

An evidence-based review of the ethnomedicinal, phytochemical, and pharmacological properties of *Typhonium flagelliforme*

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Author contributions

Mohammad Amin SA contributed to the study conception and design, data collection, analysis and interpretation of results, and drafted the manuscript. Choo YM contributed to the study conception and design, analysis and interpretation of results, and manuscript drafting. All authors reviewed the results and approved the final version of the manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

A549, adenocarcinomic human alveolar basal epithelial cells; BCL-2, B-cell lymphoma 2; bp, base pairs; DCM, dichloromethane; DPPH, 2,2-diphenyl-1-picrylhydrazyl; GAE, gallic acid equivalent; HeLa: cervical cancer immortal cell line; HepG2, human liver carcinoma cell line; HER2/neu, human epidermal growth factor receptor 2; HS578T, human breast cancer cell line; KB, oral cancer cell line; MCF-7, michigan cancer foundation-7; MDA-MB-231, human breast cancer cell line; NCI-H23, lung cancer cell line; ORL, oral squamous cell carcinoma; OVCAR3, ovarian adenocarcinoma cell line; SCC-25, squamous cell carcinoma; T-47D, breast tumor cells; TF, *Typhonium flagelliforme*; TFS, *Typhonium flagelliforme* syrup; TMT, tocopherol methyltransferase; TNF- α , tumor necrosis factor; TPGS, tocopheryl polyethylene glycol 1000 succinate; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; WiDr, colon cancer cell line.

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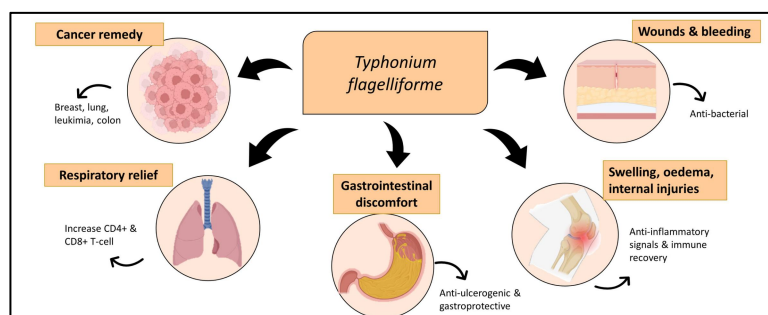
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Abstract

Typhonium flagelliforme (TF) is a Southeast Asian medicinal plant traditionally used for cancer, respiratory disorders, gastrointestinal complaints, wound healing, inflammation, and general health. Contemporary studies validate these uses, showing potent anticancer, immunomodulatory, anti-inflammatory, gastroprotective, antibacterial, antioxidant, and wound-healing activities. Ethanol, dichloromethane, methanol, and ethyl acetate extracts exhibit strong cytotoxicity against breast (MCF-7, T47D), lung (NCI-H23), colon (WiDr), and leukemia (CEM-ss, WEHI-3) cells via apoptosis, telomerase inhibition, HER2/neu and BCL-2 suppression, and antiangiogenesis. Notably, 2-octenoic acid and 2-hexenoic acid show exceptional activity (IC_{50} = 2.66 and 3.10 μ g/mL) against MCF-7 cells. TF also restores lymphocyte proliferation, enhances macrophage activity, increases both CD4⁺ and CD8⁺ T-cell levels, and modulates cytokines (TNF- α , IL-1 α , IL-10). Gastroprotective, anti-ulcer, antibacterial, antioxidant, and wound-healing effects further support traditional claims. Key phytochemicals include flavonoids (isovitexin, kaempferol, vitexin), phenolics (vanillin, 4-hydroxybenzaldehyde), phytosterols (β -sitosterol, campesterol, stigmasterol, daucosterol), chlorophyll derivatives (pheophorbides), and long-chain fatty acids (linoleic, linolenic, oleic, stearic). These findings highlight TF as a source of multifunctional bioactive compounds, warranting further pharmacokinetic, safety, and clinical evaluation for evidence-based therapeutic development.

Keywords: *Typhonium flagelliforme*, ethnomedicine, phytochemicals, anticancer activity, immunomodulation



Highlights

1. Comprehensive synthesis of the phytochemistry, ethnomedicinal relevance, and pharmacological activities of *Typhonium flagelliforme*.
2. Evidence supports notable anticancer potential, including potent cytotoxic effects of 2-hexenoic and 2-octenoic acids against MCF-7 cells.
3. Antioxidant, anti-inflammatory, and immunomodulatory activities highlight bioactivity beyond direct cytotoxic effects.

Medical history of objective

The history of *Typhonium flagelliforme* is rooted in ancient East and Southeast Asian medicinal traditions, where it has been valued for over two millennia as a treatment for respiratory and inflammatory conditions. Early Chinese medical texts, such as the *Shennong Bencao Jing* (circa 1st–2nd century AD), first classified species of the *Typhonium* genus for their detoxifying properties, a role further elaborated by the Ming Dynasty physician Li Shizhen in his 16th-century work *Bencao Gangmu*. In this work, the rhizomes were described as being used to alleviate pathological accumulations associated with abnormal mucus and fluid retention, reduce localized masses, and treat inflammatory swellings and suppurative lesions such as abscesses. In Southeast Asia, particularly Malaysia and Indonesia, the plant is known as “*keladi tikus*” and has a long-standing history as a folk remedy for coughs, asthma, and skin diseases.

Introduction

Natural products are secondary metabolites characterized by distinct biological activities, obtained through extraction and isolation from various sources including plants, animals, microorganisms, and marine organisms [1]. Plants possess a substantially greater number of genes than many other living organisms, including mammals and bacteria. However, despite this remarkable genetic diversity, only about 400,000 plant species worldwide have been extensively investigated for their phytochemical composition [2, 3].

Typhonium flagelliforme (TF) also known as “rodent tuber” in English or “*keladi tikus*” in Malay, is a tropical plant belonging to the *Araceae* (Arum) family [4]. It has recently gained taxonomic and pharmacological attention. Normally this plant grows in damp, soft and shady place in certain countries including Southeast Asia, South India, Sri Lanka and Australia [5]. In the beginning, it has been used to treat coughs, relieve asthma and treat cancer [4].

In Southeast Asian traditional medicine, this plant is frequently used to cure a variety of illnesses [6]. In ethnomedicine, this plant is used to cure cancer and is characterized as poisonous, warming, and phlegm-resolving. It is also used to relieve coughing and swelling [7]. As a substitute therapy for several forms of cancer, TF is traditionally consumed in Malaysia with fruit juice or as a dry extract along with other herbal medicines [7]. This plant has been widely utilised as a component of traditional herbal remedies to treat liver, lung, breast, and colon cancers [7].

Beyond cancer-related uses, TF has also been traditionally used to manage inflammatory, respiratory, and injury-related conditions. Traditional uses of the plant's rhizomes include treating various lung conditions and acting as an expectorant for coughs. Additionally, it has anti-inflammatory, anti-asthmatic, analgesic, and sedative properties [8]. TF has been used to treat oedema and internal injuries [7]. The blooms of TF have been used as a remedy for wounds and to reduce bleeding [9]. This plant is also used to treat lymphatic swellings, reduce inflammation, decrease pain, and calm spasms. TF helps to minimise epigastric and abdominal distention, fight nausea

and vomiting, and calm the stomach. It also has strong antihepatotoxic properties [10, 11].

Typically, the juice of the fresh, complete TF plant is made into a drink with honey [7]. With some other customs, the leaves are wrapped with Longan flesh and consumed uncooked [12]. Additionally, pharmacological research on rats showed that the juice extract might stop the development of hepatocarcinogenesis [13]. TF appears to be a promising medicinal plant with notable antioxidant and antibacterial properties [14].

This paper presents a comprehensive narrative review of TF. The primary objective of this review is to identify the chemical constituents of TF and to summarize the biological activities and ethnomedicinal uses. By compiling and analyzing the available chemical constituents and biological evidence, this review provides an organized overview of TF, highlights patterns and inconsistencies in current research and identifies areas where further study is needed.

Methodology

A systematic and comprehensive literature search was conducted using SciFinder (<https://scifinder-n.cas.org/>), with the final search performed in November 2025, to identify relevant studies on TF. A wide range of keywords associated with the plant were employed to ensure thorough coverage. Publications of all formats, including original research articles, review papers, and conference proceedings, were included to comprehensively capture available evidence on its chemical composition, biological activities, and ethnomedicinal applications.

