound classes in *Ficus* species were flavonoids, phenolics, alkaloids, and terpenoids. It is important to note that this review focuses solely on compounds from these species that have demonstrated anticancer-related activities, excluding other compounds that may have been identified but lack such activities.

Flavonoids were the most widespread, found in seven species: *Ficus altissima*, *Ficus hispida*, *Ficus carica*, *Ficus sycomorus*, *Ficus vasta*, and *Ficus bubu*. These compounds were primarily concentrated in the fruits, with quercetin being common across such species (58,60,61). Isoflavones such as alpinumisoflavone and isowigtheone, as well as other compounds like rutin and luteolin were also identified from the species' fruits. Isowighteone and isowighteone hydrate are related compounds

first isolated from *Ficus altissima* and *Ficus hispida*, respectively. Isowighteone significantly inhibited nitric oxide (NO) production compared to the nonsteroidal anti-inflammatory drug (NSAID) indomethacin (59). Other compounds isolated in the same study included isolupalbigenin, lupinalbin, luteolin, and two unidentified isoflavones, all of which demonstrated antiproliferative and cytotoxic effects against breast (MDA-MB-231) and liver (HepG2) cancer cell lines. Isowighteone hydrate, on the other hand, exhibited cytotoxic activity against the human promyelocytic leukemia (HL-60) cell line by activating caspases 3, 8, and 9 (56).

Ficus elastica and *Ficus beecheyana* contained flavonoids in their roots, with a new compound named Ficusoside B being isolated for the first time from the aerial roots of *Ficus elastica* (65). Flavonoids were also found in the bark of *Ficus drupacea* and *Ficus glumosa*; in the leaves of *Ficus deltoidea*, *Ficus pseudopalma*, and *Ficus carica*, as well as in the latex of *Ficus carica*. Notably, quercetin was found in nearly all parts of *Ficus carica* studied (40,58,75,76).

Phenolic compounds were found in the fruits, latex, roots, leaves, and bark of *Ficus* spp. The leaves had the most diverse species containing potent phenolic compounds including *Ficus carica*, *Ficus rumphii*, *Ficus religiosa*, *Ficus crocata*, *Ficus benghalensis*, and *Ficus auriculata* (39-41,48-50). Four species (*Ficus palmata*, *Ficus hispida*, *Ficus carica*, and *Ficus vasta*) had phenolics in their fruits, with gallic acid being common to all of them (56,60,62). *Ficus carica* and *Ficus dubia* contained phenolics in their latex (75-77), while *Ficus religiosa* had phenolic acid in its bark (73). *Ficus beecheyana* roots also contained phenolic compounds including caffeic acid, gallic acid, and protocatechuic acid (66).

Alkaloids were most prevalent in the leaves, with *Ficus septica* having most of the compounds, including newly isolated phenanthroindolizidine alkaloids, such as Ficuseptines B-D, (+)-isotylocrebrine, tylocrebrine, and (+)-tylophorine. In addition to the leaves, alkaloids were also found in the roots and stems of *Ficus septica*. The leaves of *Ficus fistulosa* also contained a species-specific alkaloid, Fistulopsene B, while its bark contained a similar alkaloid, Fistulopsene A. Both compounds belong to a unique class of septicine-type alkaloids, which have been shown to arrest cancer cells in the G1 phase without inducing apoptosis (35). Moreover, the leaves of *Ficus hispida* also contained a species-specific alkaloid, Hispiloscine (38).

Terpenoids were identified in the least diverse plant parts, limited to the leaves, fruits, and bark. Most of the species, including *Ficus crocata*, *Ficus pomifera*, *Ficus microcarpa*, *Ficus deltoidea*, *Ficus pseudopalma*, *Ficus ovata*, *Ficus natalensis*, *Ficus elasticoides*, and *Ficus benghalensis*, contain terpenoids in their leaves, with phytol and lupeol being common among them. *Ficus carica* and *Ficus hispida* had terpenoids in their fruits, with the unique isolation of Ficutirucins, a type of tirucallane triterpenoid, from *Ficus carica* which exhibited cytotoxic activity against several cancer cell lines. Additionally, *Ficus drupacea*, *Ficus glumosa*, and *Ficus exasperata* contain terpenoids in their bark, including oleanolic acid and epilupeol acetate, both of which exhibit antiproliferative activity (71). Other terpenoids from *Ficus drupacea*, such as epifriedelanol and friedelin, have also been reported to exhibit high cytotoxicity against the tested cancer cell lines (71).

