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Euphol: Chemical And Biological Aspects: A Review

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Abstract

The growing interest in herbal medicine as a potential source for drug development is being increasingly supported, particularly for addressing challenging therapeutic areas such as anti-inflammatory treatment, cancer, immunomodulatory effects, combating antimicrobial resistance, managing cardiovascular diseases, and tackling multiple sclerosis. Cancer stands as a leading cause of mortality globally. Harnessing the potent bio actives from nature presents a promising avenue in the fight against cancer. Euphol is a widely occurring tetracyclic triterpenoid found in various plants. It exhibits notable antitumoral properties, offering a potential alternative for cancer therapy. Euphol exhibits not only antitumoral potential but also antiviral activity. Additionally, Euphol demonstrates anti-inflammatory properties by inhibiting the activation of nuclear factor-kappa B (NF-κB), thereby mitigating colitis in mice. Furthermore, it inhibits the inflammatory response triggered by 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced activation of protein kinase C in mouse skin. The natural sources of euphol triterpenoids have been explored, encompassing various plant families such as Euphorbiaceae, Clusiaceae, Cucurbitaceae, Theaceae and Guttiferae. This review aims to consolidate natural origins, biosynthesis, chemical synthesis, physicochemical properties, spectroscopic data and documented pharmacological activities of euphol. It delves into the potential beneficial effects of this bioactive triterpene and examines strategies to augment its pharmacological significance.

Keywords: *Euphol;Terpenes; Tetracyclic triterpenes; Anti-inflammatory; Cytotoxic; Antibacterial; Antiviral.*

1. Introduction

The drug discovery process encounters both advantages and challenges when working with natural compounds, which exhibit distinct characteristics compared to traditional synthetic molecules. In traditional medicine, extracts from species of the genus Euphorbia (Euphorbiaceae) are commonly used to treat ulcers and warts [1]. Euphol ($C_{30}H_{50}O$), a tetracyclic triterpene alcohol Fig. [1] is the primary component of *Euphorbia tirucalli*, also known as aveloz. Euphol has demonstrated anti-inflammatory effects, as well as analgesic and nociceptive properties. These effects are primarily attributed to its ability to inhibit pro-inflammatory mediators regulated by Protein kinase C epsilon type (PKCε), and its capacity to down-regulate mRNA and protein expression of certain pro-inflammatory mediators in the central nervous and digestive systems [3] . Euphol also inhibits the release of algic proteins and other inflammatory mediators, thus inhibiting persistent hypersensitivity [4]

Passos elucidated the molecular mechanisms underlying euphol anti-inflammatory activity in cutaneous inflammation in mice. They found that topical application of euphol reduced leukocyte influx by decreasing chemokine levels derived from keratinocytes (CXCL1/KC) and macrophagic inflammatory protein (MIP)-2. Additionally, euphol reduced the activation of TPA-induced extracellular signal-regulated protein kinase (ERK) and upregulation of cyclooxygenase-2 (COX-2) [5].

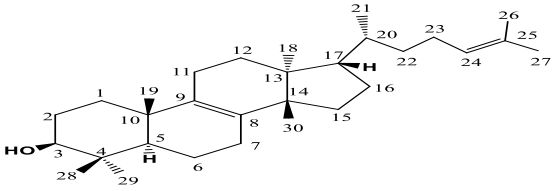

Fig.1. Structure of Euphol

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Orally administered euphol demonstrated anti-inflammatory and immunomodulatory effects in experimental models of colitis and experimental autoimmune encephalomyelitis in C57BL/6 mice [6]. Euphol effectively inhibited monoacylglycerol lipase (MGL) activity *via* a reversible mechanism with an IC_{50} value of 315 nm. MGL is a serine hydrolase responsible for the biological deactivation of the endocannabinoid 2-arachidonoyl-sn-glycerol (2-AG) [7]. Recent findings also propose that inhibiting MGL in the periphery modulates the endocannabinoid system, thus preventing the development of inflammatory pain [8]. Euphol have been found to modulate the complement system [9, 10]. The complement system plays a crucial role in connecting the innate and adaptive immune systems. In innate immunity, it serves as an initial defense mechanism against pathogens by inducing inflammation, recruiting leukocytes, and eliminating target cells [11]. However, dysregulation of complement activities can lead to immune and inflammatory diseases, transforming the complement system from a defense system into an aggressor [12]. Consequently, the complement system has emerged as a significant therapeutic target [13, 14]. Regarding its pharmacokinetics, *in vitro* evaluations of euphol stability, distribution, and metabolism have indicated that it is not highly stable in gastric and intestinal fluids. It exhibits moderate binding to plasma proteins and possesses an appropriate elimination half-life. Additionally, it undergoes potential hepatic metabolism [15] .