Chemical constituents

The chemical profiling of TF has revealed a diverse spectrum of secondary metabolites encompassing flavonoids, phytosterols, hydrocarbons, fatty acids, and phenolic derivatives. Among flavonoids, compounds such as isovitexin 1, kaempferol 2, kaempferol 3-O-rutinoside 3, vitexin 4, and kaempferol 3-O-(6"-acetylglactoside)-7-O-rhamnoside 5 have been identified (Figure 1), contributing to its anticancer, antioxidant and antibacterial activity. The phytosterols fraction includes β -sitosterol 6, campesterol 7, stigmasterol 8, and daucosterol 9 (Figure 2), which are known for their anticancer properties. Long-chain hydrocarbons and fatty acids, including squalene 11, linoleic acid 51, linolenic acid 52, oleic acid 53 (Figure 3, 4), stearic acid 57, and their methyl/ethyl esters, along with various alkanes and aldehydes, constitute another major class, highlighting the lipid-rich chemical profile of TF. In addition, other compounds such as ferulic acid 64, *p*-coumaric acid 66, caffeic acid 65, cinnamic acid 67, vanillin 62 and coniferin 69 (Figure 5) have been reported, further supporting the pharmacological relevance of the plant. Collectively, these diverse phytoconstituents suggest that TF possesses significant therapeutic potential due to the synergistic contributions of flavonoids, sterols, lipids, and phenolic derivatives. The compounds identified from TF are summarized in Table 1 [5, 11, 13, 15–24], and their chemical structures are illustrated in Figures 1–5.

Although a wide range of chemical constituents has been reported from TF, not all compound classes are likely to contribute equally to its pharmacological activities. Long-chain hydrocarbons and common fatty acids are present in large amounts, but these compounds usually show weak or non-specific biological effects. Nevertheless, isolated compounds such as 2-hexenoic acid (54) and 2-octenoic acid (55) demonstrated strong cytotoxicity against MCF-7 cells (IC_{50} = 3.10 and 2.66 μ g/mL, respectively), which indicates potent activity according to National Cancer Institute standards (IC_{50} < 20 μ g/mL), highlighting their potential relevance as bioactive constituents (Table 2) [13, 17, 19–22, 24–30, 33]. In contrast, secondary metabolites

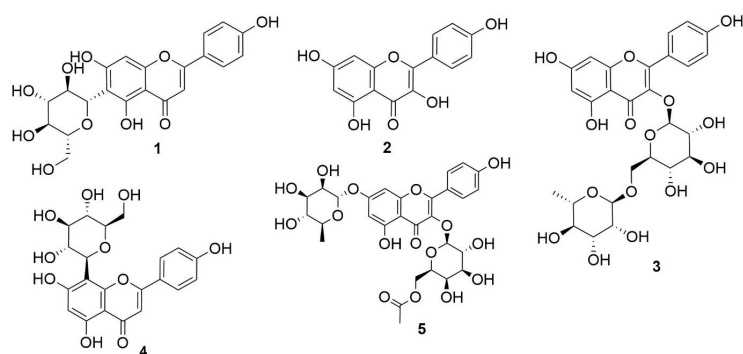


Figure 1 Flavonoids reported from *Typhonium flagelliforme*.

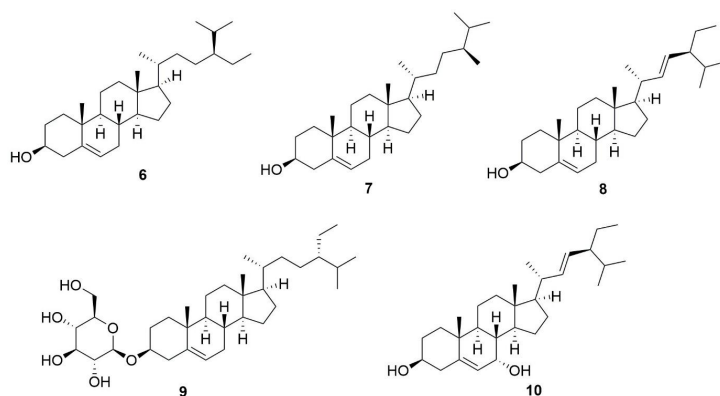


Figure 2 Phytosterols reported from *Typhonium flagelliforme*.

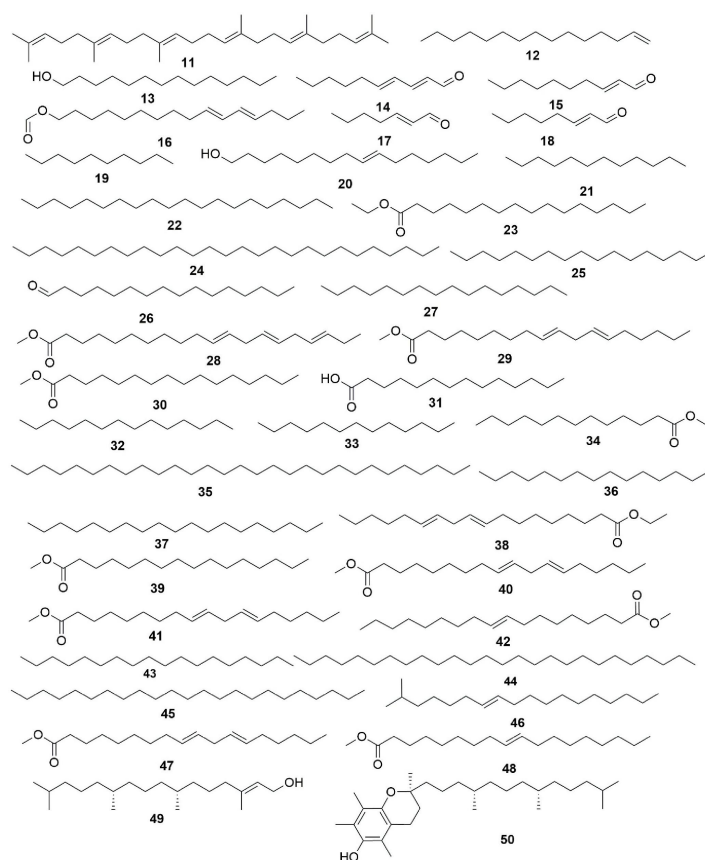
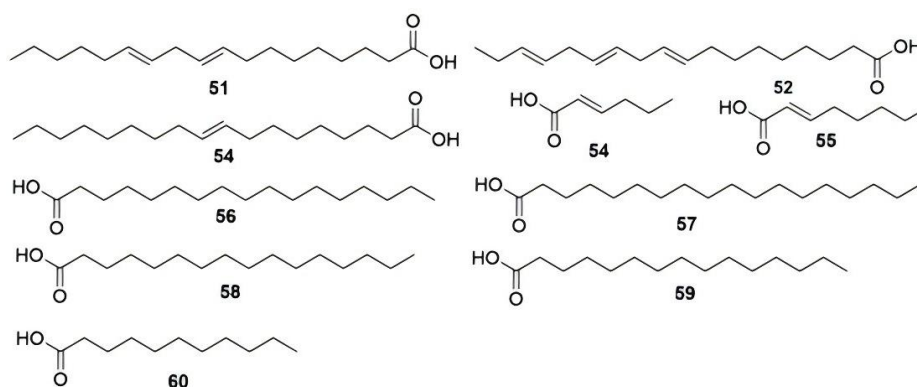
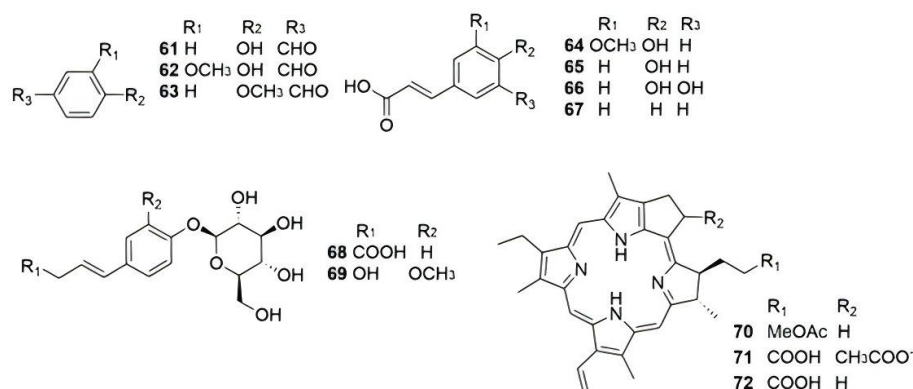


Figure 3 Long-chain hydrocarbon reported from *Typhonium flagelliforme*.

