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Review Article

Isolation, Purification, Characterisation and Multifunctional Biological Activities of Dieckol: A Review

Anupama Sobhana Sreekumar[1*], Parvathy Bindu[2], Fathima Beevi[3], Harisankar Haridasan Pllai Sudha[3], Nevin Kottayath Govindan[4], Smitha Chandrika Krishnan[5], Anil Kumar Appu Kuttan[5]

[1]*Department of Marine Biosciences, Faculty of Ocean Science and Technology, Kerala University of Fisheries and Ocean Studies, Panangad, Kerala, India.*
[2]*Department of Integrative Biology, School of Biosciences and Technology,Vellore Institute of Technology, Vellore, Tamil Nadu, India.*
[3]*Department of Biochemistry, T.K.M.College of Arts and Science, Kollam, Kerala, India.*
[4]*Department of Marine Biosciences, Faculty of Ocean Science and Technology & Centre for Bioactive Substances from Marine Organisms, Kerala University of Fisheries and Ocean Studies, Panangad, Kochi, Kerala, India.*
[5]*Department of Botany, Government College for Women, Thiruvananthapuram, Kerala, India.*

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ABSTRACT

Marine environments are a valuable source of chemically diverse bioactive compounds with biomedical potential. Among marine macroalgae, brown seaweeds of the genus Ecklonia are rich in phlorotannins, a unique class of polyphenolic metabolites. Dieckol, a hexameric phlorotannin mainly derived from Ecklonia species, has gained significant attention due to its wide range of biological activities. This review summarizes current knowledge on its extraction, purification, structural characterisation, and functional properties. Conventional solvent extraction as well as advanced techniques such as ultrasonic and microwave-assisted extraction have been employed to enhance yield and preserve bioactivity. Analytical methods including HPLC, NMR spectroscopy, and mass spectrometry are essential for its identification and purity assessment. Experimental evidence indicates that dieckol exhibits antioxidant, anti-inflammatory, antidiabetic, anticancer, antimicrobial, bone protective, and neuroprotective effects through modulation of oxidative stress, inflammatory signaling, and cell survival pathways. However, its clinical application remains limited due to poor bioavailability arising from its large molecular size, high polarity, low membrane permeability, gastrointestinal instability, and extensive metabolism. Recent strategies focusing on nano-based and lipid-based delivery systems show promise in improving its stability and absorption. Overall, dieckol represents a promising therapeutic and nutraceutical candidate, but further in-vivo and clinical studies are required to establish its safety and efficacy.

Introduction

The marine environment serves as an unparalleled repository of biologically active natural substances due to the vast ecological and chemical diversity present across its numerous maritime zones. Organisms inhabiting these dynamic marine ecosystems contribute significantly to the advancement of human well-being by acting as abundant and novel sources of diverse bioactive metabolites. Marine natural products represent valuable resources for health-promoting bioactive compounds.[1,2]

These compounds have increasingly been recognised as promising alternatives to conventional synthetic drugs with side effects and have demonstrated effectiveness against both infectious and non-infectious diseases.

The macroalgae constitute one of the richest and most reliable sources of marine natural products for the development of antioxidant, antityrosinase, anti-inflammatory, antimicrobial, anticancer, and antidiabetic agents.[3-5] Seaweeds are a diverse group of photosynthetic organisms that inhabit marine ecosystems. Despite their

***Corresponding Author:** Ms. Anupama Sobhana Sreekumar

Address: Dept. of Marine Biosciences, Faculty of Ocean Science and Technology, Kerala University of Fisheries and Ocean Studies, Panangad, Kochi, Kerala, India.

Email ✉**:** anupamasreehari@gmail.com

Tel.: 91-9447435797

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immense biological potential, many seaweed species remain insufficiently explored due to geographical inaccessibility and environmental constraints. Seaweeds are broadly classified into three major groups Chlorophyceae (green algae), Rhodophyceae (red algae), and Phaeophyceae (brown algae) based on differences in morphological, anatomical, and reproductive characteristics.[6] Among these groups, brown seaweeds possess a wide array of bioactive compounds, including polysaccharides, phlorotannins, carotenoids, sterols, and free fatty acids, which exhibit promising pharmaceutical and nutraceutical applications. Consequently, these macroalgae have attracted considerable attention from marine biopharmaceutical researchers. Among the brown algae investigated to date, the genus *Ecklonia* has been identified as an important marine macroalgal resource rich in several bioactive compounds, such as carotenoids, fucoidan, sterols, and phlorotannins.

Among the diverse range of phycobioactive compounds, phlorotannins represent an important class of polyphenolic metabolites with a wide spectrum of biological activities, including antioxidant, anticancer, antidiabetic, and antiallergic properties. Phlorotannins are polyphenolic compounds exclusively synthesised by brown algae through the acetate–malonate biosynthetic pathway. These secondary metabolites occur in various structural forms ranging from simple monomers to complex polymers and are known for their remarkable structural diversity and complexity. In addition to their pharmacological potential, phlorotannins play crucial ecological roles in marine environments, including protection against ultraviolet radiation and deterrence against herbivory.[7]

Dieckol(4-[6-(3,5-dihydroxyphenoxy)-4,7,9-trihydroxydibenzo-p-dioxin-2-yloxy-3,5-dihydroxyphenoxy dibenzo-p-dioxin-1,3,6,8-tetrol; molecular weight ≈ 742 Da) is a naturally occurring marine-derived hexameric phlorotannin that exhibits a wide range of biological and pharmacological activities. Earlier studies successfully isolated dieckol from brown algae and elucidated its chemical structure, revealing its complex phlorotannin framework. These pioneering studies paved the way for subsequent research exploring the biological and pharmacological potential of dieckol across various disease models, establishing it as a promising candidate for drug development from marine resources. This review focuses on the isolation, characterisation, and biological activities of dieckol.

Methodology

A comprehensive literature review was conducted to evaluate the isolation, purification, characterisation, and multifunctional biological activities of dieckol. Biomedical and multidisciplinary databases, including PubMed, Scopus, Web of Science, and Google Scholar, were systematically searched to retrieve relevant studies published between 2005 and 2026. The search strategy incorporated specific keywords such as biological activities, bioavailability, dieckol, *Ecklonia*, marine natural products, and phlorotannins. Boolean operators (AND, OR) were applied to refine and optimize the search results. Including article type (original research articles and reviews), availability of full text, and relevance to marine-derived bioactive compounds were used to enhance the quality of the selected literature. The initial search yielded a large number of publications, which were subsequently screened based on titles, abstracts, and full text evaluation to ensure relevance to the scope of the review. Following this systematic screening process, a total of 47 references were selected for inclusion.

The selected studies encompassed both experimental and review-based evidence, providing insights into extraction and purification techniques, structural characterisation methods, pharmacokinetics, and a wide range of biological activities of dieckol, including antioxidant, anti-inflammatory, anticancer, and cardioprotective effects. This integrative approach enabled a comprehensive understanding of the molecular properties, bioavailability, and therapeutic potential of dieckol derived from marine brown algae, particularly species of the genus *Ecklonia*.

Ecklonia species as a source of dieckol

The genus *Ecklonia*, belonging to the family Lessoniaceae, comprises nine recognized species, including *E. biruncinata*, *E. brevipes*, *E. cava* (EC), *E. fastigiata*, *E. kurome* (EK), *E. maxima* (EM), *E. muratii*, *E. radiata* (ER), and *E. stolonifera* (ES). These brown macroalgae are widely distributed along the western coast of South Africa and the eastern coasts of South and North America. Structurally, *Ecklonia* species possess a typical thallus organisation consisting of a holdfast, stipe, and laminae (blades), enabling them to adapt to dynamic marine environments efficiently.