Recently, its potential antitumor activity has also been observed [16]. This compound exhibits biological effects such as anti-herpetic and anti-mutagenic properties [17]. It demonstrated its ability to alleviate pain induced by B16F10 melanoma cell injection and inflammatory pain in rat models [4]. It's suggested that these effects may be mediated through the modulation of the epsilon C protein kinase pathway (PKCe), leading to the inhibition of transcription factors like NF-kB and cyclic AMP response-binding protein (CREB).

2. Material and methods

Information was collected from diverse databases, including the Egyptian Knowledge Bank, Scopus, Web of Science, Reaxys, PubMed, Google Scholar and Elsevier databases up to June 2024. The search incorporated a wide range of keywords related to euphol, encompassing its natural origins, isolation, structure, solubility, synthesis, bioavailability, applications, biological effectiveness, mechanism, pharmacokinetics, and clinical studies.

3. Results and Discussion

Triterpenes existed in different plant families such as Euphorbiaceae [18] [19], Clusiaceae [20] , Cucurbitaceae [21], Theaceae [22] and Guttiferae [23]. Triterpenes are organic compounds built from 30 carbon atoms, generally formed by the polymerization of six isoprene units $(C_5H_8)_6$. Their molecular formula is typically $C_{30}H_{48}$. Triterpenes can be broadly categorized based on their structure into acyclic, tetracyclic, and pentacyclic types. Acyclic Triterpenes: These have a linear structure without rings. An example is squalene, a precursor for the biosynthesis of steroids. Tetracyclic Triterpenes: Tetracyclic triterpenoids are produced through reactions catalyzed by oxidosqualene cyclase (OSC). These reactions originate from two intermediate carbocations: the protosteryl cation and the dammarenyl cation. The diversity of tetracyclic triterpenoids is attributed to the distinct enzymatic rearrangements of these carbocations during the cyclization of 2,3-oxidosqualene. Tetracyclic triterpenoids are categorized into various classes, including lanostane, euphane, protostane, dammarane, cucurbitane and tirucallane. Tetracyclic triterpenoid classes are represented in Fig. [2]

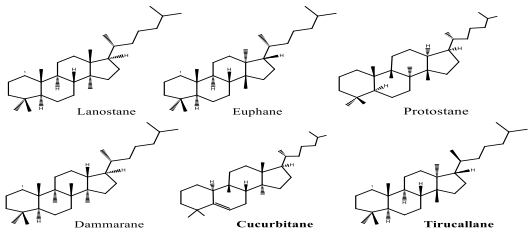

Fig.2. Chemical Classes of Tetracyclic Triterpenes

Occurrence of Euphol

Triterpenes are found abundantly across various organisms, including plants, fungi and on occasion, animals. Notably, euphol stand out as naturally occurring tetracyclic triterpene extracted from several higher plant families Table [2]. Euphol occurred predominantly in plant species within the Jatropha and Euphorbia genera, belonging to the Euphorbiaceae family. Additionally, they are also found in other plant families such as Theaceae, Cucurbitaceae and Clusiaceae.

Biosynthesis of Tetracyclic Triterpenes

The biosynthesis of tetracyclic triterpenes originates from the isoprenoid pathway *via* the C5 units, isopentenyl diphosphate (IPP) or dimethylallyl diphosphate (DMAPP), which are produced through either the mevalonate (MVA) pathway or the methylerythritol 4-phosphate (MEP) pathway. In the phytosterol biosynthetic pathway, IPP and DMAPP are combined to

form geranyl diphosphate (C10, GPP) through the action of geranyl diphosphate synthase (GPPS). Subsequently, farnesyl diphosphate synthase (FPPS) catalyzes the condensation of IPP with GPP, resulting in farnesyl diphosphate (C15, FPP). Following this, two FPP molecules are converted into squalene-by-squalene synthase (SQS). The proposed biosynthetic pathway from isopentyl pyrophosphate (IPP) to squalene is illustrated in Fig. 3.[24]