Figure 4 Fatty acid reported from *Typhonium flagelliforme*.Figure 5 Other compounds reported from *Typhonium flagelliforme*.Table 1 Chemical constituents of *Typhonium flagelliforme*

Chemical constituents of <i>Typhonium flagelliforme</i>			
Flavonoids			
Isovitexin 1 [15]	Kaempferol 3-O-rutinoside 3 [16]	Vitexin 4 [16]	Kaempferol 3-O-(6"-acetylglactoside)-7-O-rhamnoside 5 [16]
Phytosterols			
β-Sitosterol 6 [17, 18]	Campesterol 7 [17]	Stigmasterol 8 [17-19]	7α-Hydroxyl stigmasterol 10 [20]
Long-chain hydrocarbon			
Squalene 11 [18, 19]	Eicosane 22 [21]	Tetradecanoic acid 31 [5]	9,12-octadecadienoic acid methyl ester 41 [5]
1-Hexadecene 12 [13]	Hexadecanoic acid ethyl ester 23 [19]	Tetradecane 32 [21]	Methyl octadecenoate 42 [21]
1-Tetradecanol 13 [5]	Heptacosane 24 [19]	Tridecane 33 [21]	Octacosane 43 [19]
2,4-Decadienal 14 [5]	Heptadecane 25 [21]	Methyl 13-phenyltridecanoate 34 [21]	Octadecane 44 [21]
2-Decenal 15 [5]	Hexadecanal 26 [5]	Nonacosane 35 [19]	Tricosane 45 [19]
10,12-Hexadecadien-1-ol, 1-acetate 16 [19]	Hexadecane 27 [21]	Pentadecane 36 [21]	cis-2-Methyl-7-octadecene 46 [5]
2-Heptenal 17 [5]	Methyl 11,14,17-eicosatrienoate 28 [5]	Nonadecane 37 [21]	Methyl 9,12-octadecadienoate 47 [21]
2-Octenal 18 [5]	Linoleic acid methyl ester 29 [19]	Ethyl linoleate 38 [19]	Methyl 9-octadecenoate 48 [21]
Decane 19 [5]	Methyl hexadecanoate 30 [21]	Methyl palmitate 39 [5]	Phytol 49 [13]
9-Hexadecen-1-ol 20 [5]		Methyl linoleidate 40 [22]	Tocopherol 50 [23]
Dodecane 21 [21]			
Fatty acid			
Linoleic acid 51 [17, 19]	2-Hexenoic acid 54 [24]	Stearic acid 57 [18, 22]	Pentadecanoic acid 59 [5]
Linolenic acid 52 [17]	2-Octenoic acid 55 [24]	Hexadecanoic acid 58 [5]	Undecanoic acid 60 [5]
Oleic acid 53 [5]	Heptadecanoic acid 56 [5]		
Other			
4-Hydroxybenzaldehyde 61 [16]	Ferulic acid 64 [16]	Cinnamic acid 67 [16]	Methylpyrophephorbide-a 70 [17]
Vanillin 62 [5]	Caffeic acid 65 [16]	p-Coumaric acid glucoside 68 [16]	Pheophorbide-a 71 [17]
p-Anisaldehyde 63 [16]	p-Coumaric acid 66 [16]	Coniferin 69 [11]	Pyrophephorbide-a 72 [17]

such as flavonoids, phytosterols, phenolic acids, and chlorophyll-derived compounds are more frequently associated with strong biological activities in TF. Compounds such as the flavonoids, the phytosterol such as stigmasterol, and chlorophyll derivatives like pheophorbide-a are repeatedly linked to anticancer, antioxidant, and immunomodulatory effects.

Biological activities of *Typhonium flagelliforme*

TF, commonly known as “*keladi tikus*” in Malaysia, demonstrates diverse anticancer, antioxidant, and immunomodulatory properties. Among its extracts, the dichloromethane (DCM) and ethyl acetate fractions exhibit the most potent cytotoxicity against multiple cancer cell lines, including breast (MCF-7, HS578T), lung (NCI-H23), and leukemia (CEMss) cells, with IC_{50} values frequently below 30 $\mu\text{g/mL}$. Ethanolic extracts show notable anticancer potential by inducing apoptosis and modulating immune responses through enhanced cytokine and lymphocyte activity. Furthermore, methanolic and ethyl acetate extracts display strong antioxidant activity, effectively scavenging free radicals and contributing to cellular protection. In summary, these findings position TF as a promising multipotent medicinal plant with potential therapeutic applications in cancer treatment and oxidative stress regulation. It should be noted that the majority of biological activity studies on TF have been conducted using in vitro cancer cell models, with limited in vivo validation and mechanistic elucidation.

Anticancer activity of TF

Anticancer activity is the most extensively investigated biological property of TF. Studies have evaluated its cytotoxic effects using various extract types and experimental models, primarily focusing on breast, lung and leukemia cancer cell lines. The following subsection summarizes and compares these findings.

Breast cancer cell lines. Extensive studies have demonstrated the cytotoxic potential of TF extracts and isolated compounds against various breast cancer cell lines, including MCF-7, HS578T, T-47D, MDA-MB-231, and breast cancer stem cells (bCSCs). The dichloromethane (DCM) extract and its fractions displayed strong antiproliferative effects, particularly fraction DCM/F19, which exhibited potent cytotoxicity against HS578T breast cancer cells ($IC_{50} = 2.6 \mu\text{g/mL}$) after light activation [17], and inhibited bCSCs derived from MCF-7 cells ($IC_{50} = 50.89 \mu\text{g/mL}$) [25]. In addition, the methanol:DCM (1:1) extract showed age-dependent cytotoxicity toward MCF-7 cells, with the most active sample from two-month-old plants ($GI_{50} = 6.2 \mu\text{g/mL}$) [26]. The methanol extract of TF also exhibited cytotoxicity toward MDA-MB-231 cells ($IC_{50} = 110 \mu\text{g/mL}$) [27].

Formulation and processing approach further influenced efficacy. Nanoemulsion formulations, mutant plant extracts, and fractionated samples generally exhibited enhanced cytotoxicity compared to crude extracts, suggesting improved bioavailability or enrichment of active constituents. In contrast, some isolated compounds, such as methyl 13-phenyltridecanoate (34), displayed weaker activity than their parent fractions, indicating that synergistic effects within complex extracts may contribute substantially to cytotoxic outcomes.

These findings indicate that TF exhibits substantial and reproducible cytotoxic activity against multiple breast cancer cell lines, with the most pronounced effects observed in ethanol, ethyl acetate, and DCM extracts, as well as in nanoemulsion and mutant plant formulations. Detailed IC_{50} values and experimental conditions are summarized in Table 2.

Overall, TF exhibits notable in vitro cytotoxic activity against breast cancer cell lines, particularly in dichloromethane, ethyl acetate, and ethanolic extracts, with IC_{50} values frequently below 30 $\mu\text{g/mL}$. Highly active samples include DCM-derived fraction 19 (DCM/F19) ($IC_{50} = 2.6 \mu\text{g/mL}$), ethyl acetate fractions ($IC_{50} = 1.09 \mu\text{g/mL}$), and nanoemulsion formulations ($IC_{50} = 1.89 \mu\text{g/mL}$), indicating strong antiproliferative potential. In contrast, polar

fractions such as aqueous extracts were inactive, and some methanol extracts showed only moderate activity (e.g., $IC_{50} = 110 \mu\text{g/mL}$ against MDA-MB-231 cells), highlighting solvent-dependent efficacy. These findings suggest that anticancer activity is concentrated in specific mid-polarity fractions, while several extracts exhibit limited or negligible effects.

