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Review Article

Unveiling Tigliane Derivatives as Novel Therapeutics for Alzheimer's Disease

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ABSTRACT

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder with limited therapeutic options. Current treatments offer only symptomatic relief without halting disease progression. Natural products and their derivatives have garnered increasing interest for neuroprotection. Among them, tigliane diterpenoids, primarily derived from the Euphorbiaceae family, have shown potent biological activities, including anti-inflammatory, antioxidant, and neuroprotective properties. This review examines the therapeutic potential of tigliane derivatives in the treatment of Alzheimer's disease, concentrating on their pharmacological effects, molecular mechanisms, and structure-activity relationships. Furthermore, we discuss challenges and prospects of tigliane-based drug development as novel interventions for AD.

Keywords: Tigliane, Alzheimer's disease, Neuroinflammation, Antioxidant, Amyloid-β, Diterpenoids, Protein Kinase C.

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INTRODUCTION

Alzheimer's Disease (AD) is a progressive neurodegenerative condition and the most prevalent cause of dementia, occurring in about 60-80% of cases worldwide.[1] Featuring a decrease in cognitive capacity, memory loss, and changes in behaviour, Alzheimer's is primarily found in older people but can start before the age of 65 in cases of early-onset forms.[2] The pathology of Alzheimer's disease is characterized by the deposition of extracellular Amyloid-Beta (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. They lead to dysfunction at the synapses, neuronal loss, and brain atrophy, especially in brain areas important for memory and executive function, including the hippocampus and cerebral cortex.[3]

The pathogenesis of AD is multifactorial, with genetic, environmental, and lifestyle components. The APOE ε4 allele is the most prevalent risk allele for late-onset AD, and mutations in APP, PSEN1, and PSEN2 genes are associated with uncommon familial forms of early-onset AD.[4] Alzheimer's disease goes through phases clinically, with mild cognitive impairment initially and the progression to severe dementia. Early signs include difficulty recalling current events, followed by confusion, impaired judgment, language impairment, and ultimately, total dependency for activities of daily living.[5]

Despite years of research, there is no cure for Alzheimer's disease to date. Treatment focuses on managing symptoms and slowing disease progression. FDA-approved medications, such as donepezil, rivastigmine, and memantine, offer modest symptom relief. Newer anti-amyloid drugs such as lecanemab and aducanumab have been introduced, which target amyloid pathology with variable clinical outcomes and continuous controversies surrounding efficacy and safety.[6] Preventive measures focus on modifiable risk factors, such as cardiovascular well-being, cognitive activation, exercise, and diet. Public health interventions focus on increasing awareness, providing support to caregivers, and securing research funding to address this emerging global health issue.[7]

As global populations age, the burden of Alzheimer's disease is expected to rise significantly. Understanding its mechanisms, improving early diagnosis, and developing effective treatments are critical priorities for healthcare systems worldwide.[8]

Tigliane is a diterpene hydrocarbon that occurs naturally and is the structural backbone of a series of biologically active compounds, notably the phorbol esters. The compounds are primarily found in species of the Euphorbiaceae and Thymelaeaceae plant families, such as Euphorbia and Croton species. The tigliane skeleton is distinguished by a tetracyclic ring system of a fused 5-7-6-3 ring

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structure and is a unique and complex framework within natural products chemistry.[9]

Chemically, tigliane (Figure 1) is a class of diterpenoids, biosynthetically derived from Geranylgeranyl Pyrophosphate (GGPP). By a series of cyclization and rearrangement reactions, GGPP is converted into casbene, a principal precursor in the biosynthesis of tigliane and related diterpenes.[10] Prototypical tigliane derivative phorbol and its esters (e.g., 12-O-Tetradecanoylphorbol-13-Acetate or TPA) have well-documented potent biological activity, including tumor promotion through activation of Protein Kinase C (PKC) isoforms. Due to this activity, tigliane-type compounds have found widespread use in cancer research, dermatology, and virology. For example, phorbol esters have been employed as reagents to examine signal transduction processes and cell differentiation.[11]