Ficus spp. anticancer phytochemical profile and mechanisms of action

The anticancer activity of the bioactive compounds has been mechanistically varied, depending on the compounds present, the pathways involved, and the type of cancer cell line targeted. The diversity in mechanisms allows these compounds to act on multiple cellular processes, thereby contributing to their potential as anticancer agents (Table 3).

Comparative phytochemical profiles and therapeutic potential of *Ficus* spp.

Various *Ficus* species exhibit significant anticancer activities on various cancer cell lines, with distinct pharmacodynamic contributions from different plant parts. Notably, *Ficus carica* has notable activities. For instance, its latex extracts induced apoptosis and enhanced temozolomide (TMZ) efficacy in glioblastoma cells by upregulating Let-7D expression (75). Meanwhile, its leaf extracts downregulated GATA3 in breast cancer cells (MDA-MB-231), promoting cell cycle arrest while exhibiting antiproliferative, anti-metastatic, and antiangiogenic properties by modulating ERK2, CREB, and AKT2 pathways (84). Furthermore, *Ficus carica* fruits demonstrated complex apoptosis-inducing effects in ovarian (SKOV-3) and breast (AMJ-13) cancer cells through the upregulation of P53, Caspase-8, and Bax (55).

Ficus altissima, rich in flavonoids, demonstrated antiproliferative activity and nitric oxide production inhibition on breast (MDA-MB-231) and liver (HepG2) cancer cells (59), emphasizing its potential for targeting cancer cell growth. *Ficus auriculata* showed cytotoxic effects on gastric (AGS) cancer cells and induced cell cycle changes and apoptosis in lung (A549) cancer cells through a caspase-independent pathway, attributed to its phenolic content (49,78). Similarly, species like *Ficus deltoidea* and *Ficus drupacea*, containing flavonoids and terpenoids, demonstrated significant cytotoxic and apoptotic effects (45,54,71,90).

Antiproliferative effects were also exhibited by *Ficus benghalensis*, which was abundant in carotenoids, esters, ketones, phenolics, and terpenoids, against breast (MDA-MB-468) and colon (Colo320) cancer cells (41,80). It also demonstrated neuroprotective activity against oxidative stress in neuroblastoma cells (81, 82). Notably, novel compounds with anticancer activity were isolated

Table 3. Phytochemical profiles of different parts of *Ficus* species and their anticancer pharmacodynamics

Ficus spp.	Plant part	Plant preparation	Compound/ Extract	Mechanism of action	Ref.
altissima	Fruit	Air-dried	Flavonoids	Antiproliferative activity and NO production inhibition on breast (MDA-MB-231) and liver (HepG2) cancer cells	(59)
*auriculat*a	Leaves	Shade-dried	Phenolics	Cytotoxic activity on gastric (AGS) cancer cells	(49)
auriculata	Fruits	Freeze-dried	Extract	Induction of cell cycle profile changes and apoptosis induction via caspase-independent pathway on lung (A549) cancer cells	(78)
awkeotsang	Seeds	Fresh	Extract	Induction of cell cycle arrest at G2/M phase and apoptosis induction via mitochondrial pathway involved with exceeding ROS level	(79)
beecheyana	Roots	Air-dried	Flavonoids, phenolics	Growth inhibition of leukemia (HL-60) cells	(66)