Lung carcinoma cell line (NCI-H23). Previous investigations have highlighted the potent cytotoxic activity of TF extracts and fractions against NCI-H23 human lung carcinoma cells. The DCM extract exhibited marked growth inhibitory activity, with an IC_{50} value of $15.4 \pm 2.7 \mu\text{g/mL}$, whereas the hexane extract showed moderate potency ($IC_{50} = 53.9 \pm 1.9 \mu\text{g/mL}$) and the methanol extract was inactive ($IC_{50} > 100 \mu\text{g/mL}$) [13]. Further fractionation of these extracts enhanced the cytotoxic potential. The hexane extract produced several active fractions such as H/F1/04 ($IC_{50} = 9.51 \pm 1.68 \mu\text{g/mL}$), H/F1/05 ($IC_{50} = 9.60 \pm 1.45 \mu\text{g/mL}$), and H/F13/03 ($IC_{50} = 13.37 \pm 1.05 \mu\text{g/mL}$), all showing significant inhibition of NCI-H23 cell proliferation. Similarly, DCM-derived fractions including DCM/F18 ($IC_{50} = 9.6 \pm 1.9 \mu\text{g/mL}$), DCM/F19 ($IC_{50} = 6.0 \pm 0.4 \mu\text{g/mL}$), and D/F21 ($IC_{50} = 7.5 \pm 0.8 \mu\text{g/mL}$) demonstrated pronounced cytotoxicity [13].

A subsequent study confirmed the exceptional potency of DCM/F19, which exhibited the strongest cytotoxic response against NCI-H23 cells with an IC_{50} of 2.7 $\mu\text{g/mL}$ after light activation [17]. The methanol-derived fractions of TF also showed strong cytotoxicity toward lung carcinoma cells [28]. Among the extracts from both in vitro plantlets and mature plants, the hexane fraction exhibited the highest potency. The chloroform fraction demonstrated moderate activity, while the butanol fraction showed comparable or slightly higher efficacy. Notably, extracts from mature plants consistently outperformed those derived from in vitro plantlets, indicating possible enhancement of cytotoxic constituents during plant maturation [28].

Overall, studies on NCI-H23 lung carcinoma cells demonstrate that TF exhibits strong and reproducible in vitro cytotoxic activity, with clear differences in potency among extract and fraction types. Dichloromethane fractions showed the highest activity, particularly fraction DCM/F19, which displayed the lowest IC_{50} value (2.7 $\mu\text{g/mL}$) and was identified as the most active component to date. This activity has been attributed to the presence of pheophorbide-a (71) and pyropheophorbide-a (72). Hexane fractions exhibited moderate cytotoxicity ($IC_{50} \approx 9\text{--}13 \mu\text{g/mL}$), whereas methanol extracts were largely inactive ($IC_{50} > 100 \mu\text{g/mL}$), indicating that non-polar to mid-polar constituents are primarily responsible for the observed effects. These findings are summarized in Table 3 [13, 17, 28], and collectively, these results highlight both the relative potency of specific fractions and the preliminary nature of the available evidence.

Leukemia cell lines. Previous studies have demonstrated the cytotoxic and anti-leukemic potential of TF extracts and their fractions against various leukemia and lymphoma cell lines. The ethanol extract of TF significantly inhibited telomerase expression in Raji lymphoma cells, showing moderate cytotoxicity and a marked reduction in telomerase activity at both half- IC_{50} and IC_{50} concentrations, suggesting telomerase suppression as a potential mechanism of action [31]. Among solvent extracts, the DCM extract consistently exhibited the strongest cytotoxic effects across leukemia models.

TF demonstrates selective and potent cytotoxicity against leukemia cell lines, particularly in DCM extracts and their fractions. The DCM/F7 fraction exhibited strong activity against CEM-ss cells ($IC_{50} = 3 \mu\text{g/mL}$), comparable to the standard drug 5-fluorouracil ($IC_{50} = 1.43 \mu\text{g/mL}$). Conversely, hexane and methanol extracts showed weaker or moderate activity ($IC_{50} = 15\text{--}88 \mu\text{g/mL}$), and isolated compounds such as methyl 13-phenyltridecanoate (34) displayed limited potency ($IC_{50} = 44 \mu\text{g/mL}$). These findings indicate that synergistic effects within fractions contribute more significantly than individual constituents. Overall, these findings indicate that DCM extracts and their active fractions represent the most potent anti-

Table 2 Anticancer activity of *Typhonium flagelliforme* against breast cancer cell lines

Extract / compound	Active	Cell line(s)	IC ₅₀ (µg/mL)	Key findings	Ref.
Methanol extract		MDA-MB-231	110	Moderate cytotoxicity; also affected CHO cells (IC ₅₀ = 100 µg/mL)	[27]
DCM extract		bCSCs	50.89	Moderate inhibition of bCSCs proliferation	[25]
Ethanol extract		T-47D, HeLa, Vero	66.90, 30.20, 60.50	Broad activity, moderate potency	[33]
Fractions from hexane extract		P388 (comparison study)	15.0 (F2), 5.2 (F4)	F4 active; isolated compound methyl 13-phenyltridecanoate 34 weak (IC ₅₀ = 44.0 µg/mL)	[21]
Ethanol extract		HeLa, MCF-7	30.19, 5.59	Higher inhibition with increasing concentration	[13]
DCM extract (Fraction 19; DCM/F19)		HS578T	2.6	DCM/F19 showed potent cytotoxicity (IC ₅₀ = 2.6 µg/mL) against HS578T after light activation; subfractions less active.	[17]
Ethanol extract		MCF-7	27.55	Maintained cytotoxicity post gamma-irradiation	[29]
Ethanol extract of TF from two mutant clones (KB-6-1-3-4 and KB-6-9-5)		MCF-7	12.48 (KB-6-1-3-4), 7.04 (KB-6-9-5)	Enhanced activity in mutant clones vs control (IC ₅₀ = 19.11 µg/mL)	[22]
Ethanol extract		MCF-7	25.87	Baseline cytotoxic effect	[29]
Methanol:DCM (1:1) extract		MCF-7	6.2–57.5	Best activity from two-month-old plants (GI ₅₀ = 6.2 µg/mL)	[26]
Methanol extract fractions (Hexane, CHCl ₃ , BuOH)		T-47D	12.2 (Hexane), 23.0 (CHCl ₃), 54.6 (BuOH)	Mature plant fractions more potent than in vitro	[28]
Tuber protein		MCF-7	≤ 100 ppm (non-toxic to fibroblasts)	Selective antiproliferation of cancer cells	[28]
Ethanol nanoemulsion (F22)		MCF-7	1.89	Nanoemulsion enhanced potency vs crude extract (IC ₅₀ = 2.35 µg/mL)	[19]
2-Hexenoic acid 54 , 2 octenoic acid 55		MCF-7	3.10 (21), 2.66 (23)	Isolated compounds showed strong cytotoxicity	[24]
Stigmasterol 8 , 7α-hydroxyl stigmasterol 10		MCF-7	9.13 (8), 12.97 (10)	Both compounds exhibited potent cytotoxic effects, showing stronger activity	[20]
DCM extract		bCSCs co-cultured with TAMs	50.89	TF may promote the increase of Hsp-70 expression in TAMs.	[30]

DCM: dichloromethane; MDA-MB-231, T-47D, MCF-7, and HS578T: human breast cancer cell lines; bCSCs: breast cancer stem cells; HeLa: cervical cancer immortal cell line; P388: mouse leukemia cell line; TAMs: tumor-associated macrophages.

Table 3 Anticancer activity of *Typhonium flagelliforme* against NCI-H23 lung carcinoma cells

Extract / Active compound	IC ₅₀ (µg/mL)	Key findings	Ref.
Hexane, DCM, and methanol extracts; DCM and hexane fractions (H/F1–H/F16, D/F18–D/F21)	6.0–53.9	DCM extract showed strong cytotoxicity (IC ₅₀ = 15.4 µg/mL); D/F19 was most potent (IC ₅₀ = 6.0 µg/mL). Hexane fractions H/F1/04–H/F13/03 also exhibited notable activity (IC ₅₀ ≈ 9–13 µg/mL), while methanol extract was inactive.	[13]
DCM extract and its subfractions (DCM/F19–F19/04; pyropheophorbide-a (72), pheophorbide-a (71))	2.7–18.4	Fraction DCM/F19 showed strongest cytotoxicity (IC ₅₀ = 2.7 µg/mL) after light activation; subfractions DCM/F19/01–F19/05 also active (IC ₅₀ = 4.4–6.8 µg/mL). Activity attributed to chlorophyll derivatives such as pyropheophorbide-a (72) and pheophorbide-a (71).	[17]
Methanol extract and derived hexane, chloroform, and butanol fractions (from in-vitro and mature plants)	1.2–18.7	Methanol-derived fractions exhibited potent cytotoxicity, especially butanol (1.2 µg/mL, mature plants) and hexane (1.5–1.8 µg/mL); chloroform fraction moderately active (5.2–14.6 µg/mL). Mature plant fractions showed higher potency than in-vitro plantlets.	[28]

DCM: dichloromethane.

leukemic components of TF, with synergistic effects within fractions likely contributing more significantly than individual constituents (Table 4) [4, 5, 21, 31].