New research has sparked increased interest in tigliane analogues due to their potential therapeutic applications, including antiviral, anti-inflammatory, and anticancer activities. Alterations of tiglianes, like ingenol mebutate, have been formulated into topical agents for the treatment of actinic keratosis.[12] Even though tigliane derivatives hold therapeutic potential, most are linked with toxicity, requiring structural adjustments and drug delivery systems to minimize side effects.[13]

Plant Sources of Tigliane

The important plant sources of Tigliane are listed in Table 1.[14-20]

Other Sources of Tigliane

Marine Organisms (Infrequent/Putative)

Few and largely putative accounts of tigliane-like or structurally related diterpenoids in marine organisms, especially sponges and tunicates, have been reported. These types of compounds tend to have structural elements similar to phorbol or daphnane backbones, but are yet to be fully substantiated as tigliane derivatives per se. A few diterpenoids found in marine sponges, such as *Spongia* spp., share similarities with polycyclic structures in terrestrial tigliane-type compounds.[21]

Microbial and Fungal Biosynthesis (Theoretical/ Potential Source)

Although naturally occurring tigliane diterpenoids have no direct evidence of production by fungi or bacteria in nature, microbial biosynthetic engineering presents an attractive alternative for their manufacture. With synthetic biology, plant diterpene biosynthetic pathways have been introduced into microbial hosts, such as *Escherichia coli* and *Saccharomyces cerevisiae*, to produce precursors like casbene or phorbol-related compounds. Fermentation of phorbol-related diterpenes by engineered yeast.[22]

Total Synthesis (Laboratory-Based Source)

Tigliane and related derivatives have been the target of prolific synthetic chemistry research. Several laboratories have successfully synthesized the total tigliane structures and their derivatives, including phorbol, ingenol, and daphnane-type compounds. Utilizing multistep organic synthesis, usually through Diels-Alder reactions, cyclopropanation, and oxidative rearrangements, to construct the intricate tetracyclic tigliane core.[23]

Cell and Tissue Cultures (Plant-Derived but Non-whole-plant)

Although in a technical sense from plants, callus and cell suspension cultures are alternative biotechnological sources that need not entail the harvesting of whole plants. The systems can be manipulated to give high yields of tigliane compounds in bioreactors under tight control. *In vitro* cultures of *Croton tiglium* and *Euphorbia tirucalli*.[24]

Derivatives of tigliane

A detailed list of tigliane derivatives was given in Table 2.[25-31]

Pharmacological activities of tigliane

Tumor Promotion and Protein Kinase C (PKC) Activation

Tigliane-type diterpenoids, especially phorbol esters like Phorbol 12-Myristate 13-Acetate (PMA/TPA), are potent tumor promoters that exert their biological effects primarily through the sustained activation of Protein Kinase C (PKC), a key regulator of cellular proliferation, differentiation, and survival. These compounds structurally mimic the endogenous PKC Activator Diacylglycerol (DAG) by binding to the C1 domain of both conventional and novel PKC isoforms, thereby causing sustained translocation to the plasma membrane and activating downstream signaling cascades that involve transcription factors NF-κB, AP-1, and members of the MAPK pathway.[32] The sustained activation causes abnormally sustained proliferation, inflammation, angiogenesis, and suppression of apoptosis, all of which contribute to the promotion of tumors. Classical phorbol esters, such as TPA, have played a key role in two-stage mouse skin carcinogenesis models, where initiation is achieved using DMBA and promotion is induced using TPA, illustrating their non-mutagenic yet pro-proliferative roles.[33] Structure-activity relationship analyses highlight the pivotal significance of ester substitution at C-12 and C-13 in conferring tumor-promoting ability. In contrast, modified tiglianes, such as 4-deoxyphorbol and Prostratin, retain PKC activity without tumorigenicity, providing therapeutic utility in applications like HIV latency reversal and immunomodulation.[34]