Ecklonia species are rich sources of diverse bioactive compounds such as polyphenols, carotenoids, fucoidan, and phlorotannins. These secondary metabolites play crucial ecological roles by acting as chemical deterrents against herbivory, preventing microbial fouling, and protecting algae from ultraviolet radiation–induced stress, thereby enhancing their ecological fitness in coastal ecosystems.[8] Among these metabolites, phlorotannins constitute an important chemical defense system in brown algae. Dieckol, a major phlorotannin compound, has been identified in several *Ecklonia* species like *E. bicyclis*, *E. cava*, *E. stolonifera*, and *E. kurome*. Its concentration varies depending on species, growth stage, and environmental conditions. Mature *E. cava* thalli contain approximately 1.82 mg/g dry tissue of dieckol, with higher concentrations observed in blade tissues compared to stipe or holdfast regions. Dieckol has gained significant scientific attention due to its multifunctional biological activities, including antimicrobial, antitumor, antioxidant, anti-ageing, and antidiabetic properties.[9]

Extraction, Purification and Characterisation of Dieckol

The extraction and purification of dieckol from marine brown algae remain technically challenging due to its structural complexity and the presence of structurally related phlorotannins. Conventional solvent extraction and chromatographic methods often results low yield and partial loss of bioactivity. Consequently, advanced extraction strategies, including enzymatic hydrolysis, pressurised liquid extraction, and green extraction technologies, have been explored to improve recovery and preserve bioefficacy.[10]

Extraction Methods

The isolation of dieckol generally involves extraction from brown algal biomass followed by chromatographic purification. Optimising extraction conditions is crucial to maximise yield, maintain bioactivity, and ensure reproducibility. Although traditional solvent extraction methods are widely used, modern techniques are increasingly adopted to improve efficiency and reduce solvent consumption.

Solvent Extraction

Solvent extraction remains the most common method for isolating dieckol. Various solvents, including methanol, ethanol, ethyl acetate, dichloromethane, butanol, acetone, and water, have been used for extraction. Among these, ethanol is preferred for large-scale applications due to its high extraction efficiency, safety, and low toxicity.[11] Subsequent purification is typically achieved using chromatographic techniques such as thin layer chromatography (TLC), fast centrifugal partition chromatography (FCPC), high performance liquid chromatography (HPLC), and open column chromatography using Sephadex LH-20 or RP-18 stationary phases.[9]

Ethanolic extracts of *Ecklonia cava* were partitioned into n-hexane, ethyl acetate, and aqueous fractions, and the ethyl acetate fraction was further purified using silica gel and C-18 column chromatography to isolate dieckol.[12] Similarly, Diaion HP-20 resin adsorption followed by fractionation produced highly purified dieckol (87.2%). Methanolic extraction of algal biomass followed by solvent fractionation and purification using silica gel and Sephadex LH-20 chromatography yielded phlorotannins, including dieckol, in amounts of 50–130 mg.[13] Optimised extraction using 62.6% ethanol at 54°C for approximately 13 min yielded up to 6.4 mg dieckol/g of *E. cava*, highlighting ethanol as a suitable solvent under GRAS guidelines.[14] Additionally, prolonged ethanol extraction followed by reversed phase chromatography produced dieckol with purity exceeding 97%.[15]

Advanced Extraction Techniques

To overcome the limitations of conventional extraction, several advanced techniques have been developed, including centrifugal partition chromatography (CPC), ultrasonic-assisted extraction (UAE), microwave-assisted extraction (MAE), and hot pressurised liquid extraction (HPLE).

CPC and high-performance CPC (HPCPC) enable efficient isolation of phlorotannins using biphasic solvent systems such as n-hexane:EtOAc:MeOH:water (2:7:3:7, v/v). CPC has been reported to produce dieckol with purity above 90%, while HPCPC achieved purity levels exceeding 98% from *E. maxima* extracts.[16]

Ultrasonic-assisted extraction enhances compound recovery by generating cavitation bubbles that disrupt algal cell walls and improve solvent penetration. Using this method, phlorotannin yields of 179 mg GAE/L were obtained from *E. arborea*, and optimised conditions yielded dieckol (44.61 mg/g extract) from *E. cava*, with biomass yields of approximately 6 mg/g.[17]

Microwave-assisted extraction improves extraction efficiency through dielectric heating, enabling rapid solvent penetration and uniform heating. Using Prethanol A as solvent, MAE yielded 16.5 mg/g dieckol from *E. bicyclis*, while further optimisation produced 17.3 mg/g dieckol within six minutes.[18, 19]The comparative performance of conventional and advanced extraction techniques for phlorotannin recovery, including their yields, advantages, and limitations, is summarised in Table 1.

Purification Methods

Chromatographic Techniques

Chromatography remains the primary method for purifying dieckol and other phlorotannins from brown algae. Commonly used techniques include silica gel column chromatography, Sephadex LH-20 chromatography, reverse phase chromatography, HPLC, UPLC, and CPC, which enable the isolation of high purity fractions (>90%).

Silica gel chromatography separates compounds based on differential adsorption. For example, the ethyl acetate fraction of *Eisenia bicyclis* was fractionated using EtOAc–MeOH (15:1), followed by gradient elution (20–100% MeOH) on an RP-18 column to obtain purified phlorotannins.[20] Sephadex LH-20 chromatography is often used as a complementary size exclusion technique to improve purification of complex extracts.

In *Ecklonia cava*, ethanol extracts are frequently fractionated sequentially with hexane, chloroform, and ethyl acetate. The ethyl acetate fraction is further purified by preparative CPC and HPLC, yielding dieckol with purity up to 95%, confirmed by HPLC–DAD–ESI/MS.[21] CPC offers advantages by preventing irreversible adsorption onto solid supports, thereby improving compound recovery.

Validated HPLC methods are widely used for dieckol quantification. Kim et al. developed an analytical method using a Supelco Discovery C18 column with UV detection at 230 nm, demonstrating excellent linearity ($R^2 > 0.999$) and recovery rates of 100.9–102.3%.[22]

Table 1: Comparison of Extraction Methods for Dieckol

Method	*Source Species*	*Yield/Purity*	*Advantages*	*Limitations*
Solvent Extraction	E. cava	6.4 mg/g	Simple, inexpensive	High solvent use, longer extraction time
UAE	E. cava	44.61 mg/g extract	Higher recovery, shorter time	Scale-up challenges [17]
MAE	E. bicyclis	16.5–17.3 mg/g	Rapid extraction	Thermal degradation risk [18,19]
CPC/HPCPC	E. maxima	>90–98% purity	High purity	Expensive equipment [16]

Abbreviations: UAE, Ultrasonic-Assisted Extraction; MAE, Microwave-Assisted Extraction; CPC, Centrifugal Partition Chromatography; HPCPC, High-Performance Centrifugal Partition Chromatography.

Reverse phase HPLC has also been used to isolate dieckol from *E. cava*, *E. stolonifera*, and *E. bicyclis*, achieving recovery yields of 86%, 93%, and 98%, respectively.[23] Additionally, advanced UPLC-QTOF-MS/MS techniques have enabled the identification of major phlorotannins—including eckol, bieckol, dieckol, and phlorofucofuroeckol-A—in ethanol extracts of cultivated *E. cava*.[19]

Resin Based Purification

Resin adsorption–desorption techniques provide scalable purification of phlorotannins. Synthetic polymeric resins such as Diaion HP-20, SP-580, XAD-7HP, and XAD-2 are widely used, with HP-20 demonstrating superior adsorption and desorption performance.[24] Hot pressurised liquid extraction combined with HP-20 resin purification (HPLE-RP) offers an eco-friendly and efficient approach for recovering phlorotannins while reducing solvent consumption.[25]

Characterisation of Dieckol

Characterisation of dieckol is essential for confirming its molecular structure, purity, and functional properties. Due to its structural complexity, accurate identification requires the integration of spectroscopic, spectrometric, and chromatographic techniques.