beecheyana	Roots	Air-dried	Flavonoids, phenolics	Induction of apoptosis via *Fas*- and mitochondrial-mediated pathway and reduction of mitochondrial membrane potential of leukemia (HL-60) cells	(66)
benghalensis	Leaves	Dried	Carotenoid, ester, ketone, phenolics, terpenoids	Antiproliferative activity on breast (MDA-MB-468) cancer cells	(41)
benghalensis	Root	Shade-dried	Extract	Antiproliferative activity on colon (Colo320) cancer cells	(80)
benghalensis	Bark	Air-dried	Extract	Neuroprotective activity (against oxidative environment generated by H_2O_2 treatment) on neuroblastoma (SK N SH) cells	(81)
benjamina	Extract	Dried	Coumarins	High binding affinity of compounds to PARP-1 (an anticancer therapy target)	(82)
bubu	Fruit	Air-dried	Flavonoids, stilbenes, terpenoids	Peracetylation-induced increase in antiproliferative activity and cytotoxic activity on lung (A549) and skin (SKMEL-28) cancer cells	(57)
carica	Latex	Fresh	Flavonoids, phenolics	Cell proliferation inhibition (reduced invasion via induction of Let-7D expression), apoptosis induction, enhancement of TMZ effect, and inhibition of angiogenesis on glioblastoma cells	(75)
carica	Leaves	Fresh	Coumarins	Antiproliferative activity, downregulation of breast cancer marker gene GATA3, cell cycle arrest, and decrease in cell mobility on breast (MDA-MB-231) cancer cells	(42)
carica	Fruit	Air-dried	Amide	Increased ROS synthesis, reduction of MMP via *Bax* upregulation by P53, Caspase-8, and Caspase-9 and Bcl-2 downregulation, inhibition of proliferation, and induction of apoptosis via activated P53 and caspase-8 signaling on ovary (SKOV-3) and breast (AMJ-13) cancer cells	(55)
carica	Fruit	Air-dried	Flavonoids, phenolics	Antiproliferative activity by alleviating plasma cytokine levels and phenolic composition on breast (MDA-468) cancer cells	(58)
carica	Extract	Dried	Phenolic	Cytotoxic activity (decreased cell viability) and induction of apoptosis on bone (MG-63) and colon cancer (HT-29) cancer cells	(50)
carica	Leaves	Shade-dried	Sterols	Cytotoxic activity on liver (HepG2), kidney (HEK-293), and breast (MCF-7; MDA-MB-231) cancer cells	(51)
carica	Fruit	Air-dried	Terpenoids	Cytotoxic activity on liver (HepG2), breast (MCF-7) and bone (U2OS) cancer cells	(63)
carica	Leaves	Air-dried	Flavonoids	The regulatory substance of MCM protein expression in anticancer mechanisms	(83)
carica	Latex	Fresh	Flavonoids, phenolics	Apoptosis induction, invasion prevention via Let-7d expression in glioblastoma (e U-138 MG, T98G, and U-87 MG) cells	(76)
carica	Extract	Extract	Flavonoids, terpenoids	High binding affinity of compounds to PARP-1 (an anticancer therapy target)	(82)
carica	Leaves	Air-dried	Carboxylic acid, flavonoids, phenolics, sterols	Cytotoxic activity, anti-colonization activity, cell cycle arrest at S phase, increase in ROS leading to loss of mitochondrial membrane potential, downregulation of TP53, Bcl-2, CDK1, 5, and 9, on liver (HepG2) cancer cells	(40)
carica	Latex (leaves)	Fresh	Extract	Antiproliferative activity, anti-metastatic, genotoxic, and cytotoxic activity, and downregulation of ERK2, CREB, and AKT2 on breast (MDA-MB-231) cancer cells	(84)