Anticancer/Cytotoxic Activity

Phorbol ester and structurally modified analogs of the tigliane-type diterpenoids have demonstrated remarkable anticancer and cytotoxic activities against various types of cancer cells, producing both pro-apoptotic and antiproliferative effects. Although traditional phorbol esters such as TPA (phorbol 12-myristate 13-acetate) are most recognized for their tumor-promoting activities through continuous activation of Protein Kinase C (PKC), some derivatives-e.g., ingenol mebutate, Prostratin, and 4-deoxyphorbol esters-proved to be endowed with noteworthy cytotoxicity but lacked tumorigenic activity.[35] Such compounds are capable of triggering apoptosis, cell cycle arrest, and modulation of oncogenic signaling pathways, including both PKC-dependent and -independent processes. Ingenol mebutate, isolated from Euphorbia peplus, is approved for the topical management of actinic keratosis and demonstrated cytotoxicity against basal cell and squamous cell carcinomas through rapid cell membrane disruption and inflammatory necrosis.[36,37] Prostratin, a non-tumorigenic phorbol ester, restores latent HIV and possesses antiproliferative effects against leukemia and glioblastoma models through selective modulation of PKC isoforms.[38,39] Besides, tigliane derivatives are also noted to trigger mitochondrial-mediated apoptosis, generation of ROS, and anti-angiogenesis in several cancer cell lines such as colon, liver, breast, and melanoma cells.[40] Structure-activity relationship studies indicate that alterations in the ester groups at the C-12 and C-13 positions of the tigliane skeleton can significantly decrease tumor-promoting activity while increasing cytotoxic potential, making them very encouraging leads for anticancer drug development.[41]

Anti-HIV and Antiviral Activity

Tigliane-type diterpenoids have been found to possess promising anti-HIV and broad-spectrum antiviral activity, primarily by their potential to modulate Protein Kinase C (PKC) pathways and induce latent viral reactivation or suppress viral replication. Among the most important of these is Prostratin, a non-tumorigenic phorbol ester from *Homalanthus nutans*, that activates PKC and HIV-1 provirus latent infection in resting CD4+ T cells, thus exposing the virus to antiretroviral drugs without activating all T cells worldwide-a tactic referred to as "shock and kill".[42] Prostratin has also been found to downregulate the HIV-1 coreceptors CCR5 and CXCR4, further inhibiting new infections.[43] Other tigliane analogs, such as ingenol derivatives, are also antiviral, exhibiting anti-herpesvirus, anti-papillomavirus, and anti-HBV activities, often through the PKC-mediated augmentation of immune mechanisms or apoptosis induction in infected cells.[44] Furthermore, tiglianes such as 12-deoxyphorbol 13-phenylacetate have also displayed antiviral activity against Epstein-Barr Virus (EBV)-carrying cells by suppressing lytic activation.[45] Notably, the antiviral efficacy of tiglianes can be optimized by adjusting their ester side chains to meet both efficacy and toxicity requirements, providing significant leads for therapeutic development, particularly in the context of HIV cure and latent viral infections.[46]

Anti-inflammatory Activity

Tigliane-type diterpenoids exhibit significant anti-inflammatory activity, primarily through the modulation of Protein Kinase C (PKC) signaling and the subsequent blockade of key pro-inflammatory targets, including NF-κB, COX-2, and MAPKs.[47] Agents such as ingenol mebutate and some 4-deoxyphorbol analogs have been shown to exhibit anti-inflammatory activity through the inhibition of cytokine release (e.g., TNF-α, IL-1β, IL-6) and leukocyte invasion in numerous *in vitro* and *in vivo* systems. Ingenol mebutate, for example, has also been shown to exhibit biphasic pro-inflammatory and anti-inflammatory activity, depending on the dose and context.[48] It causes an acute local inflammatory reaction, leading to prolonged lesion clearance and resolution when applied to treat actinic keratosis, partially through the enhancement of neutrophil-mediated cytotoxicity and wound healing.[49] Further, the non-tumorigenic phorbol ester prostratin has been found to inhibit chronic inflammation through PKC modulation without tumorigenesis promotion.[50] Certain tiglianes also suppress COX-2 expression and Nitric Oxide (NO) production through downregulation of inducible Nitric Oxide Synthase (iNOS) to contribute to their anti-inflammatory action within macrophages and epithelial tissues.[51,52] A Structure-Activity Relationship (SAR) investigation emphasizes that the character and orientation of ester substituents on the tigliane nucleus significantly impact their inflammatory response profile, with specific analogs demonstrating therapeutic potential for chronic inflammatory and autoimmune diseases.[53]