Table 1. Occurrence of Euphol and methods of extract

Plant name	Part Used	Method of extraction	Reference
Euphorbiaceae			
Euphorbia antiquorum	Latex	Latex was mixed with water and extracted sequentially using diethyl ether, ethyl acetate, and butanol. Euphol was isolated from ethyl acetate fractions using different systems column and preparative chromatography.	[25]
Euphorbia antiquorum	Latex	Fresh latex was mixed with distilled water and extracted with n-hexane. The insoluble fraction from the n-hexane extraction was further extracted with ethyl acetate (EtOAc). The EtOAc-soluble fraction was concentrated under reduced pressure to obtain the EtOAc extract. Euphol was isolated from soluble fraction of EtOAc using column chromatography, by gradient elution of n-hexane, EtOAc and finally methanol.	[26]
Euphorbia caducifolious	Latex	Latex was washed with acetone at -20°C, the residue was repeatedly extracted with acetone at room temperature. Acetone extract was evaporated resulting in a sticky residue. Using column chromatography, elution with n-hexane-chloroform (9.8:0.2) mixture and euphol was subsequently crystallized from methanol-acetone.	[27]
Euphorbia cospicua N.E. Br.	Latex	Latex was collected and frozen at -20°C. After defrosting, the latex was dissolved in methanol at 50°C and kept at room temperature until a solid is formed. This solid was filtered out and thoroughly extracted with acetone at 40°C. The acetone fraction was then evaporated, redissolved in a methanol-water (1:1) mixture and extracted with n-hexane. The resulting n-hexane fraction containing triterpene compound was subjected to column chromatography using gradient elution using n-hexane, n-hexane/toluene (95:5, 9:1, 8:2, 7:3, 1:1) and toluene/EtOAc (99:1, 95:5, 9:1, 8:2, 7:3, 6:4, 1:1) yielded euphol.	[28]
Euphorbia dracunculoides Lam.	Aerial parts	The powdered air-dried aerial parts of E. dracunculoides Lam. was extracted with 70% aqueous acetone at room temperature over 6 days. The extracts were concentrated under reduced pressure. The remaining aqueous residue was sequentially partitioned with petroleum ether, ethyl acetate and n-butanol. The petroleum ether layer was further processed using different column chromatography and different solvent systems and finally purified euphol was obtained through preparative TLC technique.	[29]
Euphorbia formosana Hayata	Roots	The dried roots were boiled in water thrice, cooled and then freeze-dried (lyophilized). The resulting residue was dissolved in water and filtered through a 0.22 μm filter. Euphol was isolated using different column chromatography with different solvent systems.	[30]
Euphorbia formosana Hayata	Roots	Dried roots were first extracted with methanol. The resulting extract was then suspended in water and partitioned into three solvents: n-hexane, ethyl acetate, and n-butyl alcohol. The n-hexane fraction was further processed using a silica gel column with a step gradient of n-hexane and EtOAc to gradually increase polarity, yielding 10 distinct fractions. Fraction 2 was chromatographed using silica gel column eluted with n-hexane – ethyl acetate (14:1) to obtain euphol.	[31]

Table 1. (continued….)