Other human carcinoma cell lines and antiproliferation activity.

The cytotoxic evaluation of TF against various human carcinoma cell lines beyond breast and leukemia models demonstrates moderate to selective anticancer potential, depending on the extraction solvent and target cell type. The ethyl acetate extract exhibited limited cytotoxicity toward WiDr human colon carcinoma cells [32], suggesting weaker antiproliferative activity compared to more nonpolar fractions. In contrast, ethanol extracts showed notable inhibition of HeLa human cervical carcinoma cells [33], highlighting

consistent and reproducible activity across studies. Similarly, the ethanol extract demonstrated dose-dependent cytotoxicity against colorectal cancer cells (HCT-116) [6]. These findings indicate that ethanol-soluble constituents in TF may selectively target cervical cancer cells. Meanwhile, the distilled water extract demonstrated only moderate cytotoxicity against KB oral carcinoma cells and was largely inactive against ORL-48 oral squamous carcinoma cells [34].

In hepatocellular carcinoma models (HepG2), methanol-derived fractions of TF, including hexane, chloroform, and butanol fractions, exhibited weak or no cytotoxic effects (EC₅₀ > 100 µg/mL), indicating limited activity when the extract was fractionated [28]. In contrast, a separate study demonstrated that the methanolic extract

Table 4 Anticancer activity of *Typhonium flagelliforme* against leukemia cell lines

Extract / compound	Active	Cell line(s)	IC ₅₀ (µg/mL)	Key findings	Ref.
Ethanol extract		Raji	53.8	The ethanol extract of <i>T. flagelliforme</i> significantly suppressed telomerase expression in Raji lymphoma cells in a dose-dependent manner, with marked reduction observed at half-IC ₅₀ and IC ₅₀ concentrations ($p < 0.01$), suggesting a telomerase-inhibitory mechanism of anticancer action.	[31]
DCM extract and fractions (DCM/F1–F12)		CEM-ss	3–25	The crude DCM extract exhibited potent cytotoxicity (IC ₅₀ = 6 µg/mL), while fractions F7 (3 µg/mL), F11 (5 µg/mL), and F12 (6.2 µg/mL) showed the highest activity, comparable to 5-fluorouracil (IC ₅₀ = 1.43 µg/mL), indicating that the active constituents are concentrated in these fractions.	[5]
DCM extract (fraction DCM/F7, linoleic acid (51)-rich)		CEM-ss	3 ± 0.08	The linoleic acid (51)-rich fraction DCM/F7 demonstrated strong cytotoxicity (IC ₅₀ = 3 µg/mL), exceeding that of pure linoleic acid (IC ₅₀ = 22 µg/mL), suggesting synergistic interactions among multiple compounds in inducing apoptosis and growth inhibition.	[4]
Hexane, DCM, ethyl acetate, and methanol extracts		WEHI-3	24.0 ± 5.2 (DCM); 75–88 (others)	The DCM extract displayed the strongest antiproliferative effect (IC ₅₀ = 24.0 µg/mL), meeting the NCI criterion for active cytotoxicity (IC ₅₀ < 30 µg/mL), while hexane, ethyl acetate, and methanol extracts showed weaker activity.	[4]
Hexane, DCM, ethyl acetate, and methanol extracts		CEM-ss	5.8–37.5	The DCM and ethyl acetate extracts showed high cytotoxicity (IC ₅₀ = 6.5–10.8 µg/mL), whereas methanol exhibited moderate activity (IC ₅₀ = 37.5 µg/mL) and hexane was inactive, confirming DCM and ethyl acetate as the most potent fractions.	[4]
Hexane extract and fractions (F1–F4); Methyl 13-phenyltridecanoate (34)		P388	5.2–15 (extract/fractions); 44.0 (compound 65)	The hexane extract showed weak cytotoxicity (IC ₅₀ = 15 µg/mL). Fraction F4 exhibited enhanced activity (IC ₅₀ = 5.2 µg/mL), but the isolated compound methyl 13-phenyltridecanoate 34 was less potent (IC ₅₀ = 44.0 µg/mL), implying synergistic effects in the fraction.	[21]

DCM: dichloromethane; Raji: human B lymphocyte cell line; CEM-ss: human leukemia cell line; WEHI-3 and P388: murine leukemia cell lines.

of TF showed moderate cytotoxicity toward multiple cancer cell lines, including tongue squamous cell carcinoma (SCC-25) (41 µg/mL), adenocarcinomic human alveolar basal epithelial cells (A549) (38 µg/mL), ovarian adenocarcinoma cell line (OVCAR3) (67.1 µg/mL), and HepG2 (45 µg/mL) cell lines, suggesting that whole-extract synergy may contribute to its activity rather than isolated fractions alone [35].

The biological activities of TF extracts have been explored across various models, revealing notable anticancer and immunomodulatory properties. In an in vivo study on C3H mice bearing mammary adenocarcinoma, the ethanol extract of TF induced a significant increase in tumor cell apoptosis, particularly at 200 mg/kg (33.5 ± 2.25%) compared to control (5.0 ± 0.89%), without affecting TNF-α levels [36]. Similarly, the ethanolic extract demonstrated pronounced antiproliferative and antiangiogenic effects in veterinary cancer models [37]. When combined with recombinant or natural canine interferons (rCaIFN, nCaIFN), it achieved up to 54.03% inhibition of squamous cell carcinoma proliferation and markedly enhanced inhibition of neovascularization (32.2% versus 14.8% for extract alone), indicating synergistic interactions between TF constituents and interferons.

Beyond cytotoxicity, several studies highlight the immunomodulatory potential of TF. The ethanolic extract restored lymphocyte proliferation suppressed by cyclophosphamide and enhanced macrophage phagocytic activity, with 250 mg/kg identified as the optimal immunostimulatory dose [38]. Treatment also elevated CD8⁺ T-cell populations (3.72% → 24.63%) and normalized cytokine profiles by increasing TNF-α and IL-1α while balancing IL-10 levels, effectively reversing chemotherapy-induced immune suppression.

These findings highlight the multifaceted bioactivity of *T. flagelliforme* extracts, with ethanol-based preparations showing the most promising anticancer and immunomodulatory potential across both human and veterinary models (Table 5) [4, 6, 28, 29, 32–39].

TF exhibits variable anticancer effects across different carcinoma models. Ethanolic extracts showed moderate cytotoxicity against HeLa cells (IC₅₀ ≈ 30 µg/mL), whereas ethyl acetate extracts were

weakly active against WiDr colon cancer cells (IC₅₀ = 70 µg/mL). Distilled water extracts demonstrated limited activity against KB oral carcinoma cells (IC₅₀ = 80.75 µg/mL) and were inactive against ORL-48 cells. Notably, methanol-derived fractions were largely ineffective against HepG2 cells (EC₅₀ > 100 µg/mL), with some fractions promoting cell growth.

Collectively, these findings highlight the multifaceted but variable bioactivity of TF. While ethanol-based preparations appear the most promising across human and veterinary models (Table 5). The marked inconsistencies ranging from moderate cytotoxicity to cell growth promotion underscore the critical influence of extract composition and cancer-type specificity. Consequently, while in vitro anticancer activity is evident, differences in experimental models and extract formulations limit direct comparisons and preclude conclusions regarding clinical relevance.

Hepatoprotective activity and toxicity of TF

The ethanol extract of TF has been reported to exhibit hepatoprotective effects in rats with thioacetamide-induced liver injury, as evidenced by improvement of liver biochemical markers, antioxidant enzyme activities, and lipid peroxidation levels. Histopathological and macroscopic analyses further demonstrated attenuation of hepatic damage and fibrosis, with effects comparable to the reference hepatoprotective agent silymarin [40].