Antimicrobial/Antibacterial Activity

Tigliane-type diterpenoids, particularly phorbol esters and their analogs that lack tumorigenicity, have demonstrated significant antimicrobial and antibacterial activity against a wide range of pathogens, including Gram-positive and Gram-negative bacteria, fungi, and certain parasites. Among them, ingenol mebutate, a derivative of *Euphorbia peplus*, has demonstrated bactericidal activity against skin-colonizing microorganisms, such as *Staphylococcus aureus* and *Propionibacterium acnes*, due to its cell-membrane-disrupting properties and induction of local immune responses.[54] Phorbol esters of Croton and Euphorbia plants have also been shown to be antibacterial, possibly due to PKC-mediated immune stimulation or direct cytotoxic action on microbial membranes.[55] Some tiglianes have also been shown to be active against Mycobacterium tuberculosis and Helicobacter pylori, but their clinical utility is still under early evaluation. Antimicrobial activity is commonly associated with structural features like long-chain ester substituents at C-12 and C-13, which increase membrane affinity and permeability. They indicate tigliane derivatives as potential lead compounds

for topical antimicrobials or immune-modulating adjuncts, particularly against resistant skin pathogens and opportunistic infections.[56]

Immunomodulatory Actions

Tigliane-type diterpenoids exhibit potent immunomodulatory actions, primarily due to their ability to activate Protein Kinase C (PKC) and their influence on various aspects of immune cell function, including T cell activation, cytokine release, and macrophage modulation. Compounds such as phorbol 12-myristate 13-acetate (PMA or TPA) and Prostratin can powerfully activate PKC isoforms, inducing the production of IL-2, TNF-α, and IFN-γ in T lymphocytes and increasing the proliferation of both T and B cells, thereby mimicking Diacylglycerol (DAG) in immune signaling cascades.[57] Prostratin has gained interest because it could selectively trigger immune responses without tumorigenesis induction, positioning it as a potential candidate for HIV latency reversion and T-cell activation in therapeutic vaccines.[58] At the same time, ingenol mebutate was able to induce localized inflammation, followed by immune-mediated removal of lesions, involving the recruitment of neutrophils, activation of macrophages, and the generation of Neutrophil Extracellular Traps (NETs) that mediate the elimination of tumors and pathogens.[59,60] These immunostimulatory activities have positioned tiglianes as potential immunotherapy tools, in the development of vaccine adjuvants, and cancer immunomodulation approaches. The immunological effects are specific and depend on substitution patterns in the tigliane core, dosage, and usage context, allowing for the adjustment of pro- or anti-inflammatory effects.[61]

Neuropharmacological Effects

Tigliane-type diterpenoids have demonstrated novel neuropharmacological activities, primarily by modulating Protein Kinase C (PKC) signaling, a key player in synaptic plasticity, neuronal survival, and neurotransmitter release. Phorbol esters, such as Phorbol 12-Myristate 13-Acetate (PMA), are potent PKC activators and have been extensively utilized to investigate neuronal signaling, including dopaminergic and glutamatergic transmission, Long-Term Potentiation (LTP), and neuroplasticity.[9,62] Some tigliane derivatives have shown neuroprotective activity by suppressing oxidative stress, blocking apoptosis, and boosting neurotrophic factors, potentially through PKC-dependent upregulation of anti-apoptotic proteins like Bcl-2 and downregulation of pro-apoptotic mediators like caspase-3.[63,64] In models of neurodegeneration, phorbol esters have also been shown to safeguard dopaminergic neurons and promote neurite outgrowth, which may have therapeutic implications for Parkinson's disease and other conditions characterized by synaptic dysfunction.[65] Furthermore, tigliane-type molecules can modulate pain control and seizure threshold, and have been shown to influence nociceptive signaling pathways through spinal PKC activation. Nevertheless, their tumor-promoting activity limits systemic application, and non-tumorigenic analogs, such as Prostratin, have been developed that maintain neuroactive effects without carcinogenic liability. The continuous development of such derivatives holds promise for targeting neuroinflammation, neurodegeneration, and neuronal repair.[66]