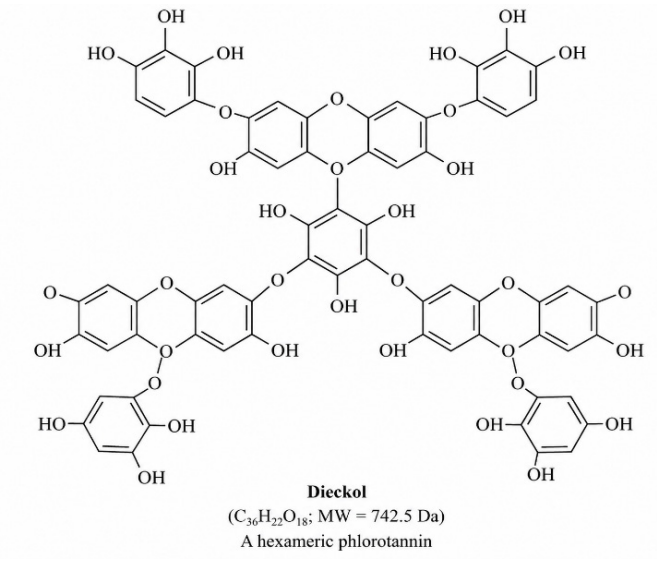
Chemical structure of dieckol

Dieckol ($C_{36}H_{22}O_{18}$; molecular weight 742.5 Da) is a naturally occurring hexameric phlorotannin found mainly in brown seaweeds such as Ecklonia cava, Ecklonia stolonifera, and Eisenia bicyclis. Structurally, it is composed of six phloroglucinol units interconnected through ether and dibenzo-1,4-dioxin linkages, resulting in a highly polyphenolic molecule with multiple hydroxyl groups. These structural features are largely responsible for its strong free radical scavenging capacity and its ability to modulate various cellular signaling pathways involved in oxidative stress, inflammation, apoptosis, and metabolic regulation. Consequently, dieckol has emerged as a promising marine bioactive compound with significant pharmaceutical and nutraceutical potential.

The chemical structure and molecular architecture of dieckol, a hexameric phlorotannin characterized by multiple hydroxyl groups and ether linkages contributing to its antioxidant and bioactive properties, are illustrated in Fig. 1.

Spectroscopic Techniques

UV–Visible spectroscopy reveals characteristic absorption peaks between 230 and 290 nm, corresponding to the aromatic phenolic structure of dieckol.[9] Structural elucidation is commonly performed using ^{1}H and ^{13}C-NMR spectroscopy. In ^{1}H-NMR spectra, dieckol typically shows signals at δ 5.92 to 6.15 ppm corresponding to phenolic protons, while ^{13}C-NMR spectra display peaks between δ 143.3 and 161.8 ppm associated with aromatic and hydroxyl-substituted carbons.[9,17] These spectra confirm the presence of characteristic dibenzo-1,4-dioxin linkages. Electrospray ionisation time-of-flight mass spectrometry (ESI-TOF-MS) confirms the molecular weight of dieckol (742 Da; $C_{36}H_{22}O_{18}$), while MS/MS fragmentation patterns further verify its structural identity.[26] Computational methods such as density functional theory (DFT) and natural bond orbital (NBO) analysis have also been employed to examine electronic structure and molecular stability.[27]



Chemical structure of dieckol ($C_{36}H_{22}O_{18}$; molecular weight: 742.5 Da), a hexameric phlorotannin composed of interconnected phloroglucinol units through ether and dibenzodioxin linkages. The high number of hydroxyl groups contributes to its antioxidant activity and diverse biological properties.

Fig. 1: Structure of dieckol

Table 2: Characterisation Techniques for Dieckol

Category	*Technique*	*Key Features / Observations*	*Purpose*	*Reference*
Spectroscopic Techniques	UV–Visible Spectroscopy	Absorption peaks at 230–290 nm associated with aromatic phenolic structures	Preliminary identification and characterization of phenolic compounds	[9]
	^{1}H NMR Spectroscopy	Signals at δ 5.92–6.15 ppm corresponding to phenolic proton environments	Identification of hydrogen environments and structural confirmation	[26]
	^{13}C NMR Spectroscopy	Peaks at δ 143.3–161.8 ppm representing aromatic and hydroxyl carbons	Confirmation of carbon framework and molecular structure	[26]
	NMR (General)	Detection of dibenzo-1,4-dioxin linkages characteristic of dieckol structure	Structural elucidation of phlorotannin backbone	[26]
	ESI-TOF-MS	Molecular ion corresponding to approximately 742 Da ($C_{36}H_{22}O_{18}$)	Molecular mass confirmation of dieckol	[26]
	MS/MS Fragmentation	Characteristic fragmentation patterns of phlorotannins	Structural verification and identification of molecular fragments	[26]
	Computational Analysis (DFT, NBO)	Provides electronic structure, bonding, and molecular stability information	Theoretical validation of molecular properties	[17]
Chromatographic & Analytical Methods	HPLC (UV detection)	High reproducibility with purity levels exceeding 95% under optimized conditions	Quantification, separation, and purity assessment of dieckol	[9]
	LC–MS	Enables qualitative and quantitative identification of dieckol in complex algal extracts	Detection and characterization of dieckol in biological and algal matrices	[26]
	HILIC	Improved retention and separation efficiency for highly polar phlorotannins compared with conventional reversed-phase chromatography	Enhanced resolution and separation of polar dieckol-related compounds	[17]

Abbreviations: UV–Visible spectroscopy (Ultraviolet–Visible spectroscopy), NMR (Nuclear Magnetic Resonance), MS (Mass Spectrometry), HPLC (High-Performance Liquid Chromatography), LC–MS (Liquid Chromatography–Mass Spectrometry), HILIC (Hydrophilic Interaction Liquid Chromatography), and DFT (Density Functional Theory) are complementary techniques used for structural elucidation, purity assessment, and molecular characterization of dieckol.

Chromatographic and Analytical Methods

Chromatographic techniques are widely used for separation, quantification, and purity assessment of dieckol. High-performance liquid chromatography (HPLC) with UV detection is the standard analytical method and can achieve purities exceeding 95% under optimised conditions.[9] Liquid chromatography–mass spectrometry (LC/MS) provides both qualitative and quantitative identification of dieckol in complex algal extracts. [26] Hydrophilic interaction liquid chromatography (HILIC) further improves separation efficiency for polar phlorotannins compared with conventional reversed-phase chromatography. [17]

Table 2 shows the spectroscopic, chromatographic, and computational techniques used for the structural characterisation, identification, and purity assessment of dieckol, including UV–Visible spectroscopy, NMR, mass spectrometry, HPLC, LC–MS, HILIC, and DFT-based analyses.

Multifunctional Biological Activities

Dieckol, a phlorotannin derived from brown algae, exhibits a broad spectrum of biological activities including antioxidant, anti-inflammatory, antidiabetic, anticancer, antimicrobial, anti-osteoporotic, and neuroprotective effects.