Euphorbia kansui Liou	Roots	The powdered root of the plant was extracted twice for 24 hours with a mixture of methanol, acetone and petroleum ether (1:1:1) at room temperature. After defatting, the extract was separated by column chromatography (CC) into 9 fractions. Crystallization of fractions F-I from petroleum ether yielded euphol.	[32]
Euphorbia kansui	Dried roots	The dried roots of *Euphorbia kansui* were extracted twice for 2 hours each with 95% ethanol under reflux. The ethanol was then evaporated under reduced pressure to yield a crude extract. This extract was further processed with ethyl acetate to obtain an ethyl acetate fraction. This fraction was subjected to silica gel column chromatography with a gradient elution of petroleum ether and ethyl acetate (from 100:1 to 1:1) to produce various fractions. Fr. G (2 g) was eluted with Pet: EtOAc (100:20). Euphol was isolated by HPLC (MeCN: H2O, 95:5) with (Ultimate XB-C8, 30 × 150 mm, 5 μm) flow rate 16 mL/min (t_R 35.452 min).	[33]
Euphorbia nematocypha	Root	Powdered root was extracted by with 70% acetone at room temperature. After filtration and evaporation under reduced pressure, the combined acetone extract was dissolved in water and then partitioned with chloroform, resulting in $CHCl_3$-soluble fraction. The $CHCl_3$ -soluble fraction was subjected to CC (column chromatography) over silica gel, using a mixture of petroleum ether (PE) and acetone gradient elution (1 : 0 - 0 : 1). Seven crude fractions (A – G) were obtained. Fr. D was subjected to silica gel CC and eluted with PE/ EtOAc (100: 0 to 70: 30) to give ten subfractions (Fr. D.01 – Fr. D.10). Fr. D.03 and Fr. D.04 were combined and further separated by silica gel CC and eluted with *n*-hexane/ EtOAc (gradient from 95: 5 to 90: 10), to give five subfractions Fr. D.03.01 – Fr. D.03.05. Fr. D.03.02 (720 mg) was subjected to silica gel CC with *n*-hexane/ EtOAc (95: 5) repeatedly and gave euphol (5 mg).	[34]
Euphorbia resinifera	Latex	The latex was left in ethyl alcohol for 24 hours with occasional shaking. The solution was then filtered and concentrated to half its original volume before being extracted several times with *n*-hexane. The combined n-hexane extracts were washed with water, dried over sodium sulfate, and concentrated to a small volume, leading to crystallization upon cooling. The collected crystalline product (20 grams) mainly consisted of euphol and euphorbol. This mixture was chromatographed through a column packed with Florisil. Elution with a 1:1 *n*-hexane-benzene mixture yielded euphol.	[35]
Euphorbia sapinii (De Wild.)	Whole plant	The air-dried powdered plant material was extracted using percolation with acetone, resulting in a crude acetone extract. This acetone extract was then subjected to vacuum liquid chromatography on silica gel, using mixtures of *n*-hexane and ethyl acetate (EtOAc) with increasing polarity, yielding five main fractions (A–E). Fraction A (17.5 g) was further processed through flash chromatography with 800 ml each of *n*-hexane-EtOAc mixtures in ratios of 80:20, 70:30, and 50:50, producing a significant amount of fats along with two sub-fractions, A1 and A2. Sub-fraction A2 (3.1 g) was further purified on the same column with n-hexane-EtOAc mixtures in ratios of 80:20, 70:30, and 60:40, ultimately yielding euphol (1 g).	[36]

Table 1. (continued….)

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Euphorbia tangutica	Whole plant	Fresh whole plant was ground and extracted with 90% ethanol (EtOH) at room temperature, for four times, each lasting 5 days. The extracts were then concentrated using a rotary evaporator. The concentrated extract was suspended in water (H_2O) and successively partitioned with ethyl acetate (EtOAc) and *n*-butanol. The ethyl acetate layer was evaporated at 50°C under vacuum to remove the solvent and then subjected to CC, eluted with 90% ethanol and acetone. The 90% EtOH portion was chromatographed over a silica gel column, using a chloroform ($CHCl_3$) gradient system (40:1 to 1:1) to obtain 12 fractions. Fraction 3 (1.2 g) was separated by silica gel CC using a petroleum ether (PE) gradient system (10:1 to 1:1) to yield four subfractions (Fr.3a, Fr.3b, Fr.3c, and Fr.3d). Subfraction Fr.3a was further subjected to Sephadex LH-20, eluted with $CHCl_3$ (1:1), and then to silica gel CC with a petroleum ether. Ethyl acetate gradient system (8:1 to 1:1), resulting in the isolation of euphol.	[37]
Euphorbia triangularis Euphorbia tirucall	Latex	latex was coagulated by adding salt. The resulting coagulum was extracted using alcohol. The resin obtained was then purified by percolating it through a column of alumina activated at 300°C and eluted with petroleum ether. Petroleum ether fraction evaporated to yield a solid residue, Euphol is crystalized out using methanol.	[38]
Euphorbia tirucalli L	Stems	Fresh stems were extracted with 95% ethanol (EtOH) at room temperature four times and then concentrated under vacuum to yield a dark brown syrup. This EtOH extract was partitioned between water (H2O) and ethyl acetate (EtOAc), producing an aquous layer and an EtOAc layer. The concentrated EtOAc extract was subjected to column chromatography over silica gel, eluted with a gradient solvent system of n-hexane and EtOAc (n-hexane: EtOAc = 10:1, 6:1, 4:1, 2:1, 1:1, 0:1), resulting in six fractions. The separation of chemical components was monitored by TLC analysis. Fractions 1 and 2 were combined and re-chromatographed on silica gel, eluted with n-hexane and EtOAc (n-hexane: EtOAc = 10:1 to 2:1), yielding euphol.	[39]
Euphorbia umbellata (Pax) Bruyns	latex	The collected latex was diluted in 100 ml of 1% sulfuric acid solution. The suspension was filtered, and the precipitate was loaded onto a silica gel chromatographic column. Elution was performed using n-hexane and ethyl acetate mixtures (95:5, 92.5:7.5, 90:10, 85:15, 80:20, 50:50, 100:0), yielding 618 fractions. These fractions were pooled according to their Rf values as determined by TLC. Sub-fractions 244-254, eluted with hexane: ethyl acetate (90:10), contained euphol.	[9, 10]

Table 1. (continued….)