Table 3. Continued

Ficus spp.	Plant part	Plant preparation	Compound/ Extract	Mechanism of action	Ref.
carica	Peel, pulp, leaves, fruit, latex	Air-dried	Extract	Inhibition of proliferation of colorectal (HT-29) and colon (HCT-116) cancer cells; apoptosis induction on colorectal cancer cells	(85)
carica	Fruit, leaves, latex	Air-dried	Extract	Decreased cell viability of cervical (HeLa) cancer cells	(86)
carica	Leaves	Sun-dried	Extract	Anti-angiogenesis activity is implicated via the number of blood vessels and VEGF expression of CAM of embryonated chicken eggs	(87)
carica	Fruits	Air-dried	Extract	Cytotoxic activity, apoptosis induction, DNA damage, Increase in iCa2+ levels on breast (MCF-7) cancer cells	(88)
carica	Leaves	Air-dried	Extract	Apoptosis induction via proteolytic cleavage of PARP, downregulation of Bcl-2, and upregulation of *Bax*, cell viability reduction, colony formation inhibition via caspase- and mitochondrial-dependent apoptotic pathways on oral (FaDu) cancer cells	(89)
crocata	Leaves	Fresh	Alkane, phenolics, sterols, terpenoids	Cytotoxic activity, reduction of cancer cell migration, reduction of invasion capacity and secretion of MMP-2 and MMP-9, reduction of actin polymerization, and probably EMT on the breast (MDA-MB-231; MCF-7) cancer cells	(39)
crocata	Leaves	Air-dried	Fatty acids, sterols, terpenoids	Antiproliferative activity, apoptosis induction, and increased p53, procaspase-8, and procaspase-3 expression in breast (MDA-MB-231) cancer cells	(44)
deltoidea	Leaves	Fresh	Flavonoids	Cell reduction of prostate (DU145) cancer cells by apoptosis	(45)
deltoidea	Leaves	Fresh	Flavonoids	Decreased cell viability on prostate (DU145) cancer cell lines	(45)
deltoidea	Leaves	Oven-dried	Terpenoids	Cytotoxic activity on colorectal (HCT-116) and breast (MDA-MB-231) cancer cells	(54)
deltoidea	Leaves	Oven-dried	Terpenoids	Inhibition of micro-vessels outgrowth in rat aortic rings and inhibition of chick CAM vascularization	(54)
deltoidea	Leaves	Oven-dried	Terpenoids	Cytotoxic activity against colon (HCT-116) and breast (MDA-MB-231) cancer cells	(54)
deltoidea	Leaves	Air-dried	Extract	Antiproliferative activity and apoptosis induction via upregulation of Fas1, Bax, Cdk-1, TNF-α and Cdk-2 and downregulation of Bcl-2 and Tp53 on breast (MCF-7, MDA-MB-231, HCC 1937) and colon (HCT-116) cancer cells	(90)
deltoidea	Leaves	Oven-dried	Extract	Apoptosis induction, promotion of cell detachment, and inhibition of proliferation through DNA fragmentation on ovarian (A2780) cancer cells	(91)
deltoidea	Leaves	Air-dried	Extract	Regression on tumor progression, reduced incidence of oral squamous cell carcinoma (OSCC), decreased expression of cyclin D1 (tumor marker), and increased expression of β-catenin and e-cadherin antibodies reduced the expression of the TWIST1 and RAC1 (EMT) and downregulated the COX-2 and EGFR (angiogenesis, metastasis, and chemoresistance)	(92)
drupacea	Bark	Air-dried	Flavonoids, terpenoids	Antiproliferative activity on cervical (HeLa), breast (MCF-7), leukemia (Jurkat), and colorectal (HT-29, T24) cancer cells	(71)
dubia	Latex	Fresh	Phenolics	Antiproliferative activity, cell cycle arrest by NF-κB, cyclin D1, CDK4, p21 downregulation, selective apoptosis induction by down-regulating NF-κB and Bcl-xl and up-regulating Bid, Bak, cleaved caspase-7 and caspase-3 in colorectal (HCT-116 and HT-29) cancer cells.	(77)
elastica	Liana	Air-dried	Alkaloids, saponins, tannins, terpenoids	Antiproliferative activity on oligodendroglioma (Hs683) and breast (MCF-7) cancer cells	(65)
elastica	Roots	Oven-dried	Amide, flavonoids, quinone	Antiproliferative activity on brain (U373, Hs683), breast (MCF-7), lung (A549), and skin (B16F10, SK-MEL-28) cancer cells	(65)
elasticoides	Leaves	Air-dried	Ketone, terpenoids	Compounds associated with anticancer mechanisms via apoptotic pathways	(43)
exasperata	Bark	Air-dried	Terpenoids	Cytotoxic activity on cervical (KB-3-1) and colon (HT-29) cancer cells	(74)