Antioxidant Defence Mechanisms

Dieckol demonstrates strong antioxidant activity across a variety of experimental models. In renal mesangial cells, it inhibited methylglyoxal-induced oxidative damage by suppressing the formation and cross-linking of advanced glycation end products (AGEs), thereby blocking AGE–RAGE signalling and reducing reactive oxygen species (ROS) accumulation and apoptosis. [28] Similarly, in fine dust–stimulated macrophages, dieckol reduced ROS production while enhancing antioxidant defence through activation of superoxide dismutase (SOD) and the Nrf2/HO-1 pathway. [29] Protective effects have also been

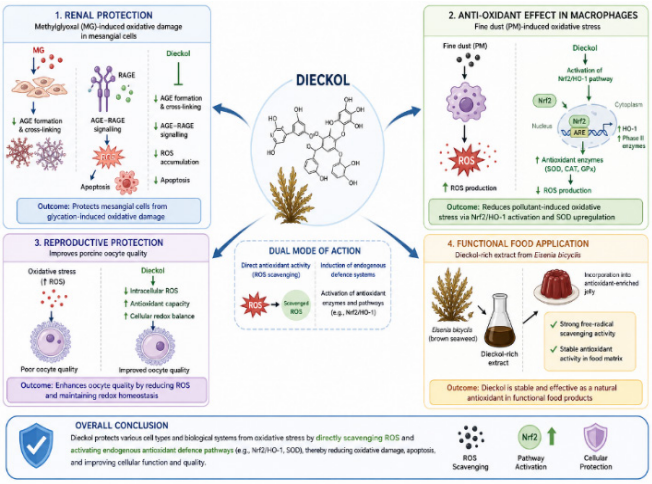
reported in reproductive systems, where dieckol improved porcine oocyte quality by reducing intracellular ROS and maintaining cellular redox balance. [30] In addition, dieckol-rich extracts from *Eisenia bicyclis* exhibited strong free radical scavenging activity and retained functional stability when incorporated into antioxidant-enriched jelly products.[18] The consistency of antioxidant effects observed across different cellular and functional systems suggests that dieckol exerts broad-spectrum cytoprotective activity. However, direct comparisons among studies remain challenging because of differences in experimental models, oxidative stress inducers, treatment durations, and concentrations of dieckol employed. Although most studies report beneficial antioxidant effects, the magnitude of protection varies considerably among experimental systems. These variations may reflect differences in cell types, biological endpoints measured, oxidative stress induction methods, and the physicochemical characteristics of the dieckol preparations used. Consequently, apparent inconsistencies in antioxidant efficacy are more likely attributable to methodological heterogeneity than to fundamental contradictions regarding the antioxidant potential of dieckol.

Despite the generally positive findings, several limitations should be considered when interpreting the current evidence. Most studies have been conducted in vitro or under controlled experimental conditions, with relatively limited validation in animal models and a lack of human clinical studies. Furthermore, variations in extraction methods, purity of dieckol preparations, and the use of either purified compounds or dieckol-rich extracts may contribute to differences in reported antioxidant efficacy across studies. These methodological differences may partly explain inconsistencies in the magnitude of antioxidant responses observed in different biological systems. Another potential source of variation is the difference between studies employing purified dieckol and those utilizing crude or enriched algal extracts, where synergistic interactions among multiple bioactive compounds may influence the observed antioxidant outcomes. Such differences make it difficult to determine the precise contribution of dieckol alone to the reported biological effects. Moreover, although activation of antioxidant pathways such as Nrf2/HO-1 appears to be a common mechanism, the clinical relevance of these findings remains uncertain because dieckol exhibits poor oral bioavailability and limited systemic exposure. Therefore, future studies should focus on standardized experimental designs, *in-vivo* validation, and clinical investigations to better establish the translational potential of dieckol as a therapeutic antioxidant.

The Fig. 2 illustrates the dual mode of action of dieckol, highlighting its renal protective, antioxidant, reproductive protective, and functional food applications through ROS scavenging and activation of cellular defense pathways.

Anti-inflammatory Properties

Dieckol exerts potent anti-inflammatory effects by regulating key inflammatory mediators.[31] It suppresses the production of nitric oxide, prostaglandin E_2, and pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6. Animal studies further demonstrated its analgesic and anti-inflammatory activities by reducing nociceptive responses and carrageenan-induced paw oedema while limiting leukocyte infiltration.[32] These effects are largely mediated through inhibition of NF-κB and MAPK signalling pathways that regulate inflammatory gene expression. Dieckol's antioxidant properties also contribute to its anti-inflammatory effects by reducing ROS-mediated amplification of inflammatory signalling. [33] Collectively, the available studies indicate that dieckol exerts anti-inflammatory activity through multiple complementary mechanisms. While cellular studies have primarily focused on the suppression of inflammatory mediators and signalling pathways, animal studies have demonstrated functional benefits such as reduced oedema, leukocyte infiltration, and pain responses. These findings suggest that the anti-inflammatory effects of dieckol extend from molecular regulation to physiological protection. However, direct comparisons among studies remain challenging because of differences in inflammatory models, experimental conditions, treatment durations, and outcome measures.



Dieckol, a phlorotannin derived from brown seaweed, exerts multifaceted protective effects through its dual mode of action—direct scavenging of reactive oxygen species (ROS) and activation of endogenous antioxidant pathways such as Nrf2/HO-1. By inhibiting AGE formation, suppressing oxidative stress, and improving cellular redox balance, dieckol protects against mesangial cell damage, enhances oocyte quality, mitigates macrophage-mediated inflammation, and demonstrates potential as a natural antioxidant in functional food applications.

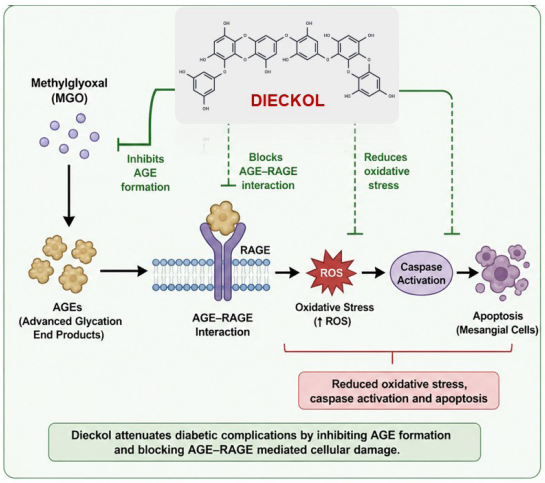
Fig. 2: Mechanistic Overview of Dieckol-Mediated Antioxidant Protection Across Cellular and Functional Systems

Despite the generally consistent evidence supporting the anti-inflammatory potential of dieckol, several limitations should be considered. Most studies have been conducted in vitro or in animal models, with limited clinical evidence available to confirm efficacy in humans. Furthermore, variations in extraction methods, compound purity, dosage, and the use of either purified dieckol or dieckol-rich algal extracts may contribute to differences in the reported anti-inflammatory responses. Such methodological heterogeneity may explain apparent inconsistencies in efficacy across studies and complicate the interpretation of results. In addition, the potential synergistic effects of other phlorotannins present in crude extracts make it difficult to determine the precise contribution of dieckol alone. Although inhibition of NF-κB and MAPK signalling pathways appears to be a consistently reported mechanism, further standardized *in-vivo* studies and well-designed clinical trials are required to establish its therapeutic relevance, optimal dosing strategies, and long-term safety as an anti-inflammatory agent.