Toxicity studies in Sprague–Dawley rats indicated no signs of toxicity or mortality up to 5,000 mg/kg (acute), and daily administration of 22.5–90 mg/kg for 90 days produced no significant hematological, biochemical, or histopathological changes, confirming the extract's safety profile [41]. Complementary assessments in zebrafish embryos further indicated that the ethanol extract exhibited low toxicity at lower concentrations, although dose-dependent developmental toxicity was observed at higher exposure levels. The LC₅₀ values were 555.787 µg/mL at 72 h post-fertilization (HPF) and 494.553 µg/mL at 96 HPF. Concentrations ≥ 400 µg/mL induced embryotoxic effects, including hatching delays, reduced heart rate, and morphological abnormalities such as pericardial edema, jaw

Table 5 Anticancer activity of *Typhonium flagelliforme* (TF) against other human carcinoma cell lines and antiproliferation activity of TF

Extract	Cell line(s)	IC ₅₀ (µg/mL)	Key findings	Ref.
Ethyl acetate extract	WiDr	70	Exhibited weak cytotoxic activity against WiDr cells, indicating limited antiproliferative potential compared to other solvent fractions.	[32]
Ethanol extract	HeLa	30.2	Showed consistent and notable cytotoxicity toward HeLa cells, suggesting effective inhibition of cervical cancer cell proliferation.	[33]
Distilled water extract	KB, ORL-48	80.75 ± 6.01 (KB); inactive (ORL-48)	Showed moderate cytotoxicity toward KB cells and inactivity against ORL-48, indicating limited efficacy of polar water-soluble components.	[34]
Ethanol extract	HCT-116	73.47	Demonstrated dose-dependent cytotoxicity after 24 h exposure. Cell viability decreased sharply at 100 µg/mL (34.78%), moderately at 80 µg/mL (41.60%) and 60 µg/mL (43.57%), while at 20 µg/mL it increased (124.67%), suggesting a hormesis effect.	[6]
Methanol extract and fractions (hexane, chloroform, butanol)	HepG2	n.a	Fractions from both in vitro and mature plants showed weak or no cytotoxicity; some induced HepG2 growth at higher concentrations (50–200 µg/mL), indicating limited anticancer activity.	[28]
Methanol extract	SCC-25, A549, OVCAR3, HepG2	41 (SCC-25); 38 (A549); 67.1 (OVCAR3); 45 (HepG2)	Showed strong cytotoxicity across multiple cancer cell lines, particularly against SCC-25 and A549.	[35]
Ethanol extract	C3H mice bearing mammary adenocarcinoma tumors	—	Treatment (200–800 mg/kg, 30 days) significantly increased apoptotic tumor cells at 200 mg/kg (33.5 ± 2.25%) vs control (5.0 ± 0.89%), suggesting dose-dependent apoptosis induction.	[36]
Ethanol extract	FSCC, CSCC, MCM-IPB-B3; rabbit endothelial & CAM assays	—	In combination with interferons (rCaIFN/nCaIFN), extract showed enhanced antiproliferative (up to 54.03%) and antiangiogenic effects (32.2% inhibition), outperforming doxorubicin and extract alone.	[37]
Ethanol extract (TF syrup)	Breast cancer-bearing mice	—	Reduced HER2/neu (245.4% → 51.6%) and BCL-2 (114.4% → 24.6%) expression at 80,000 µg/mL; however, tumor volume increased (2,563.9 → 4,392.3 mm ³), indicating complex dose-dependent effects.	[4]
Ethanol extract	Cyclophosphamide-treated mice	—	Restored lymphocyte proliferation and macrophage phagocytic activity suppressed by cyclophosphamide; optimal at 250 mg/kg. Increased CD8 ⁺ T cells (3.72% → 24.63%) and normalized cytokine balance, confirming immunostimulatory potential.	[38]
Water extract	Normal mice (thymus and spleen)	—	Enhanced CD4 ⁺ and CD8 ⁺ T-cell populations in thymus (29.1% and 14.1%) and spleen (CD8 ⁺ : 7.37% → 10.7%), indicating immune activation without toxicity.	[39]

WiDr: colon cancer cell line; HeLa: cervical cancer immortal cell line; KB: oral cancer cell line; ORL-48: oral squamous cell carcinoma; HCT-116: colorectal cancer cell line; HepG2: human liver carcinoma cell line; SCC-25: squamous carcinoma cell line; A549: adenocarcinomic human alveolar basal epithelial cells; OVCAR3: ovarian adenocarcinoma cell line; FSCC: feline squamous cell carcinoma; CSCC: canine squamous cell carcinoma; MCM-IPB-B3: canine mammary gland benign mixed tumor; CAM: chorioallantoic membrane; rCaIFN: recombinant canine interferon; nCaIFN: natural canine interferon; HER2/neu: human epidermal growth factor receptor 2; BCL-2: B-cell lymphoma 2.

malformation, and tail deformity, with complete mortality observed at 1,600 µg/mL. These findings suggest that, while the ethanol extract of TF possesses significant gastroprotective potential, its therapeutic application requires careful dose consideration to avoid embryotoxicity at high concentrations [42].

Antibacterial activity of TF

The antibacterial properties of TF have been explored across various solvent extracts, revealing that both extract type and solvent polarity strongly influence antimicrobial efficacy. In one study, the methanol extract of TF was fractionated into n-hexane, ethyl acetate, n-butanol, and water fractions, which were evaluated against *Bacillus subtilis* and *Pseudomonas aeruginosa*. The ethyl acetate fraction demonstrated the most potent antibacterial activity, producing inhibition zones of 18.1 ± 0.07 mm against *B. subtilis* and 14.2 ± 0.25 mm against *P. aeruginosa* at 50% concentration. The n-butanol fraction showed moderate inhibition with zones of 14.8 ± 0.17 mm and 12.1 ± 0.40 mm, respectively, while the water fraction displayed weak inhibition

(8.5 ± 0.50 mm and 9.0 ± 0.14 mm). The n-hexane fraction exhibited no antibacterial effect, suggesting that polar and moderately polar compounds were primarily responsible for the antibacterial activity [15].

Conversely, another investigation reported that among hexane, dichloromethane (DCM), ethyl acetate, and methanol extracts, only the hexane extract demonstrated antibacterial activity, while the others were inactive. The hexane extract effectively inhibited two Gram-negative bacteria, producing inhibition zones of 11.0 ± 1.0 mm against *Pseudomonas aeruginosa* and 12.0 ± 1.1 mm against *Salmonella choleraesuis*. However, it showed no inhibitory effect against Gram-positive *Methicillin-resistant Staphylococcus aureus* (MRSA) or *Bacillus subtilis* [14].

The antibacterial activity of TF varies markedly depending on solvent polarity. Ethyl acetate fractions demonstrated clear antibacterial effects against *Bacillus subtilis* and *Pseudomonas aeruginosa*, with inhibition zones up to 18.1 mm. In contrast, n-hexane fractions showed either weak or no activity in some studies,

while water fractions were largely inactive. These findings suggest that antibacterial constituents are primarily moderately polar compounds, and not all TF extracts possess antimicrobial efficacy.

Antioxidant activity of TF

The antioxidant potential of TF has been extensively investigated across different solvent extracts and experimental conditions, revealing notable variability in free radical scavenging efficacy depending on extraction method, plant source, and treatment conditions.

The ethanol extract from TF leaves showed moderate free radical scavenging activity of $35.06 \pm 3.05\%$ at $250 \mu\text{g/mL}$, indicating the presence of antioxidative phytochemicals in the ethanol-soluble fraction [16].

The methanol extract and its derived fractions were also evaluated for antioxidant potential, revealing that the ethyl acetate fraction exhibited the strongest DPPH radical scavenging activity ($\text{IC}_{50} = 56.32 \pm 3.13 \mu\text{g/mL}$), followed by the n-hexane ($62.53 \pm 0.85 \mu\text{g/mL}$), n-butanol ($68.29 \pm 1.65 \mu\text{g/mL}$), methanol ($81.76 \pm 12.56 \mu\text{g/mL}$), and water fractions ($116.02 \pm 9.65 \mu\text{g/mL}$) [15].

Furthermore, comparative analyses of ethyl acetate, dichloromethane (DCM), and hexane extracts revealed strong radical scavenging effects, with $77.6 \pm 0.9\%$ inhibition for ethyl acetate and $70.5 \pm 1.7\%$ for DCM, relative to the positive control butylated hydroxytoluene (BHT, $95.3 \pm 1.3\%$). The DCM extract showed the highest total phenolic content ($5.21 \pm 0.82 \text{ mg GAE/g}$), followed by hexane ($3.27 \pm 0.85 \text{ mg GAE/g}$), ethyl acetate ($2.49 \pm 0.33 \text{ mg GAE/g}$), and methanol ($2.20 \pm 0.25 \text{ mg GAE/g}$) [14].