Clusiaceae			
Garcinia amplexicaulis	Stem bark	Dried *s* stem bark was successively extracted using a Soxhlet apparatus for 24 hours, first with CH_2Cl_2 and then with 3 liters of MeOH. The solvent was removed under reduced pressure, yielding 29.7 g and 31.0 g of extracts, respectively. The CH_2Cl_2 extract (6 g) was subjected to centrifugal chromatography (1200 rpm, flow rate = 15 mL/min, P = 90 bar) with an ascendant elution using a quaternary mixture of *n*-heptane/ethyl acetate/MeOH/water (2:1:2:1), resulting in 20 fractions (F1−20). Fraction F1 (1.45 g) was loaded onto silica gel and eluted with a mixture of cyclohexane/EtOAc (1:0 to 1:1) through a 40 g silica gel column using flash chromatography, yielding the compound euphol.	[40]
Cucurbitaceae			
Cucumis melo and *Cucumis Sativus*	Seeds	Isolation of Euphol from lipid unsaponifiable matter using Preparative Argentic TLC.	[41]
Theaceae			
Camellia sasanqua Thunb	Seeds	Crude seed oil (2 kg) underwent alkaline hydrolysis using 5% KOH in methanol (MeOH) under reflux conditions for 3 hours. This process yielded nonsaponifiable lipid fractions [42]. NSL was chromatographed over a silica gel column using *n*-hexane and n-hexanes-ethyl acetate (EtOAc) gradients as eluants. The *n*-hexanes-EtOAc elution yielded a fraction that, upon rechromatography over silica gel, produced a triterpene alcohol fraction. This triterpene alcohol fraction was acetylated to obtain an acetate fraction. The acetate fraction was further separated into three major bands using argentation thin-layer chromatography (TLC). The least polar band contained euphol acetate.	[22]
Guttiferae			
Tripetalum cymosum	Leaves and bark	The leaves and bark were air-dried and ground. The powdered material was then subjected to exhaustive extraction using hot *n*-hexane. After extraction, the *n*-hexane extracts were concentrated under vacuum, resulting in a crude leaf and bark extracts. CC of Bark extract (silica gel, 3±5% EtOAc ±*n*- hexane gradient) afforded two fractions. HPLC [silica gel, 6.25% EtOAc-*n*-hexane followed by C18, Me_2CO-H_2O-AcOH (88:11:1)] of fraction 1 give euphol. Leaf extract CC on silica gel (acetone:*n*-hexane gradient) gave sixteen fractions. Fraction 2 was subjected to CC (silica gel, 7% acetone:*n*-hexane) and HPLC (silica gel, 1% acetone hexane) to give euphol.	[23]

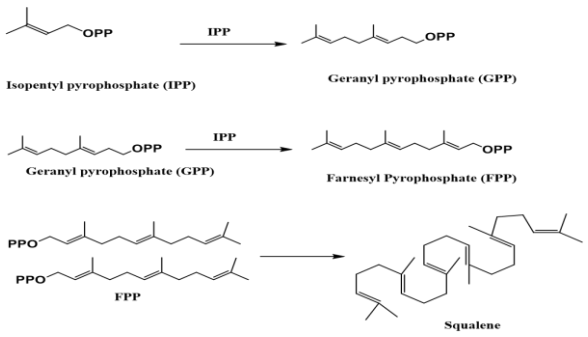


Fig.3. The proposed biosynthetic pathway from isopentyl pyrophosphate (IPP) to squalene

In eukaryotes, squalene is first converted into 2,3-epoxysqualene by the enzyme squalene epoxidase (SE), resulting in the formation of 2,3-oxidosqualene. This intermediate then undergoes cyclization, catalyzed by specific oxidosqualene cyclases (OSCs), to create the phytosterol scaffold. [43-45]. The difference in stereochemistry between lanosterol and euphol is believed to arise from distinct substrate conformations of (3S)-2,3-oxidosqualene, which are preorganized by OSC enzymes. It is proposed that the two conformations of (3S)-2,3-oxidosqualene which lead to the formation of lanosterol and euphol, are the chair-boat-chair conformation (sterol folding) and the chair-chair-chair conformation (non-sterol folding), respectively. The two conformations of (3S)-2,3-oxidosqualene are shown in Fig.4