Antidiabetic Actions

Dieckol exhibits antidiabetic potential by targeting key molecular mechanisms involved in diabetic complications. It inhibits AGE formation and blocks AGE–RAGE interactions, thereby reducing oxidative stress, caspase activation, and apoptosis in mesangial cells exposed to methylglyoxal.[28] A clinical study using *Ecklonia cava* extract rich in dieckol demonstrated a significant reduction in postprandial blood glucose following a single 600 mg oral dose, suggesting translational potential for glycaemic control, although the specific contribution of dieckol requires further investigation. [34] Together, these findings provide evidence for the antidiabetic effects of dieckol at both the cellular and clinical levels. However, the available studies differ considerably in their design, with mechanistic investigations primarily focusing on the prevention of diabetic tissue damage, whereas clinical studies have evaluated short-term glycaemic outcomes. As a result, direct comparisons between preclinical and clinical findings remain challenging.

While the available evidence supports the antidiabetic potential of dieckol, several important limitations must be considered when interpreting these findings. The mechanistic evidence is largely derived from in vitro models that may not fully replicate the complexity of human diabetes, while the clinical evidence is limited to studies using dieckol-rich extracts rather than purified dieckol. Consequently, the observed metabolic benefits may reflect the combined action of multiple bioactive compounds present in the extract. Furthermore, differences in dosage, treatment duration, patient characteristics, and study endpoints may contribute to variations in reported efficacy across studies. These factors may explain apparent inconsistencies between experimental and clinical outcomes and highlight the need for well-designed longitudinal studies and randomized clinical trials to clarify the specific therapeutic role of dieckol in diabetes management.



Dieckol, a marine-derived polyphenol from brown algae, exhibits protective effects by inhibiting advanced glycation end product (AGE) formation, blocking AGE–RAGE interaction, and reducing oxidative stress (ROS generation). These actions collectively suppress caspase activation and apoptosis, particularly in mesangial cells, thereby contributing to the attenuation of diabetic complications.

Fig. 3: Protective Role of Dieckol Against AGE–RAGE Mediated Oxidative Stress and Apoptosis

The Fig. 3 illustrates the protective mechanism of dieckol against diabetic complications by inhibiting AGE formation, blocking AGE–RAGE interaction, reducing oxidative stress, and preventing ROS-mediated apoptosis.

Anticancer Activity

The breadth of molecular targets influenced by dieckol highlights its potential as a multi-target anticancer agent. Evidence from apoptosis-focused studies[35] and signalling pathway investigations[36] suggests that dieckol interferes with several interconnected processes involved in tumour initiation and progression. Similarly, studies examining tumour invasion and chemoprevention have demonstrated its ability to modulate angiogenesis, inflammatory responses, and oxidative stress.[33,37] However, direct comparisons among studies remain difficult because of variations in cancer types, experimental systems, treatment regimens, and biological endpoints. Such methodological diversity complicates the assessment of whether specific anticancer mechanisms are universally applicable or context-dependent.

Notwithstanding these encouraging observations, important limitations remain in the current evidence base. Most available data originate from cancer cell lines and experimental animal models, with limited clinical evidence available to confirm therapeutic efficacy in humans. Furthermore, differences in tumour biology, molecular

drivers, and disease stage may contribute to variability in treatment responses reported across studies. These factors may explain apparent inconsistencies in the magnitude of anticancer effects, as signalling pathways strongly affected in one cancer type may not be equally relevant in another. In addition, the concentrations used in many experimental studies may exceed those achievable under physiological conditions due to the limited bioavailability of dieckol. Therefore, future investigations should focus on standardized experimental designs, clinically relevant dosing strategies, and well-controlled clinical trials to establish the translational potential of dieckol in cancer prevention and therapy.

Antimicrobial and Antiviral Effects

Dieckol has demonstrated broad antimicrobial and antiviral activity. [38] It inhibits pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) by disrupting bacterial membranes and interfering with enzymatic processes. Moreover, it enhances the effectiveness of β-lactam antibiotics by impairing bacterial resistance mechanisms. [20] Dieckol also exhibits antiviral activity by targeting viral proteins involved in replication and entry, including the main protease (3CLpro) of SARS-CoV and SARS-CoV-2.[39] Additionally, it inhibits Zika virus replication by interacting with viral envelope and replication proteins. Its antioxidant activity further protects host cells during infection by activating Nrf2/ARE signalling and enhancing antioxidant enzyme expression. [40] The ability of dieckol to act against both bacterial and viral pathogens highlights its potential as a versatile anti-infective agent. Notably, antibacterial studies have largely focused on direct pathogen inhibition and enhancement of antibiotic susceptibility [20] whereas antiviral investigations have emphasized interference with viral replication and host defence mechanisms. [39,40] This diversity of mechanisms suggests a broad therapeutic spectrum; however, differences in pathogen biology, experimental approaches, and efficacy assessment methods limit direct comparisons among studies.

Interpretation of the current evidence is further complicated by several methodological and translational limitations. Much of the available data originates from laboratory-based studies, with limited *in-vivo* validation and an absence of large-scale clinical investigations. In addition, the strength of evidence differs substantially across pathogens, with some antiviral effects supported primarily by computational predictions [39] whereas others have been validated through experimental infection models. [40] Such differences in study design may contribute to variations in the reported efficacy of dieckol and explain apparent inconsistencies across the literature. Furthermore, pathogen-specific factors, including resistance mechanisms, replication strategies, and host–pathogen interactions, may influence treatment outcomes and account for differences in antimicrobial responsiveness. Therefore, future studies should prioritize standardized evaluation protocols and clinical validation to clarify the therapeutic applicability of dieckol in infectious disease management.

Anti-osteoporotic Activity

Dieckol has shown promising anti-osteoporotic effects by regulating bone remodelling processes. It suppresses osteoclast differentiation through inhibition of the RANKL signalling pathway, thereby reducing bone resorption. At the same time, it promotes osteoblast activity and increases the expression of bone formation markers such as osteocalcin, alkaline phosphatase, and bone morphogenetic proteins. [41] Its antioxidant and anti-inflammatory properties also contribute to bone protection by reducing ROS levels and suppressing cytokines such as TNF-α, IL-1β, and IL-6 that promote osteoclast activation.[41,42] The dual ability of dieckol to suppress bone resorption while enhancing bone formation distinguishes it from interventions that target only a single aspect of bone remodelling. Studies investigating osteoclastogenesis have primarily focused on the inhibition of RANKL-mediated pathways, [41] whereas others have emphasized the contribution of antioxidant and anti-inflammatory mechanisms to skeletal protection. [41,42] This multifaceted mode of action suggests that dieckol may influence several interconnected processes involved in osteoporosis progression. However, the relative contribution of each mechanism remains unclear, making it difficult to determine which pathways are most critical for its bone protective effects.

Several factors also limit the interpretation of the current evidence. Most studies have been conducted in experimental models, with limited clinical data available to confirm efficacy in human populations. Furthermore, differences in osteoporosis models, treatment duration, dosage regimens, and outcome measures may contribute to variations in the reported magnitude of bone protective effects. Such methodological differences may explain apparent inconsistencies across studies and complicate comparisons of therapeutic efficacy. In addition, osteoporosis is a multifactorial disorder influenced by age, hormonal status, nutritional factors, and systemic inflammation, variables that are not consistently accounted for in preclinical investigations. Consequently, although modulation of RANKL signalling, oxidative stress, and inflammatory pathways appears to underlie the anti-osteoporotic activity of dieckol, further standardized animal studies and well designed clinical trials are required to establish its long term efficacy, safety, and translational relevance in osteoporosis management.