TF exhibits moderate to strong antioxidant activity, particularly in ethyl acetate and dichloromethane fractions, which showed low IC_{50} values ($34.39\text{--}56.32 \mu\text{g/mL}$) and high DPPH scavenging percentages. In contrast, water fractions consistently displayed weaker antioxidant effects ($\text{IC}_{50} > 100 \mu\text{g/mL}$). These results indicate that antioxidant activity correlates with phenolic and flavonoid enrichment, while highly polar extracts contribute minimally.

Overall, these studies highlight that TF possesses notable antioxidant capacity, predominantly within the ethyl acetate and DCM fractions, likely due to their higher concentrations of phenolic compounds. The findings support the potential of TF as a natural antioxidant source with pharmacological relevance.

Genetic studies of TF

Recent studies have focused on uncovering the genetic mechanisms underlying the production of anticancer compounds in TF. A study developed a lectin gene-based molecular marker (Lec183) to identify mutant lines with enhanced anticancer potential. Sequence analysis revealed a single-nucleotide polymorphism (SNP) at position 183 base pairs (bp) (guanine $\rightarrow$ cytosine), resulting in an amino-acid substitution (threonine $\rightarrow$ arginine) within the lectin protein. This nonsynonymous mutation was proposed to modify the lectin's structure and may influence its functional role in secondary-metabolite synthesis [18].

The Lec183 marker effectively distinguished mutant and wild-type genotypes and was associated with mutant plants previously shown to contain higher levels of anticancer bioactive compounds, including β -sitosterol 6, stigmasterol 8, hexadecenoic acid 58, and undecanoic acid 60 [18]. Although the study did not perform cytotoxic or apoptosis assays, the discovery of this marker represents a significant molecular advancement, providing a rapid screening tool for selecting TF lines with elevated anticancer-related metabolites. Overall, Lec183 offers an early example of integrating molecular genetics with phytochemical profiling in TF paving the way for marker-assisted selection and metabolite-gene correlation studies to improve future anticancer breeding and drug-discovery efforts.

Ethnomedicinal relevance

Typhonium flagelliforme (Lodd.) Blume, or “rodent tuber,” has been

widely used in traditional medicine, particularly in Malaysia, for ailments such as cancer, respiratory disorders, swelling, wounds, and gastric discomfort. Traditionally consumed as raw tubers, juice, or decoctions, it is regarded as a versatile remedy in Southeast Asian ethnomedicine.

Pharmacological studies support these traditional claims, revealing diverse bioactivities including anticancer, anti-inflammatory, immunomodulatory, antioxidant, antimicrobial, gastroprotective, and hepatoprotective effects. These biological actions align closely with its ethnomedicinal uses, reinforcing its therapeutic potential. A summary of the plant's traditional applications alongside current pharmacological evidence is presented in Table 6 [7–14, 46].

Future perspectives and research directions

In recent years, research on natural product-based therapeutics has advanced rapidly through the integration of metabolomics, computational approaches and nanotechnology. These approaches are particularly relevant for TF, as its chemically diverse extracts and multi-target biological activities require advanced tools for comprehensive phytochemical profiling and mechanism elucidation. Such approaches have improved the identification, characterization, and targeted delivery of plant-derived compounds with enhanced bioavailability and efficacy [43, 44]. Findings from many in vitro and in vivo studies have helped researchers build databases and use modelling approaches to understand natural compounds better. In addition, new advances in computer modelling, machine learning, and artificial intelligence make it easier to discover and predict natural product candidates with good potential for anticancer treatment [45]. These developments provide a valuable foundation for the continued exploration of TF, supporting its potential role as a source of natural pharmaceutical compounds.

Strength of evidence and research gaps

Although TF exhibits a broad range of reported biological activities, the strength of evidence supporting these activities is not uniform. Anticancer activity is the most consistently supported, particularly for dichloromethane, ethyl acetate, and ethanolic extracts, which repeatedly demonstrate IC_{50} values below $30 \mu\text{g/mL}$ across multiple cancer cell lines and experimental models. In contrast, antioxidant and antibacterial activities, while frequently reported, show greater variability depending on extraction solvent and assay type and remain largely supported by in vitro data. Immunomodulatory and gastroprotective effects are supported by limited in vivo studies but lack detailed mechanistic validation. Other reported activities remain preliminary and speculative due to inconsistent results, weak cytotoxicity, or insufficient mechanistic investigation. These differences highlight the need to distinguish well-established bioactivities from those requiring further validation.

While traditional uses of TF have guided modern research, it is important to note that most supporting evidence to date is derived from in vitro and limited in vivo studies, which cannot be directly equated with clinical efficacy in humans. Future research should therefore prioritize well-designed in vivo studies and mechanistic investigations to bridge the gap between traditional use, experimental findings, and clinical relevance.

Prioritization of bioactive compounds

TF has demonstrated considerable anticancer potential. However, most studies to date have relied on crude or fractionated extracts. As a result, the precise bioactive compounds and their underlying mechanisms of action remain largely unexplored. Among the isolated constituents, 2-octenoic acid (55) and 2-hexenoic acid (54) have shown pronounced cytotoxicity against MCF-7 breast cancer cells, with IC_{50} values of $2.66 \mu\text{g/mL}$ and $3.10 \mu\text{g/mL}$, respectively. Despite these promising results, the molecular pathways mediating their effects remain unknown.

Table 6 The traditional use and pharmacological evidence of *Typhonium flagelliforme*.

Traditional use	Potential therapeutic indications	Putative pharmacological mechanisms	Pharmacological evidence
Consumed as juice or dry extract for cancers, often with other herbs [7, 46]	Oncology support (liver, lung, breast, colon cancers)	Anticancer (cytotoxicity, apoptosis induction, anti-angiogenesis), antioxidant, immunomodulation	Various solvent extracts exhibited cytotoxicity against breast, lung, leukemia, and other carcinoma cell lines, inducing apoptosis and antiproliferation.
Used to relieve cough, phlegm, and asthma; rhizomes as expectorant [8, 46]	Respiratory disorders	Expectorant, mucolytic, anti-asthmatic, bronchodilator, anti-inflammatory, immunomodulation	Extracts enhanced lymphocyte proliferation, macrophage phagocytosis, and CD8 ⁺ T-cell levels, restoring cytokine balance in immunosuppressed models.
Applied for swelling, oedema, lymphatic swellings, internal injuries; also, analgesic and sedative [8, 46]	Musculoskeletal and inflammatory conditions	Anti-inflammatory, antinociceptive, antioedematous, mild sedative, immunomodulation	Extracts demonstrated anti-inflammatory effects by modulating TNF- α , IL-1 α , and IL-10 levels, reducing oedema and inflammatory pain.
Blooms applied to wounds and used to reduce bleeding [9]	Dermatological healing and haemostasis	Wound healing, antimicrobial, astringent, haemostatic	Extracts showed antibacterial and antioxidant effects that promoted wound healing and haemostatic recovery.
Taken for gastric discomfort, abdominal distention, nausea, vomiting [46]	Gastrointestinal disorders	Gastroprotective, anti-ulcerogenic, antispasmodic, anti-emetic, anti-inflammatory	Ethanol extract produced potent gastroprotective and anti-ulcerogenic effects, comparable to omeprazole, with safety confirmed by toxicity studies.
Used to support liver health, reduce hepatotoxicity, and prevent hepatocarcinogenesis in rats [10, 11, 13]	Hepatoprotection and chemoprevention	Antioxidant, cytoprotective, hepatoprotective, anticancer	Ethanol extract provided hepatoprotection and chemoprevention in rat models through antioxidant and cytoprotective actions.
Reported antioxidant and antibacterial properties [14]	Infection control and oxidative stress mitigation	Direct antibacterial activity and free radical scavenging	Methanol, DCM, and ethanol extracts displayed strong radical scavenging (DPPH, ABTS) and antibacterial activities against <i>S. aureus</i> and <i>E. coli</i> .
Consumed traditionally with honey or eaten raw with longan [12]	General vitality and health	Adaptogenic, antioxidant, antimicrobial	Extracts improved immune recovery, reduced oxidative stress, and enhanced general vitality in preclinical studies.