Anti-parasitic Activity

Tigliane-type diterpenoids have demonstrated promising antiparasitic activity, particularly against protozoan parasites such as *Plasmodium falciparum, Trypanosoma brucei*, and *Leishmania donovani*. Phorbol esters and congeners from *Croton tiglium, Euphorbia* spp., and *Synadenium grantii* have exhibited potent *in vitro* antiplasmodial activity, primarily due to their membrane-disruptive activity and activation of the PKC pathway, which disrupts parasite signaling and host-parasite recognition.[67] Some 4-deoxyphorbol analogs have exhibited selective inhibition of *P. falciparum* growth with IC_{50} values in the low micromolar range with negligible cytotoxicity to human cells, which identifies their therapeutic window.[68] Additionally, Prostratin, a non-tumorigenic tigliane, has exhibited moderate activity against Leishmania species and Trypanosoma, likely by modulating host immune responses and inhibiting intracellular parasite replication. These activities are dependent on the substituents at the C-12 and C-13 positions of the tigliane ring, which influence lipophilicity and membrane penetration. While the mechanism awaits further investigation, tiglianes are regarded as good leads for the creation of new antiparasitic drugs, especially for diseases with poor drug therapy and increasing drug resistance.[69]

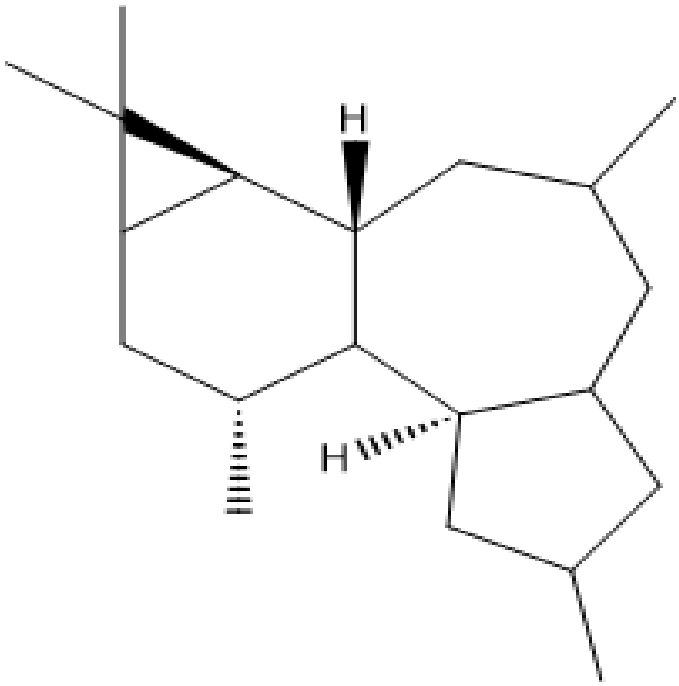

Figure 1: Chemical structure of Tigliane.

Skin Irritant and Vesicant Activities

Tigliane-type diterpenoids, especially phorbol esters, are known to possess strong skin irritant and vesicant (blistering) activities, which have been widely reported in toxicology and dermatology experiments. These activities are primarily mediated by the activation of Protein Kinase C (PKC), resulting in the production of pro-inflammatory mediators such as interleukins (IL-1, IL-6), TNF-α, and prostaglandins, which lead to erythema, edema, and blistering.[70] Phorbol esters such as Phorbol 12-Myristate 13-Acetate (PMA or TPA) have been employed as model irritants in skin inflammation models. They are known to be tumor promoters because they cause chronic inflammation and epidermal hyperplasia on repeated treatment.[71] Ingenol mebutate, another tigliane derivative administered clinically for actinic keratosis, causes similar irritant effects upon local application, typically followed by local inflammation, crusting, and vesiculation, which are critical to its therapeutic action but also restrict tolerability.[72] The irritant activity of these compounds is determined by their ester substitution pattern at C-12 and C-13, which impinges upon PKC affinity and dermal permeability. Thus, the vesicant property of tiglianes is a double-edged sword-functional in therapeutic applications such as immunogenic lesion destruction, but dangerous in unrestricted exposure, particularly from toxic Euphorbiaceae and Thymelaeaceae plant taxa.