Neuroprotective Effects

Dieckol exhibits neuroprotective activity through antioxidant, anti-inflammatory, and anti-apoptotic mechanisms. In neuronal models of glutamate induced toxicity, dieckol reduced ROS production and preserved mitochondrial membrane potential. It also suppresses microglial activation

and reduces neuroinflammatory mediators associated with neuronal damage. [43] Furthermore, dieckol regulates apoptosis related proteins by increasing anti-apoptotic Bcl-2 expression while suppressing caspase activation. In Alzheimer's disease models, it modulates amyloid precursor protein processing through the PI3K/Akt/GSK-3β pathway, reducing amyloid-β production. [44] Protective effects on hippocampal neurons and synaptic function have also been reported. [18] The neuroprotective actions of dieckol appear to involve the coordinated regulation of multiple pathological processes associated with neurodegeneration. While studies employing oxidative stress and excitotoxicity models have primarily highlighted its antioxidant and anti-apoptotic properties, [43] investigations in Alzheimer's disease models have emphasized its ability to modulate amyloidogenic pathways and preserve neuronal function. [44] These findings suggest that dieckol may target both general mechanisms of neuronal injury and disease specific pathways implicated in neurodegenerative disorders. However, direct comparisons among studies are complicated by differences in experimental models, neurological endpoints, and disease contexts, making it difficult to determine the relative importance of individual neuroprotective mechanisms.

Several challenges also limit the interpretation of the current evidence. Most neuroprotective effects have been demonstrated in cellular or experimental animal models, with limited clinical data available to confirm efficacy in humans. Furthermore, differences in disease models, treatment duration, dosage, and outcome measures may contribute to variability in the reported neuroprotective effects across studies. Such methodological heterogeneity may explain apparent inconsistencies in the magnitude of neuronal protection observed under different experimental conditions. In addition, although modulation of oxidative stress, neuroinflammation, and amyloid-β production has been consistently reported, [43,44] the ability of dieckol to achieve therapeutically effective concentrations within the central nervous system remains uncertain because of potential bioavailability and blood–brain barrier permeability constraints. Consequently, further studies are required to clarify its pharmacokinetic properties, validate its efficacy in clinically relevant models, and establish its translational potential for the prevention and treatment of neurodegenerative diseases.

Bioavailability, Pharmacokinetics, and Clinical Translation of Dieckol

Despite its broad spectrum of biological activities, including antioxidant, anti-inflammatory, antidiabetic, neuroprotective, and anticancer effects, the therapeutic application of dieckol is constrained by its low oral bioavailability. This limitation arises from a combination of physicochemical characteristics, gastrointestinal instability, restricted intestinal absorption, and extensive metabolic transformation, all of which reduce systemic exposure following oral administration.

Mechanistic Basis of the Low Bioavailability of Dieckol

Structural and Physicochemical Limitations

Dieckol is a high molecular weight phlorotannin composed of multiple phloroglucinol units. Its numerous hydroxyl groups confer high polarity and facilitate extensive hydrogen bonding, resulting in low lipophilicity and limited passive diffusion across intestinal epithelial membranes. In addition, its relatively large molecular size restricts transcellular transport and further impairs membrane permeability. Collectively, these physicochemical properties contribute to inefficient gastrointestinal absorption and low systemic availability following oral administration. Although these characteristics are consistently recognized as major barriers to dieckol bioavailability, the relative contribution of individual factors such as molecular size, polarity, and membrane permeability remains incompletely understood. Furthermore, differences in experimental models and assessment methods used to evaluate absorption may contribute to variability in reported bioavailability estimates across studies. These limitations highlight the need for standardized pharmacokinetic investigations and optimized delivery strategies to improve the clinical translation of dieckol. [45]

Gastrointestinal Instability and Metabolic Transformation

Following oral ingestion, dieckol is exposed to the complex gastrointestinal environment, where variations in pH and digestive enzymes may compromise its structural integrity prior to absorption. Furthermore, intestinal microbiota metabolizes phlorotannins into smaller phenolic derivatives. Although some metabolites may retain biological activity, microbial biotransformation reduces the amount of intact dieckol available for systemic absorption. These gastrointestinal and microbial processes are important determinants of the pharmacokinetic behavior of marine derived polyphenols. However, the extent to which gastrointestinal degradation and microbial metabolism influence dieckol bioavailability remains incompletely characterized, as existing studies employ different experimental approaches and analytical methods. Such methodological variations may contribute to discrepancies in reported metabolic profiles and absorption estimates across studies. Moreover, the biological activity of many dieckol derived metabolites has not been fully elucidated, highlighting an important gap in the current understanding of its pharmacokinetic and therapeutic properties.[46]

Limited Absorption and First Pass Metabolism

The fraction of dieckol that successfully crosses the intestinal barrier undergoes extensive first pass metabolism

in enterocytes and hepatocytes. Phase II conjugation reactions, including glucuronidation, sulfation, and methylation, enhance aqueous solubility and facilitate excretion but simultaneously decrease circulating concentrations of the parent compound. Consequently, dieckol exhibits low plasma exposure and rapid clearance following oral administration. Studies comparing oral and intravenous delivery have demonstrated substantially greater systemic exposure after intravenous administration, highlighting the significant impact of first pass metabolism on its bioavailability. Nevertheless, the relative contribution of individual metabolic pathways to dieckol disposition remains insufficiently characterized, and variations in experimental design and pharmacokinetic assessment methods may account for differences in reported bioavailability parameters across studies. Furthermore, most available evidence is derived from preclinical investigations, limiting the extrapolation of these findings to humans. These limitations underscore the need for comprehensive pharmacokinetic studies to better define the metabolic fate and systemic exposure profile of dieckol. [11]

Pharmacokinetic Evidence and Bioavailability–Activity Relationship

Pharmacokinetic investigations consistently indicate that dieckol displays low systemic exposure after oral administration, characterized by limited peak plasma concentrations and reduced overall drug exposure. [47] These findings reflect a combination of poor intestinal absorption, extensive metabolic conversion, and rapid elimination. Notably, the potent biological activities observed *in vitro* often exceed those achievable under physiological conditions *in-vivo*. This discrepancy suggests that the biological effects of dieckol may be mediated not only by the parent compound but also by its metabolites or by local actions within the gastrointestinal tract. [33] Understanding the contribution of both intact dieckol and its metabolites is therefore essential for accurately evaluating its therapeutic potential. The marked difference between in vitro efficacy and *in-vivo* exposure represents a significant challenge in translating experimental findings into clinical applications. Furthermore, variations in pharmacokinetic models, dosing strategies, and analytical methodologies may contribute to differences in reported exposure profiles across studies. These limitations complicate direct comparisons of pharmacological outcomes and may partly explain inconsistencies between promising laboratory results and more modest effects observed under physiological conditions. Consequently, further studies are needed to clarify the respective roles of dieckol and its metabolites in mediating biological activity and therapeutic efficacy. [33,47]

Nanodelivery Strategies to Enhance Dieckol Bioavailability

To overcome the pharmacokinetic limitations of dieckol, various nanotechnology-based delivery systems have been investigated. These approaches are designed to improve solubility, protect the compound from gastrointestinal degradation, enhance intestinal permeability, and prolong systemic circulation. Nanoparticle-based formulations can shield dieckol from enzymatic and chemical degradation

Table 3: Comparative Characteristics of Nanotechnology-Based Delivery Systems for Enhancing Dieckol Bioavailability and Clinical Translation

Delivery System	*Loading Efficiency*	*Stability*	*Release Behavior*	*Advantages*	*Limitations*	*Translational Potential*	*Reference*
Liposomes	Moderate	Moderate	Fast–moderate release	Biocompatible	Physical instability	High	[51,52
Polymeric nanoparticles	High	High	Sustained release	Mucoadhesive	Complex manufacturing	Moderate–High	[49,52
Solid lipid nanoparticles (SLNs)	Moderate–High	High	Controlled release	Scalable	Drug expulsion during storage	High	[49
Nanoemulsions	Moderate	Moderate	Rapid release	Enhanced absorption	Droplet instability	Moderate	[49
Mesoporous silica nanoparticles	Very high	Very high	Tunable release	Large loading capacity	Long-term safety concerns	Moderate	[50