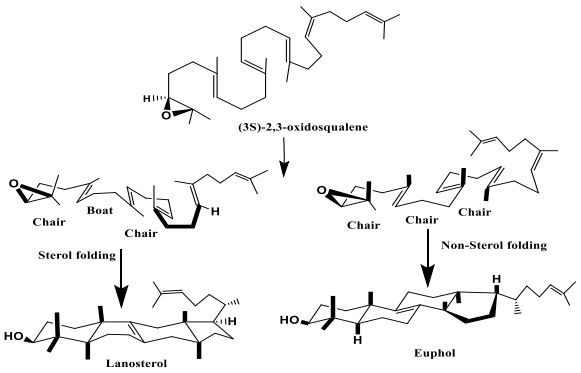


Fig.4. two conformations of (3S)-2,3-oxidosqualene

This comprehensive understanding highlights the complexity and adaptability of triterpene biosynthesis in plants, with potential species-specific roles and a broad range of enzymatic products. [46]

Euphol

Euphol is a triterpene alcohol with the molecular formula $C_{30}H_{50}O$. It belongs to the class of tetracyclic triterpenes and is derived from the eupholane skeleton. The structure of euphol is characterized by the presence of four interconnected rings and an alcohol group attached to the carbon at position 3.

Euphol **(**(3S,5R,10S,13S,14S,17S)−4,4,10,13,14-pentamethyl-17-[(2R)−6-methylhept-5-en-2-yl]−2,3,5,6,7,11,12,15,16,17- decahydro-1H-cyclopenta[a]phenanthren-3-ol**)**, a tetracyclic triterpene alcohol, is the main constituent found in the latex of *Euphorbia tirucalli* [47] .

Molecular Formula: $C_{30}H_{50}O$, Molecular Weight 426

Physical Data of Euphol [28]

White amorphous solid, soluble in chloroform [48]. Soluble in DMSO, methanol or ethanol (all 5-10mg/ml). Dichloromethane, Ethyl Acetate and Acetone. Melting Point 114 – 117 °C [27, 35]

$[\alpha]_D^{20}$ + 35.0º (c 0.70, $CHCl_3$), TLC (Silica gel G 60); R_f = 0.49 (*n*-hexane – ethyl acetate, 80:20).

UV λmax 236, 320 *n*m, ethanol [49]

IR (KBr) ν_{max}/cm^{-1}: 3580, 3089, 2980, 1640, 1450, 1375, 1151, 1131.

Spectral characters of Euphol:

The ^{1}-H NMR spectra exhibited signals mostly concentrated in the high field region which are typically triterpene signals. The more peculiar signals in the proton NMR included an olefinic proton (δH 5.08, 1H, t) and an axial proton on an oxygen-bearing carbon (δH 3.21, dd, J=11.4, 4.2 HZ). It further exhibited seven singlets characteristic of tertiary methyl groups (δH 1.66, 1.58, 0.98, 0.93, 0.85, 0.78, 0.73) and a secondary methyl group (δH 0.84, d, J= 6.0) which form the eighth methyl groups in the skeleton.

^{1}-H NMR (600 NMR, CDCl3) d 5.09 (app. t, J = 7.1 Hz, 1H), 3.24 (dd, J = 11.8, 4.5 Hz, 1H), 2.11 – 2.00 (m, 3 H), 1.96 – 1.82 (m, 4H), 1.79 – 1.66 (m, 6H), 1.68 (s, 3H), 1.63 – 1.36 (m, 4H), 1.60 (s, 3H), 1.35 – 1.16 (m, 4H). 1.12 (m, 1H), 1.07 – 1.00 m, 2H), 1.00 (s, 3H), 0.95 (s, 3H), 0.87 (s, 3H), 0.86 (d, J = 6.0 Hz, 3H), 0.80 (s, 3H), 0.75 (s, 3H).

The ^{13}-C NMR spectra showed 30 carbon signals suggesting that the compound could possess a triterpenoid skeleton. The ^{13}-C NMR spectra exhibited four signals (δc 134.27, 133.78, 131.03 and 125.43) characteristic of olefinic carbons indicating that the compound is unsaturated and contains two double bonds. The carbon signal (δc 79.29) was characteristic of carbon bearing a hydroxyl group [48] .^{13}-C NMR (150 MHz, CDCl3) d 134.0, 133.7, 131.0, 125.4, 79.2, 51.1, 50.2, 49.8,44.3, 39.1, 37.4, 36.0, 35.6, 35.4, 31.0, 29.9, 28.3, 28.2, 28.1, 27.8, 25.9, 24.9, 24.6, 21.7, 20.3, 19.10,19.07,17.8,15.8,15.7.