Prodrugs for Topical Therapy

Tigliane prodrugs have been explicitly designed for topical therapy to reduce systemic toxicity and increase dermal targeting, particularly in the treatment of precancerous and cancerous cutaneous lesions. A good example is ingenol mebutate (PEP005), a semisynthetic esterified ingenol derivative, which acts as a topical prodrug in the treatment of actinic keratosis. When applied dermally, ingenol mebutate quickly enters the epidermis and is subject to enzymatic hydrolysis, which exposes the active ingenol responsible for initiating direct cytotoxicity against dysplastic keratinocytes as well as immune-mediated removal by activating Protein Kinase C (PKC), particularly PKCδ and PKCε isoforms.[73] Through both processes, there occurs immediate necrosis, inflammatory infiltration, and regression of the tumor within days after application. The esterification of ingenol (to yield mebutate) increases lipophilicity and skin permeability, rendering it amenable to cutaneous delivery while controlling systemic exposure and the carcinogenic risk generally associated with other tiglianes, such as phorbol esters. The prodrug design enhances skin permeability and achieves localized action with minimal systemic absorption, thereby reducing the risk of adverse effects associated with conventional phorbol esters. The Success of ingenol mebutate as a commercial topical drug shows the therapeutic potential of reformulating tigliane scaffolds as prodrugs for targeted dermatologic application, combining efficacy with better safety profiles.[74]

Side effects and toxicity

Tigliane-type diterpenoids, although pharmacologically active, are also associated with a variety of side effects and toxicities, primarily due to their structural similarity to phorbol esters, which are known tumor promoters and skin irritants. The most frequently observed side effects include severe skin irritation, blistering, erythema, pain, and inflammatory reactions, particularly when applied dermally. These actions are primarily a broad result of PKC activation, which initiates downstream inflammatory cascades, cytokine secretion (e.g., TNF-α, IL-1, IL-6), and immune cell infiltration.[75] Systemically, tiglianes induce gastrointestinal distress, hepatotoxicity, and renal toxicity at toxic doses or upon repeated dosing, notably with crude plant extracts of Euphorbia, Croton, or Daphne species. Repeated exposure to phorbol esters such as TPA has been found to stimulate tumor growth in animal models through induction of epidermal hyperplasia, oxidative stress, and DNA damage. Despite the diminished systemic toxicity of ingenol mebutate, a semisynthetic prodrug of a broad range of tiglianes approved for actinic keratosis treatment, it can trigger localized adverse effects such as ulceration, swelling, crusting, and secondary infection. Therefore, while these tiglianes are considered therapeutic candidates, their clinical use necessitates careful dosing,

Table 1: Various plant sources of Tigliane.

Plant name	Family	Geographical distribution	References
Croton tiglium L.	Euphorbiaceae	Southeast Asia, India, China	[14]
Euphorbia tirucalli L.	Euphorbiaceae	Africa, India, Southeast Asia, Brazil	[15]
Euphorbia lathyris L.	Euphorbiaceae	Mediterranean, Central Asia	[16]
Daphne genkwa Sieb. and Zucc.	Thymelaeaceae	China, Korea, Japan	[17]
Wikstroemia indica (L.) C.A.Mey.	Thymelaeaceae	East and Southeast Asia (China, Taiwan, Vietnam, India)	[18]
Excoecaria agallocha L.	Euphorbiaceae	Coastal Asia, mangrove swamps (India, Sri Lanka, Southeast Asia)	[19]
Trigonostemon howii	Euphorbiaceae	Taiwan	[20]

Table 2: A list of derivatives of Tigliane.