Abbreviations: SLNs, Solid Lipid Nanoparticles. The table summarizes the relative performance of major nanocarrier systems used for the delivery of polyphenolic compounds such as dieckol with respect to loading efficiency, physicochemical stability, release behavior, key advantages, limitations, and translational potential. The classifications (low, moderate, high, and very high) are qualitative assessments derived from published studies on polyphenol and marine bioactive compound nanodelivery systems and are intended to provide a comparative overview rather than absolute quantitative values. Translational potential reflects considerations related to biocompatibility, scalability, formulation reproducibility, regulatory feasibility, and prospects for clinical application.

during gastrointestinal transit while enabling controlled release within the intestinal environment, thereby improving systemic exposure through mechanisms such as transcellular uptake, endocytosis-mediated transport, and modulation of paracellular pathways. [48] Several classes of nanocarriers have demonstrated promise for polyphenol delivery, including solid lipid nanoparticles (SLNs), nanoemulsions, polymeric nanoparticles, nanocrystals, polymersomes, liposomes, phytosomes, ethosomes, invasomes, nanogels, and metal based nanoparticles. [49] Mesoporous silica nanoparticles, particularly polyethylene glycol (PEG) and graphene oxide-modified systems, offer high drug loading capacity, controlled release behavior, and enhanced structural stability,[50] while liposomal and polymer-based carriers improve aqueous solubility, mucoadhesion, gastrointestinal residence time, and absorption efficiency. [51,52]

A comparative evaluation of these delivery systems indicates that each carrier possesses distinct advantages and limitations for improving the bioavailability of dieckol. Liposomes offer excellent biocompatibility and enhanced solubility but are limited by moderate stability and potential physical instability during storage. Polymeric nanoparticles provide high loading efficiency, strong stability, and sustained release characteristics, although their large-scale production can be technically complex. SLNs combine good stability, controlled release, and scalability, making them attractive candidates for pharmaceutical applications, despite concerns regarding drug expulsion during prolonged storage. Nanoemulsions effectively enhance absorption and dispersion of bioactive compounds but may exhibit droplet instability and relatively rapid release profiles. In contrast, mesoporous silica nanoparticles demonstrate the highest loading capacity, superior stability, and tunable release behavior; however, uncertainties regarding long-term safety and regulatory approval may limit their immediate clinical translation. Overall, polymeric nanoparticles, SLNs, and mesoporous silica nanoparticles appear particularly promising for dieckol delivery because they provide a favourable balance between loading efficiency, stability, and controlled release.

Nevertheless, direct comparisons among studies remain difficult because of differences in carrier composition, formulation methods, drug loading efficiency, release kinetics, and evaluation criteria. Furthermore, most evidence is derived from experimental and preclinical investigations, with limited clinical validation of long term efficacy and safety. Such methodological variability may contribute to differences in the reported performance of individual nanocarriers and complicate the identification of the most effective delivery strategy. Therefore, standardized comparative studies, head to head evaluations of nanocarrier systems, and well-designed clinical investigations are required to establish the translational potential of nanotechnology-based approaches for enhancing dieckol therapy.[48–52]

The key characteristics of nanotechnology-based delivery systems explored for improving dieckol bioavailability, including their formulation properties, advantages, limitations, and clinical translation potential, are summarized in Table 3.

From Bioavailability to Clinical Translation: Challenges and Future Perspectives

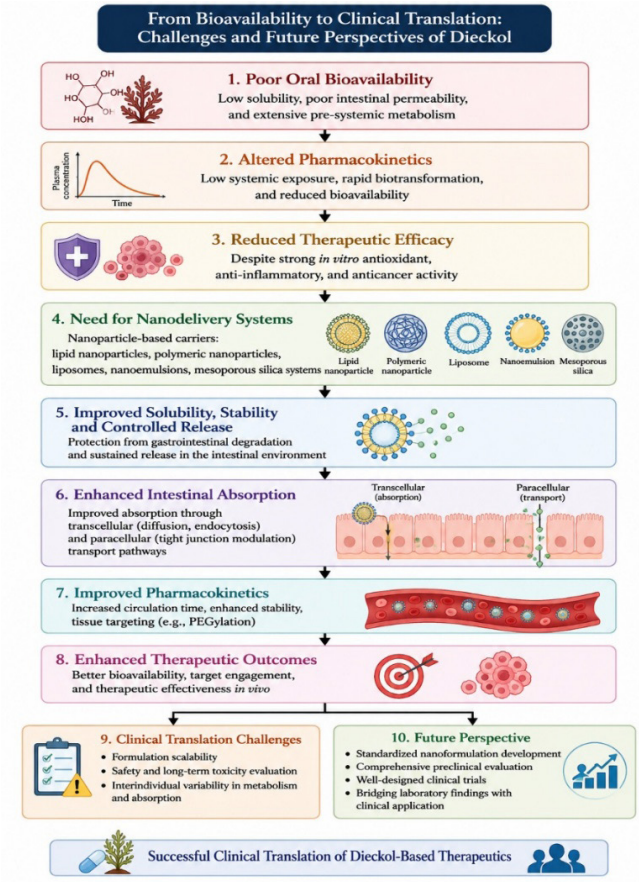
The transition of dieckol from experimental investigations to clinical application remains challenging despite its promising pharmacological properties. Poor oral bioavailability, limited intestinal permeability, and extensive pre systemic metabolism result in low systemic exposure, which may restrict therapeutic efficacy *in-vivo*. Consequently, improvements in formulation design are essential for translating the biological activities observed in preclinical studies into clinically meaningful outcomes. Nanodelivery systems represent a promising strategy to address these limitations by enhancing solubility, stability, absorption, and circulation time, thereby improving tissue exposure and therapeutic effectiveness. Nevertheless, the clinical translation of these approaches remains uncertain because most evidence is derived from preclinical studies, and direct comparisons among delivery platforms are often complicated by differences in formulation design, pharmacokinetic endpoints, and evaluation methods. Furthermore, challenges related to large scale manufacturing, long term safety, formulation reproducibility, regulatory approval, and interindividual variability in metabolic responses may contribute to differences in therapeutic outcomes and limit clinical applicability. These considerations highlight the need for standardized pharmacokinetic, efficacy, and safety assessments within well designed preclinical and clinical studies to establish the most effective strategies for bridging the gap between laboratory research and clinical application.

Fig. 4 summarizes the major barriers affecting the clinical translation of dieckol and the nanodelivery based approaches proposed to overcome these limitations.