Table 3. Continued

Ficus spp.	Plant part	Plant preparation	Compound/ Extract	Mechanism of action	Ref.
fistulosa	Bark, leaves	Fresh	Alkaloids	Growth inhibition and cell cycle arrest in the G1 phase without apoptosis induction of colon (HCT-116) and breast (MCF-7) cancer cells	(35)
fistulosa	Leaves	Air-dried	Alkaloids	Cytotoxic activity on breast (MDA-MB-468, MDA-MB-231 and MCF-7) cancer cells	(38)
foveolata	Stems	Air-dried	Terpenoids	Cytotoxic activity on colorectal (SW620), liver (HepG2). Breast (BT474) and stomach (KATO-III) cancer cells	(70)
glomerata	Whole plant	Oven-dried	Extract	Antiproliferative activity on the liver (HepG2) and breast (MCF-7) cancer cells	(93)
glumosa	Bark	Air-dried	Flavonoids, saponins, terpenoids	Cytotoxic activity on the prostate (PC-3) and fibrosarcoma (HT1080) cancer cells	(72)
heterophylla	Roots	Shade-dried	Alkaloids, flavonoids, phenolics, tannins	Compounds implicated in anticancer mechanisms via apoptotic pathways	(94)
hirta	Roots	Air-dried	Lignin derivative	Cytotoxic activity and apoptosis induction via JNK/p38 MAPK pathway on liver (HepG2) cancer cells	(67)
hirta	Roots	Air-dried	Extract	Decreased cell viability and apoptosis induction via cell cycle arrest at sub-G1 phase on cervical (HeLa) cancer cells	(95)
hispida	Leaves	Shade-dried	Fatty alcohol, sterols, terpenoids	Compounds implicated in anticancer mechanisms via apoptotic pathways	(52)
hispida	Extract	Dried	Flavonoids, terpenoids	High binding affinity of compounds to PARP-1 (an anticancer therapy target)	(82)
hispida	Fruits	Air-dried	Flavonoids, glycoside, phenolics, sterols	Cancer chemopreventive activity, cytotoxic activity on leukemia (HL60), lung (A549), breast (SK-BR-3), oral (KB), cervical (HeLa), colon (HT-29), and liver (Hep-G2) cancer cells, and apoptosis induction via both the mitochondrial and death receptor-mediated pathways by activation of caspases-3, -8, and -9 in leukemia (HL60) cells	(56)
hispida	Bark, leaves	Fresh	Alkaloids	Antiproliferative activity on breast (MDA-MB-231, MCF-7), lung (A549), and colon (HCT-116) cancer cells	(36)
hispida	Leaves	Air-dried	Extract	Cytotoxic activity via apoptosis induction and cell cycle arrest at G0/G1 phase on colorectal (HT-29) cancer cells	(96)
ingens	Leaves	Shade-dried	Sterols	Cytotoxic activity on the liver (HepG2) and breast (MDA-MB-231) cancer cells	(51)
krishnae	Bark	Dried	Extract	Inhibition of proliferation and colony formation of breast (MCF-7) cancer cells	(97)
lacor	Extract	Dried	Flavonoids, terpenoids	Contains compound/s with high binding affinity to PARP-1 (an anticancer therapy target)	(82)
microcarpa	Roots	Air-dried	Terpenoids	Antiproliferative activity by G0/G1 phase cell cycle arrest attributed to cyclin kinase inhibitors upregulation and apoptosis induction in AMPK-dependent manner on prostate (DU145, CW22Rv1, PC3) nerve (NB26), and skin (A375) cancer cells.	(98)
microcarpa	Leaves	Air-dried	Glycosides	Inhibition of TNF-α induced IL-8 secretion in the colon (HT-29) cancer cells.	(47)
microcarpa	Roots	Air-dried	Terpenoids	EMT inhibition leads to decreased migration and reverse effect, epithelial markers induction and decreased mesenchymal markers, inhibition of Rac1/NEDD9 pathway on prostate (DU145, PC3, NA22, and NB26) cancer cells	(68)
natalensis	Leaves	Air-dried	Ketone, terpenoids	Compounds associated with anticancer mechanisms via apoptotic pathways	(43)
ovata	Leaves	Air-dried	Fatty acid, ketone, terpenoids	Compounds associated with anticancer mechanisms via apoptotic pathways	(43)
palmata	Fruits	Fresh	Phenolics	Cytotoxic activity on cervical (C33A) cancer cells	(62)
pandurata	Aerial parts	Fresh	Polysaccharide	Antiproliferative activity and apoptosis induction via upregulation of caspase-3 and cleaved-PARP on cervical (HeLa) cancer cells	(99)