Derivative	Source	Structural features	Biological activity	References
Phorbol	*Croton tiglium*, *Euphorbia* spp.	Polyoxygenated tigliane with a hydroxylated A-ring and C13 esterification	Tumor promoter; activates Protein Kinase C (PKC).	[25]
12-O-Tetradecanoylphorbol-13-Acetate (TPA or PMA)	Synthetic (from phorbol)	Diester of phorbol (C12 and C13 acylated)	Potent PKC activator, widely used in cancer research as a tumor promoter.	[26]
Ingenol	Euphorbia peplus, Euphorbia tirucalli	Hydroxylated tigliane with a distinctive epoxide group	Antitumor, antiviral (especially against HPV), immunomodulatory.	[27]
Ingenol Mebutate (PEP005)	Semisynthetic	Semisynthetic ingenol derivative (angelate ester at C3)	Dual action-rapid cell necrosis + immune activation via PKC.	[28]
4-Deoxyphorbol	Synthetic	Phorbol analogue lacking a hydroxyl group at C-4	Used in SAR (structure-activity relationship) studies to explore PKC isoform selectivity.	[29]
Genkwanine	*Daphne genkwa* (Thymelaeaceae)	A methylated tigliane-type diterpenoid	Cytotoxic against tumor cells.	[30]
Daphnane and Daphnetoxin (Tigliane-related)	*Daphne, Stellera, Wikstroemia* spp.	Related to tiglianes, often fused with orthoester functionalities	Potent anticancer, neurotoxic, and immunomodulatory activity.	[31]

controlled delivery (e.g., topical application), and structural modification to reduce toxicity.[76]

Safety issues and precautions

Gliane-type diterpenoids, particularly phorbol ester-structurally related ones, exhibit significant safety concerns due to their vigorous biological activity and tumor-promoting, pro-inflammatory, and cytotoxic effects. One serious safety concern is their potent activation of Protein Kinase C (PKC), which, although therapeutically utilized, can also cause runaway inflammation, epidermal hyperplasia, and, in certain situations, carcinogenesis, especially following chronic exposure.[77] Tiglianes, therefore, need to be treated cautiously in both therapeutic and laboratory environments, with careful topical application regimes and restriction of systemic exposure. For instance, ingenol mebutate for the treatment of actinic keratosis should be applied precisely to the lesion site, avoiding mucosal surfaces and broken skin to prevent undue local irritation, blistering, or secondary infection.[78] Other safety measures involve glove use during application, careful handwashing, and avoiding contact with the eyes, since improper exposure can cause intense ocular inflammation. Moreover, tigliane-containing plant extracts used in folk medicine are risky due to inconsistent concentrations of active esters and unstandardized preparation, causing toxicity, especially in children or after oral intake. The genotoxicity of certain phorbol derivatives also calls for long-term carcinogenicity evaluations prior to clinical application. To minimize risks, tigliane derivatives are best applied in formulated, dose-controlled products, and users should be instructed on monitoring for adverse effects, primarily with repeated or high-dose applications.

Structure-Activity Relationship (SAR) Insights of Tigliane Derivatives

Tigliane diterpenoids possess a rigid tetracyclic 5/7/6/3 ring system with multiple functionalization sites that critically determine their bioactivity, receptor selectivity, and toxicity profile. SAR studies have revealed that minor modifications to specific positions on the tigliane scaffold can significantly impact their pharmacological behavior, particularly their interactions with Protein Kinase C (PKC) isoforms, Blood-Brain Barrier (BBB) permeability, and neurotoxicity. These insights are vital for designing CNS-targeted analogs for Alzheimer's disease.[79]

Free Hydroxyl Groups at C-4 and C-20 Enhance Bioactivity

Hydroxyl substitutions at C-4 and C-20 have been found to significantly influence biological activity by enhancing hydrophilicity and enabling hydrogen bonding with key molecular targets, such as PKC isoforms and Aβ aggregates. These positions are believed to be involved in crucial molecular interactions that mediate anti-inflammatory and neuroprotective effects.