Molecular Mechanisms of Dieckol's Therapeutic Effects

Dieckol exerts its therapeutic effects through the regulation of several interconnected molecular pathways involved in oxidative stress, inflammation, cell survival, apoptosis, and tissue remodeling. A central mechanism is the modulation of the PI3K/Akt/mTOR signaling axis, which influences cell proliferation, growth, and survival. In cancer models, dieckol suppresses PI3K/Akt/mTOR activation, reduces the expression of proliferative markers such as cyclin D1, CDK4, CDK6, and PCNA, and promotes apoptosis through the upregulation of Bax, caspase-9, and caspase-3

together with the downregulation of Bcl-2.[53] Dieckol also regulates inflammatory and stress-responsive pathways, including NF-κB, JAK/STAT3, MAPK/AP-1, and FAK, thereby influencing cellular proliferation, migration, angiogenesis, and immune response.[33] In cardiovascular systems, it inhibits platelet activation and thrombus formation by suppressing integrin αIIbβ3-mediated signaling and enhancing the cAMP–PKA–VASP pathway, while also modulating PI3K/Akt signaling.[54] In skin tissues, dieckol preserves extracellular matrix integrity by inhibiting MMP-1, MMP-3, and MMP-9 expression through regulation of the TGF-β/Smad2/3 and MAPK/AP-1 pathways, while maintaining hyaluronic acid metabolism via HAS and HYAL enzymes.[16] The involvement of these diverse signaling pathways highlights the pleiotropic nature of dieckol and suggests that its therapeutic effects are mediated through coordinated modulation of multiple cellular processes rather than a single molecular target. However, the relative contribution of individual pathways appears to vary across disease models, reflecting differences in tissue type, pathological context, and experimental design. Furthermore, most mechanistic evidence has been derived from preclinical studies, limiting the ability to determine which signaling networks are most relevant in human disease. Such variability may explain differences in the reported biological effects of dieckol across studies and complicate direct comparisons of therapeutic efficacy. Therefore, further standardized mechanistic investigations and clinical validation studies are required to clarify the context specific roles of these pathways and their contribution to the overall therapeutic potential of dieckol.[16,33,53,54]



Dieckol shows strong antioxidant, anti-inflammatory, and anticancer activities, but its clinical use is limited by poor oral bioavailability due to low solubility, reduced intestinal permeability, and extensive first-pass metabolism. These factors result in low systemic exposure, rapid metabolism, and reduced efficacy. Nanodelivery systems such as lipid-based nanoparticles, polymeric nanoparticles, liposomes, nanoemulsions, and mesoporous silica carriers have been developed to improve solubility, stability, controlled release, and intestinal absorption, while also prolonging circulation and enabling tissue targeting. However, challenges remain in scalability, safety, variability, and clinical translation, highlighting the need for standardized formulations and well-designed clinical studies.Top of FormBottom of Form

Fig. 4: Dieckol Bioavailability Challenges and Nanodelivery-Based Clinical Translation

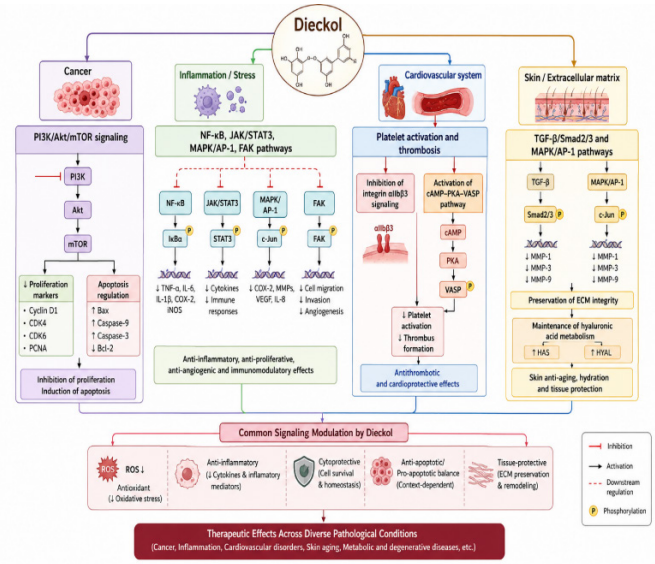
Fig. 5 illustrates the multifunctional biological activities of dieckol through modulation of key signaling pathways involved in cancer, inflammation, cardiovascular protection, and skin homeostasis, resulting in antioxidant, anti-inflammatory, cytoprotective, and therapeutic effects across diverse pathological conditions.

Novelty

This review provides an updated and integrative perspective on dieckol by combining evidence across extraction technologies, purification strategies, structural characterisation methods, multifunctional biological activities, molecular mechanisms, and emerging bioavailability enhancing approaches. Unlike previous reviews that primarily focused on the pharmacological actions of phlorotannins or individual biological effects, the present review consolidates current evidence on the complete translational pathway of dieckol—from source identification and analytical characterisation to pharmacokinetic limitations and nanodelivery based clinical advancement. Particular emphasis is placed on linking molecular mechanisms with bioavailability challenges and formulation based solutions, thereby offering a comprehensive framework for future therapeutic, nutraceutical, and functional food development. This review further highlights the importance of integrating pharmacokinetic understanding, nanotechnology assisted delivery, and clinical translation strategies to bridge the gap between promising experimental outcomes and real world biomedical applications of dieckol.

Future Directions

Improving bioavailability



Footnote: Dieckol exerts diverse pharmacological activities through the coordinated modulation of interconnected signaling pathways involved in oxidative stress, inflammation, cell survival, apoptosis, thrombosis, and tissue remodeling. By targeting PI3K/Akt/mTOR, NF-κB, JAK/STAT3, MAPK/AP-1, FAK, integrin αIIbβ3, cAMP–PKA–VASP, and TGF-β/Smad2/3 signaling cascades, dieckol regulates key cellular processes that collectively contribute to its antioxidant, anti-inflammatory, anticancer, cardioprotective, and tissue-protective effects.

Fig. 5: Common Signaling Pathways Mediating the Multi-Target Therapeutic Effects of Dieckol

Develop advanced delivery systems (e.g., nanoformulations, liposomes) to overcome poor absorption and rapid metabolism.

In-vivo and clinical validation

Conduct well designed animal studies and clinical trials to confirm efficacy, safety, and optimal dosage in humans. Metabolite and microbiome studies: Investigate the role of gut metabolism and identify active metabolites contributing to biological effects.

Standardisation and scalable production

Establish reliable extraction, purification, and quality control methods along with sustainable large scale production strategies.

Structure–activity relationship (SAR) and target identification

Elucidate molecular mechanisms and optimise dieckol derivatives for enhanced therapeutic efficacy.

Limitations

The present review has several limitations. First, much of the available evidence on dieckol is derived from **in** vitro experiments and animal studies, while well designed human clinical trials remain limited. Second, considerable methodological heterogeneity exists among studies with respect to extraction and purification methods, compound purity, dosage, experimental models, treatment duration, and outcome measures, making direct comparison of findings difficult. Third, many studies have investigated dieckol rich extracts rather than purified dieckol, making it challenging to determine the specific contribution of dieckol apart from other phlorotannins. In addition, the poor oral bioavailability, limited intestinal absorption, and extensive first pass metabolism of dieckol restrict the translation of promising experimental findings into clinical applications. Finally, although nanotechnology based delivery systems have shown potential to improve bioavailability, most remain at the preclinical stage, with insufficient data on long term safety, scalability, regulatory approval, and clinical efficacy. These limitations highlight the need for standardized experimental protocols, comprehensive pharmacokinetic investigations, and well designed randomized clinical trials to validate the therapeutic potential of dieckol.

Conclusion

Recent advances in marine natural product research have enhanced our understanding of the isolation, structural elucidation, and functional applications of bioactive metabolites derived from marine macroalgae. Among these compounds, dieckol an abundant phlorotannin found in brown seaweeds has attracted considerable attention due to its complex polyphenolic structure and diverse biological activities. Experimental studies have demonstrated that dieckol exhibits strong antioxidant, antibacterial, anticancer, anti-inflammatory, and antidiabetic properties, largely through modulation of key molecular pathways associated with oxidative stress, inflammation, and cellular signalling. These multifunctional properties highlight its potential as a promising lead compound for pharmaceutical, nutraceutical, and functional food applications. A deeper understanding of the pharmacokinetics, bioavailability, and cellular uptake of dieckol is essential for its effective therapeutic development. Future research focusing on improved extraction techniques, advanced delivery systems, and well designed *in-vivo* and clinical studies will be essential to translate the therapeutic potential of dieckol into practical biomedical and health-related applications.

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