Table 3. Continued

Ficus spp.	Plant part	Plant preparation	Compound/ Extract	Mechanism of action	Ref.
pomifera	Leaves	Air-dried	Terpenoids	Cytotoxic activity on lung (A549) cancer cells	(53)
pseudopalma	Leaves	Air-dried	Extract	Inhibition of cell growth and apoptosis induction on liver (HepG2) cancer cells	(100)
pseudopalma	Leaves	Air-dried	Flavonoids, terpenoids	Cytotoxic activity decreased cell viability and apoptosis induction in prostate (PRST2) cancer cells	(46)
pumila	Leaves	Air-dried	Extract	Decrease in number and size of tumorspheres, induction of apoptosis, cell cycle arrest at G2/M phase, upregulation of p53, p21, and GADD45A genes, downregulation of cyclin B1 and cyclin D1 genes on liver (HepG2) cancer cells	(101)
religiosa	Bark	Shade-dried	Phenolics	Cytotoxic activity on cervical (HeLa, SiHa) cancer cells	(73)
religiosa	Extract	Dried	Sterols	Chemo-preventive properties that promote antioxidant gene activity through regulation of Nrf2 factor by competing for receptor site with Keap1 during stressed conditions	(102)
religiosa	Leaves	Air-dried	Alkaloids, flavonoids, phenolics, sterols, tannins	G1 phase cell cycle arrest, sub-g0 phase induction, apoptosis induction, decrease in mitochondrial membrane potential, elevation of Caspase 9 activity, cleavage of prominent Caspases and PARP, intracellular ROS generation, photosensitizing activity through rapid mitochondrial transmembrane potential loss and partial Caspase activation, growth inhibition associated with Bax translocation and mitochondria-mediated apoptosis with the activation of Caspase 9-dependent cascade on breast (MCF-7) cancer cells.	(103)
religiosa	Leaves	-	Carotenoid, ester, ketone, phenolics, terpenoids	Antiproliferative activity on breast (MDA-MB-468) cancer cells	(41)
religiosa	Leaves	Air-dried	Extract	Antiproliferative activity on breast (MCF-7) cancer cells	(104)
religiosa	Leaves	Shade-dried	Extract	Antiproliferative activity on leukemia (Jurkat) cells	(105)
rumphii	Leaves	Air-dried	Ketone, phenolics	Antiproliferative activity on lung (A549), liver (HepG2), and breast (MDA-MB-361) cancer cells	(48)
salicifolia	Latex (leaves)	Fresh	Extract	Antiproliferative activity, anti-metastatic, genotoxic, and cytotoxic activity, and upregulation of ERK2, CREB, and AKT2 at the transcriptional level on breast (MDA-MB-231) cancer cells	(84)
septica	Leaves	Air-dried	Alkaloids	Cytotoxic activity on stomach and nasopharyngeal (NUGC and HONE-1) cancer cells	(33)
septica	Leaves	Air-dried	Alkaloids	Cytotoxic activity on cervical (HeLa) cancer cells	(34)
septica	Stem	Air-dried	Alkaloids	Cytotoxic activity on stomach and nasopharyngeal (NUGC and HONE-1) cancer cells	(69)
septica	Roots	Air-dried	Alkaloids	Cytotoxic activity on stomach and nasopharyngeal (NUGC and HONE-1) cancer cells	(64)
septica	Leaves	Air-dried	Alkaloids	Cytotoxic activity on breast (T47D) cancer cells	(37)
septica	Leaves	Fresh	Extract	Decrease cell viability on breast (T47D) cancer cell	(106)
septica	Leaves	Air-dried	Extract	Apoptosis induction via p53-independent pathway	(107)
septica	Leaves	Air-dried	Extract	Cytotoxic activity on lung (A549) and colon (HCT-116) cancer cells	(108)
sycomorus	Fruit	Air-dried	Flavonoids	Compounds implicated in anticancer activities	(61)
vasta	Fruit	Air-dried	Flavonoids, Phenolics	Reduction of cell viability, disruption of the cell membrane, leaking of cell debris, and apoptotic bodies development in lung and breast (A549; MDA-MB-231) cancer cells	(60)
virens	Leaves	Dried	Carotenoid, Ester, Ketone, Phenolics, Terpenoids	Antiproliferative activity on breast (MDA-MB-468) cancer cells	(41)

from *Ficus foveolata* stems, such as the eudesmane-type sesquiterpene eoveolide A and the sesquiterpenoid dimer Foveolide B. Foveolide A showed moderate cytotoxicity against colorectal (SW620), liver (HepG2), breast (BT474), and gastric (KATO-III) cancer cell lines, while Foveolide B exhibited cytotoxicity specifically towards colorectal cancer cells (70).

Some species have been shown to have both direct actions on cancer cells and indirect effects, such as enhancing chemotherapeutic efficacy. For instance, *Ficus carica* offers a broad range of therapeutic effects. It contains flavonoids, phenolics, and sterols with cell proliferation inhibition, apoptosis induction, and downregulation of cancer-related genes across various cancer types, such as glioblastoma, breast, and colon cancers (75-89). It is also recognized for its ability to enhance chemotherapy efficacy, such as potentiating TMZ effects on glioblastoma cells (75). Similarly, *Ficus religiosa* possesses a diverse array of compounds, including phenolics, sterols, alkaloids, and flavonoids, which are potent in inducing G1 phase arrest and apoptosis in breast cancer cells (41,103,104) and exhibiting chemo-preventive actions through antioxidant regulation (102). *Ficus microcarpa*, with its terpenoid and glycoside content, prevents the migration of cancer cells (metastasis) inhibiting cancer cell migration and metastasis by epithelial-mesenchymal transition (EMT) inhibition (47,68).

While each *Ficus* species possesses a unique phytochemical profile, they collectively present a diverse range of anticancer mechanisms, including apoptosis induction (95,96,98,101), inhibition of cancer metastasis (46,68,92), and regulation of key cancer-related pathways (78,79,89,107). The differences in their bioactive compounds and mechanisms underscore the potential for targeted cancer therapies using specific *Ficus* species, as well as the need for further research to explore their full therapeutic potential.

Mechanisms of anticancer actions

Figure 2 summarizes the anticancer mechanisms of *Ficus* species extracts and compounds based on the studies included in this review. The extracts have exhibited their effects through apoptosis, cell cycle arrest, and tumor suppression. Apoptosis is induced via death receptor pathways and mitochondrial dysfunction, involving key regulators such as BAX, BAK, and caspases (78,89,90,103). The generation of reactive oxygen species (ROS) supplements this process, further inhibiting cancer cell proliferation (40,55,79).