Phytochemical analyses indicate that the majority of TF's chemical profile is dominated by long-chain hydrocarbons, which appear largely inactive. This suggests that its bioactivity is concentrated in a minority of potent metabolites. These observations underscore the necessity for comprehensive bioactivity-guided fractionation and structure–activity relationship studies to identify and optimize the most efficacious compounds. Future research should focus on elucidating the mechanisms of action of 2-octenoic and 2-hexenoic acids, including their potential roles in apoptosis induction, cell-cycle modulation, and interference with key oncogenic signaling pathways. Future studies should therefore prioritize detailed mechanistic investigations of 2-octenoic acid and 2-hexenoic acid, including target identification, pathway mapping, and validation using apoptosis markers, cell-cycle regulators, and transcriptomic or proteomic approaches. In vivo efficacy, toxicity, and pharmacokinetic profiling are also required to determine whether their strong in vitro cytotoxicity can be translated into therapeutic relevance. Additionally, chemical modification or formulation strategies may be explored to improve their stability and selectivity.

Tocopherols and flavonoids as key molecular leads

TF is also recognized as a tocopherol-rich medicinal plant, with α -tocopherol comprising approximately 0.46% of its shoot and tuber extracts [23]. Tocopherols are potent antioxidants capable of reducing oxidative stress, preventing lipid peroxidation, and promoting apoptosis in cancer cells. The identification of TF as a tocopherol-containing species opens avenues for the development of tocopherol-based anticancer therapies. Future studies should investigate semi-synthetic modifications of α -tocopherol and related derivatives to improve bioavailability, selectivity, and therapeutic

efficacy. Tocopherol-based nanoparticles have been shown to enhance tumor targeting [47], suggesting potential for incorporating similar delivery systems in TF formulations. Further exploration of molecular targets, including Peroxisome Proliferator-Activated Receptors (PPAR γ), 3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A (HMG-CoA) reductase, and mTOR signaling, may reveal additional therapeutic opportunities [48]. However, the specific contribution of tocopherols to the overall anticancer activity of TF extracts remains unclear and should be systematically evaluated through comparative depletion, enrichment, and combination studies, alongside in vivo validation.

In addition to long chain compounds, TF contains several flavonoids, notably vitexin (4) and isovitexin (1), which have demonstrated multifaceted pharmacological activities and represent promising leads for therapeutic development [49–54]. Their anticancer effects involve modulation of critical molecular pathways such as PI3K/Akt/mTOR, NF- κ B, and p53. These mechanisms result in cell-cycle arrest, apoptosis, and inhibition of tumor proliferation and metastasis. These flavonoids also influence the tumor immune microenvironment by promoting M1 macrophage polarization and suppressing tumor-associated M2 macrophages, thereby impeding tumor progression [49]. Their antioxidant activity is primarily mediated via activation of the Nrf2/ARE signaling pathway. This leads to upregulation of antioxidant enzymes (HO-1, SOD, CAT, GPx), and suppression of oxidative stress-related MAPK and NF- κ B pathways [50–52]. Collectively, these mechanisms position vitexin and isovitexin as promising multitarget therapeutic agents against oxidative stress-driven diseases, particularly cancer [53, 54]. Despite extensive evidence from other plant sources, the roles of vitexin and isovitexin in TF have not been directly validated, and future studies

should focus on their isolation from TF, quantitative contribution to extract activity, and confirmation of their mechanisms using TF-specific models.

Nanotechnology and advanced delivery strategies

Given the strong in vitro activity of TF extracts but their limited solubility, stability, and bioavailability, advanced delivery strategies are required to improve translational potential. Advances in nanotechnology have further enhanced the anticancer potential of TF. Nanoemulsion formulations of TF ethanolic extracts exhibited higher cytotoxicity against MCF-7 cells ($IC_{50} = 1.89 \mu\text{g/mL}$) compared to crude extracts ($IC_{50} = 2.35 \mu\text{g/mL}$), likely due to improved solubility and bioavailability of hydrophobic constituents [19]. Complementary in silico and in vitro studies have demonstrated that TF-derived molecules can target cancer-related receptors such as FXR, supporting receptor-directed nanodelivery approaches [23]. Similar to other natural-product-based nanomedicines, vitamin E TPGS and polymeric carrier systems could enhance compound stability. These systems may also prolong systemic circulation, and enable controlled release [55, 56]. These strategies indicate that integrating nanotechnology with TF research can overcome formulation limitations and advance the development of clinically viable phytopharmaceuticals. Nanoformulations incorporating tocopherols could further improve targeted delivery of anticancer agents, enhancing efficacy while minimizing systemic toxicity [23]. Recent studies on TPGS-based nanocarriers co-delivering paclitaxel and siRNA have shown potential for overcoming multidrug resistance in breast cancer [55, 56]. These findings highlight the promise of nanotechnology-assisted TF therapeutics. Future research should focus on optimizing TF-based nanoformulations through controlled release studies, biodistribution analysis, and in vivo efficacy testing, as well as evaluating long-term safety and scalability for translational development.

Genetic and in-silico approaches for future optimization

To complement experimental and formulation-based approaches, computational and in silico strategies provide valuable tools for understanding bioactive compound production and guiding rational optimization. In parallel with formulation-based innovations, in silico studies have begun elucidating the genetic basis of bioactive compound production in TF. Analysis of the γ -tocopherol methyltransferase (γ -TMT) gene and its encoded protein in both wild-type and gamma-irradiated mutant lines revealed its key role in converting γ -tocopherol to α -tocopherol. α -tocopherol is the most bioactive isoform with potent antioxidant and anticancer properties [57]. Amplification using degenerate primers detected γ -TMT in both genotypes. Amplicon size variations (100 bp in wild-type, 1,300 bp in mutants) were observed, indicating sequence-level mutations induced by gamma irradiation while preserving gene functionality [23]. Sequence and bioinformatics analyses identified deletions and substitutions potentially altering protein conformation near catalytic and binding domains [58, 59]. Protein modeling revealed structural divergences in helices and loops near the C-terminal region, suggesting possible effects on enzymatic activity and tocopherol accumulation [23]. Notably, the mutant lines exhibited higher tocopherol levels and more pronounced tertiary structural changes, indicating that induced mutations may enhance γ -TMT function without compromising its catalytic activity [23]. Future work should investigate whether γ -TMT mutations can be deliberately exploited to enhance tocopherol biosynthesis through targeted mutagenesis or metabolic engineering, and whether such genetic modifications result in reproducible improvements in pharmacological efficacy.

Future research on TF should combine in vivo validation of efficacy, safety, and pharmacokinetics with mechanistic studies of key bioactive compounds. Efforts should focus on elucidating molecular pathways, optimizing structure–activity relationships, and exploring synergistic interactions with conventional chemotherapeutics. Advanced nanotechnology and targeted delivery systems could enhance bioavailability, stability, and tumor

specificity. In parallel, omics and in silico analyses of genes such as γ -TMT may guide metabolic or genetic optimization of bioactive production. Collectively, these strategies position TF as a promising source of multitarget anticancer agents with translational potential.

Conclusion

The ethnomedicinal uses of TF are increasingly supported by emerging pharmacological evidence, effectively bridging traditional knowledge with modern scientific validation. TF exhibits a broad spectrum of bioactivities, including potent anticancer, antioxidant, antibacterial, immunomodulatory, anti-inflammatory, and gastroprotective effects. These activities substantiate its traditional applications in cancer management, inflammation, respiratory ailments, wound healing, gastrointestinal discomfort, infection control, and general recovery after illness, while also highlighting new therapeutic potential in hepatoprotection and ulcer prevention.

These effects are supported by the plant chemistry. Important groups include flavonoids such as isovitexin 1, kaempferol 2, vitexin 4 and simple aromatics such as vanillin 62 and 4-hydroxybenzaldehyde 61. Other useful compounds include phytosterols such as β -sitosterol 6, campesterol 7, stigmasterol 8, and daucosterol 9, chlorophyll related compounds such as pheophorbides 70–72, and many long-chain hydrocarbons including linoleic 51, linolenic 52, oleic 53, and stearic 57 acid. Together these constituents can explain anticancer antioxidant, gastroprotective, antibacterial, and cytotoxic actions.

Overall, TF demonstrates considerable promise as a natural source of multifunctional bioactive compounds for cancer care, gastrointestinal support, infection control, and immune system enhancement. Future research should focus on rigorous evaluation of safety, pharmacokinetics, pharmacodynamics, potential drug interactions, and clinical efficacy to facilitate the development of evidence-based TF-derived therapeutics.

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