HRMS (m/z): $[M+H]^+$ Calculated for $C_{30}H_{50}O$ 426.3817; found, 426.3860, top 5 Peaks: 81.070015 (100), 95.085655 (74.19), 69.070099(54.75), 67.054482(52.39), 107.085693(42.03) [50].

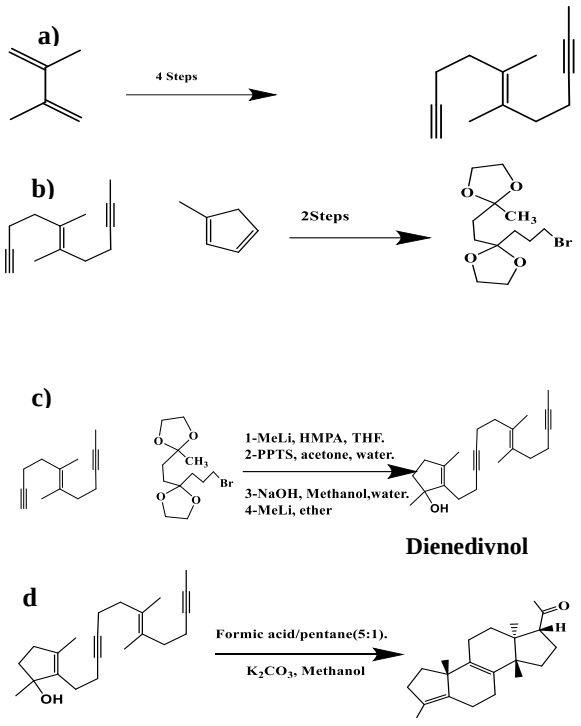
Chemical Synthesis of euphol:

Asymmetric de novo syntheses of euphol and tirucallol have been achieved through a streamlined series of chemical steps incorporating several modern stereoselective techniques. The approach taken for these complex natural product syntheses significantly deviates from the traditional biomimetic polyene cyclization methods typically used for similar tetracyclic triterpenoids. Key to this method was a diastereoselective Friedel–Crafts-type cyclization, which formed a tetracyclic structure with a stereo defined quaternary center at C9 (using steroid numbering). This structure then enabled the creation of quaternary centers at C10 and C14 through sequential stereospecific 1,2-alkyl shifts (from C9 to C10 and from C15 to C14). The stereo defined C17 side chain was subsequently introduced in a single step using a late-stage stereoselective conjugate addition to an intermediate with a D-ring enone. Remarkably, these de novo asymmetric syntheses are the first to provide fully synthetic access to enantiodefined euphane and tirucallane frameworks. Each synthesis was completed in under 20 linear chemical steps, starting from a simple Hajos–Parrish-derived ketone, with only 15 chromatographic purifications required throughout the process. [50, 51].

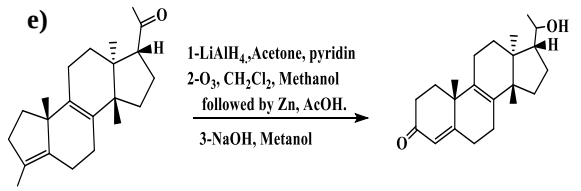
First method: Johnson's Synthesis:

Johnson's relay [52] synthesis of euphol in 1990 remains the only known synthesis of a euphane, as there has been no reported asymmetric total synthesis of euphanes. This synthesis is part of a broader group of polycyclic terpenoid syntheses that utilize biomimetic cation-olefin cyclization as a key step. Johnson and colleagues demonstrated this method using a polyene substrate containing two alkynes. The cyclization substrate was synthesized in 10 steps, beginning with 2,3-dimethyl-1,3-butadiene and 2-methyl-furan. Initial exploration of the cyclization of dienediynol with various acids led to the best results when the reaction was carried out in a vigorously stirred biphasic mixture of formic acid and pentane (5:1) at 0°C. Subsequent methanolysis of the resulting enol formats yielded a 28% mixture of tetracyclic ketones (56:44), with the major product being isolated after recrystallization.