- C-4 hydroxylation often improves water solubility and receptor binding capacity.
- C-20 hydroxylation, present in many natural tiglianes, is important for PKC activation and also contributes to cellular uptake and retention.

Strategic preservation or introduction of hydroxyl groups at these sites may enhance therapeutic potential without increasing toxicity.[80]

Acylation at C-12 and C-13 Modulates PKC Affinity and Cytotoxicity

The esterification or acylation of hydroxyl groups at C-12 and C-13 dramatically alters the binding affinity to PKC isoforms, particularly PKC-α, -δ, and -ε, which are involved in neuroprotection, synaptic plasticity, and memory formation. The length, saturation, and branching of the acyl side chains dictate the selectivity and duration of PKC activation.

- Long-chain fatty acid esters at these positions (e.g., in phorbol esters like TPA) are associated with strong but sustained PKC activation, often leading to pro-tumorigenic effects.
- In contrast, medium-chain or branched acyl groups, as in Prostratin, lead to transient PKC activation with reduced toxicity and improved neuroprotective properties.

Fine-tuning these acyl chains offers a means to balance efficacy and safety, particularly for chronic diseases like AD.

Modifications at Ring A Optimize CNS-Targeting Properties

Ring A (the five-membered ring) is relatively underexplored but plays a key role in determining molecular stability, spatial orientation, and Blood-Brain Barrier (BBB) permeability.

- Substituents at C-1 and C-2 positions can enhance lipophilicity and membrane permeability, improving CNS access.
- Cyclopropanation or fluorination in this region has been proposed to stabilize the scaffold and resist metabolic degradation.
- Electron-donating groups on ring A may also help tune pKa and influence the compound's distribution between central and peripheral compartments.

Engineering this ring with minimal polar substitutions can enhance BBB penetration, a crucial criterion for Alzheimer's disease drug candidates.[81]

Balancing Potency with Neurotoxicity

While certain tigliane derivatives, such as TPA, exhibit potent PKC activation and anti-inflammatory effects, their pro-tumorigenic potential and skin-irritant properties render them unsuitable for long-term CNS use. SAR data suggest that maintaining moderate PKC activity while avoiding prolonged activation is key to minimizing toxicity.

- Non-tumor-promoting analogs, such as Prostratin and 12-deoxyphorbols, demonstrate neurotrophic activity without exhibiting carcinogenic effects.
- Selective targeting of PKC-ε has been linked to memory enhancement and synaptic regeneration, making isoform-specific design highly valuable.

Rational Drug Design Opportunities

Incorporating SAR knowledge allows the development of semisynthetic or synthetic tigliane analogs that:

- Exhibit selective, transient PKC activation is beneficial for neuroregeneration.
- Possess enhanced BBB permeability via optimized lipophilic balance.
- Show reduced pro-inflammatory and carcinogenic properties through side chain modifications.
- Can be formulated as prodrugs or nanoformulations to improve brain bioavailability.[82]

Challenges and Future Perspectives

Despite promising preclinical outcomes, several challenges remain. These include potential toxicity, limited selectivity, and the need for improved formulation strategies. Advances in drug delivery systems, such as nanoformulations and targeted delivery, could enhance the therapeutic window of tigliane derivatives. Additionally, more robust clinical trials are essential to validate their efficacy and safety in human populations.[83]

CONCLUSION

Tigliane derivatives represent a novel and underexplored class of compounds with multifaceted potential in the treatment of Alzheimer's disease. Their diverse mechanisms of action align well with the complex pathology of AD, making them attractive candidates for further development. Strategic

chemical modification, targeted delivery, and comprehensive pharmacological evaluation will be key to unlocking their full therapeutic potential.

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AUTHOR CONTRIBUTIONS

Kausik Bhar and Saptarshi Samajdar: Conceptualization, Writing-original draft; Sumanta Mondal: Writing and Editing and Data curation; Kazi Asraf Ali: Reviewing and editing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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