Cell cycle arrest occurred through the downregulation of critical proteins like CDK1, CDK4, CDK9, and cyclin D1, which effectively halted cancer cell growth (90,92,98,101). Tumor progression and metastasis were also suppressed by reduced VEGF expression, which inhibited angiogenesis (87), and by decreased levels of MMP-2 and MMP-9, which limited cancer cell invasion (39). Cytotoxicity was driven by mitochondrial damage, modulation of cancer-related genes (e.g., TP53, Bcl-2) (40,90), and chemopreventive effects through Nrf2-mediated antioxidant pathways (102). Collectively, these mechanisms represent an integrated response that inhibits tumor growth, metastasis, and cancer progression, highlighting the broad anticancer potential of *Ficus* species as demonstrated by the studies included in this review.

Discussion

The Philippines' tropical climate provides year-round access to plant leaves, making them a sustainable resource for traditional healers (109). Leaves are preferred for their accessibility, ease of collection, minimal invasiveness, and richness in bioactive compounds. Decoction, a common traditional preparation, enhances the extraction of these compounds by utilizing their water-soluble nature, making medicinal properties more accessible (110-112). This method aids in breaking down cell walls through boiling, releasing active phytochemicals (113). Its simplicity makes decoction an essential practice in rural areas with limited healthcare access. In many Philippines' rural communities, figs are believed to house spirits and deities, highlighting their spiritual and cultural significance in healing rituals (7,8,114). Local healers often combine spiritual and physical approaches to health, making *Ficus* species central to holistic practices and alternative cancer treatments (115,116).

Plants, like all organisms, have natural defense systems to scavenge free radicals, but environmental changes lead to excessive free radical production, causing oxidative stress. This damage, in humans, can contribute to cancer (117,118). Bioactive compounds involved in plant defense against oxidative damage are typically alkaloids, phenolics, and terpenoids (119). These compounds, found in plants, play crucial roles in defense mechanisms and pharmaceutical research (120). Terpenoids, along with alkaloids and phenolics, are central to the chemical defense strategies of *Ficus* species (121). Alkaloids are toxic to herbivores and microorganisms, enhancing plant defense. This diversity of chemical defenses, crucial for addressing biotic and abiotic stresses, is also linked to their anticancer potential, targeting cellular DNA damage induced by carcinogens (122).

Flavonoids scavenge ROS and protect plants from environmental stressors like UV radiation and pathogens (123-126). In humans, they reduce oxidative stress, a key driver of DNA damage and cancer, while enhancing blood plasma antioxidant capacity and preventing LDL oxidation (127). *Ficus* fruits, rich in flavonoids, especially anthoxanthins and anthocyanins, play vital roles in seed protection and reproduction by attracting dispersers (128). The flavonoid content in *Ficus* fruits highlights their therapeutic potential, both in traditional medicine and as functional foods with health benefits.

The roots of *Ficus* species, though less diverse in compounds, are rich in alkaloids with high cytotoxic potential. This is due to structural features like a rigid phenanthrene structure and specific substitution patterns that enhance toxicity, supported by structure-activity relationship studies (129). The accumulation of alkaloids and terpenoids in the stem bark serves as chemical deterrents to herbivores and insects. Flavonoids and phenolics protect against UV radiation, oxidative damage, and fungal infections (130,131). However, the lower compound diversity in stems likely reflects their primary structural role rather than metabolite production.

Ficus spp. latex plays key roles due to its biochemical composition. Enzymes and metabolites in latex facilitate nutrient transport, ensuring efficient distribution within the plant (132). The phenolic and flavonoid content enhances the plant's protection, with phenolics providing antioxidant and antimicrobial properties and flavonoids offering anti-inflammatory and cytotoxic effects (133). Its sticky texture and irritants deter herbivores and pests. Some of these latex compounds also show anticancer activity (75,76), suggesting that *Ficus* latex not only supports the plant's survival but may also have therapeutic applications.

The traditional uses of *Ficus* species in the Philippines align with laboratory findings, further supporting their therapeutic potential. For example, *Ficus* septica and *Ficus* elastica decoctions and poultices, used for cancer symptoms such as external swelling (24–26), are supported by laboratory findings showing anti-inflammatory and antioxidant properties. These properties may help reduce oxidative stress and promote healing (65,66). The use of *Ficus botryocarpa* and *Ficus concinna* bark decoctions by the Subanen and Manobo tribes (21,22) was not supported by studies included in this review. However, extracts from other *Ficus* species' bark, such as *Ficus drupacea, Ficus exasperata, Ficus fistulosa, Ficus glumosa,* and *Ficus religiosa*, demonstrated significant cytotoxic effects against various types of cancer (35,71-74). This complex biochemical profile enables the bark to withstand external pressures, promoting the plant's resilience and enhancing its medicinal potential. The synthesis of these compounds is influenced by the bark's structural role, environmental exposure, and the need to protect vital tissues from damage, making it a reservoir of therapeutic molecules (134).

The wide range of compounds in *Ficus* species suggests that traditional preparation methods were developed to maximize the plant's therapeutic potential. Despite the lack of scientific knowledge about its chemical composition, locals utilized its benefits by applying various preparation techniques. This mirrors how modern extraction protocols in *in vitro* studies isolate potent compounds. Traditional methods like decoctions and salves correspond to the plant's bioactive compound variety. Decoction extract water-soluble compounds by boiling leaves or bark, are ideal for treating systemic issues like internal inflammation. Salves, made by crushing plant materials for topical use, concentrate compounds found in the plant's sap or oils, providing localized relief for swelling. The alignment between traditional methods and the pharmacological effects of *Ficus* phytochemicals offers a scientific rationale for their use in managing conditions such as cancer, validating the effectiveness of these practices. These correlations emphasize how traditional knowledge complements scientific research, offering valuable insights into *Ficus* species' therapeutic uses. However, they also underline the need for further studies, particularly in vivo and clinical trials, to confirm the efficacy and pharmacokinetics of these preparations in modern medicine.

Implications for therapeutic development

Variability in experimental methods, such as extraction techniques, solvents, and concentration, presents challenges in comparing results. The lack of in vivo studies limits understanding of pharmacokinetics and efficacy in living organisms. Translating *Ficus* findings into clinical applications faces additional hurdles, including the complexity of isolating active compounds, the need for standardization, and regulatory challenges. The diverse nature of *Ficus* metabolites may necessitate advanced formulation techniques to enhance bioavailability and ensure target-specific delivery.

Future research should prioritize clinical trials to evaluate the safety and efficacy of *Ficus* extracts, particularly for less-studied cancer types. Investigating molecular mechanisms, such as the modulation of signaling pathways involved in apoptosis and cell cycle regulation, will be critical to understanding their therapeutic potential. Moreover, studying underexplored *Ficus* species may lead to the discovery of novel bioactive compounds with distinct anticancer properties. This review reinforces the potential of *Ficus* species as valuable resources in cancer research and therapy, offering promising opportunities for future drug development.

Conclusion

Five *Ficus* species—*Ficus septica*, *Ficus elastica*, *Ficus congesta*, *Ficus concinna*, and *Ficus botryocarpa*—have been traditionally used in the Philippines as cancer remedies, with leaf decoctions being the most common preparation. Laboratory studies confirm a diverse array of bioactive compounds, including terpenoids, alkaloids, flavonoids, and phenolics, distributed differently across plant parts. Terpenoids were most abundant in leaves, flavonoids in fruits, and alkaloids and phenolics in roots. Novel chemical compounds unique to specific species were also identified, highlighting the distinct phytochemical profiles of different plant parts that contribute to their medicinal properties.

A correlation between traditional knowledge and

scientific findings is evident, as laboratory studies support the therapeutic potential of *Ficus* species against cancer. These species demonstrated anticancer activity across a wide range of cell lines, including those from the breast, lung, liver, colon, prostate, cervix, ovary, stomach, kidney, oral cavity, blood, skin, bone, and brain. Their mechanisms of action include inducing cell cycle arrest, apoptosis, and anti-angiogenesis, modulating antioxidant genes, and inhibiting cancer growth and metastasis. However, research variability and the scarcity of *in vivo* studies present challenges in translating these findings into clinical applications. Key limitations include differences in experimental methods, difficulties isolating active compounds, standardizing preparation techniques, and enhancing bioavailability. Future research should prioritize clinical trials, further elucidation of molecular mechanisms, and exploration of understudied species to fully harness the anticancer potential of *Ficus*. By bridging traditional knowledge with contemporary scientific evidence, this study underscores the alignment between ethnobotanical practices and laboratory results, offering a robust foundation for advancing *Ficus* species as promising candidates for cancer research and therapy. *In vivo* studies remain crucial to validate these findings and unlock the full therapeutic potential of this underexplored genus.

Authors' contribution

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Conflict of interests

The authors declare there is no conflict of interest.

Ethical considerations

The review followed the PRISMA guidelines, overseen by the PRISMA Executive, to ensure transparency and methodological rigor. Ethical issues, including plagiarism, have been completely observed by the authors.

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