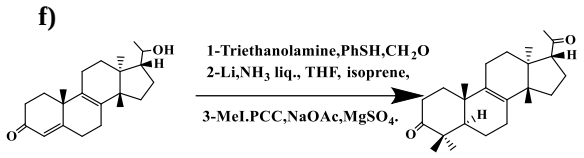
Starting with 2,3-dimethyl-1,3-butadiene and 2-methyl-furan:



The ketone was then converted into a dione containing the euphane tetracyclic system over seven additional steps, with an overall yield of 9%.

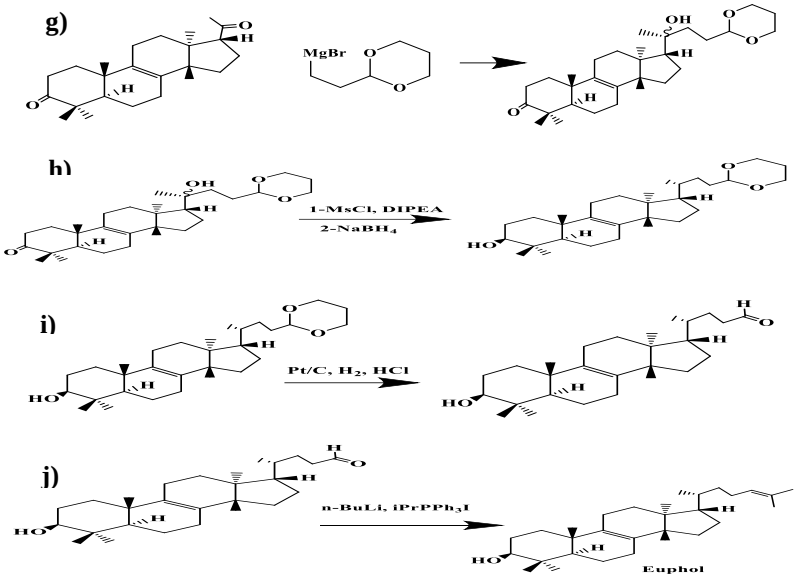


Reduction of the methyl ketone produced a diastereomeric mixture of alcohols, which were then acetylated to yield the corresponding mixture of acetates. This mixture was subsequently subjected to a two-step process to form the six-membered A-ring. Selective ozonolysis of the tetrasubstituted olefin in the five-membered A-ring followed by cyclodehydration of the resulting dione led to the formation of the desired product.



Dione

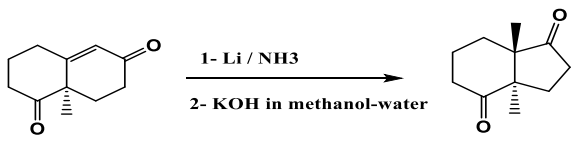
The subsequent installation of the gem-dimethyl group at C4, followed by reoxidation of the secondary alcohol, produced the tetracyclic compound. The structure and stereochemistry of the racemic dione were confirmed by comparison with an enantiomerically pure dione obtained through the degradation of naturally isolated euphol. This enantiomerically pure dione was then used as the starting material to construct the side chain at C17, ultimately leading to the synthesis of euphol. This approach qualifies the synthesis as a relay synthesis of euphol.



Second method: Reusch's Approach to Lanostane and Euphane Tetracyclic Systems

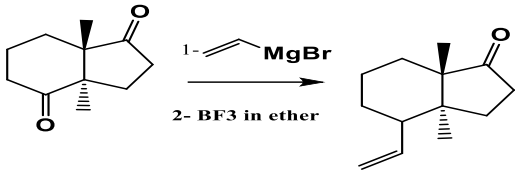
In the mid-1980s, Reusch's [46] group developed a synthetic strategy aimed at both lanostane and euphane tetracyclic systems. Unlike the two previously discussed syntheses, Reusch's approach to constructing the tetracyclic ring system employed a conceptually different strategy.

1) Starting with a racemic mixture of the readily available Wieland–Miescher ketone, trans-hydrindane was synthesized using a two-step process that involved reductive cyclopropanation followed by the opening of the cyclopropane ring.

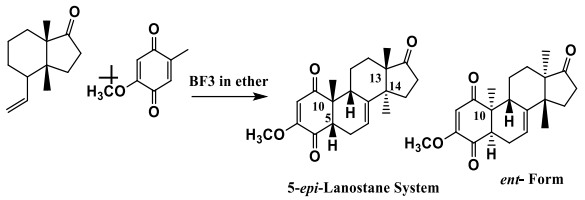


Wielend-Miescher Ketone

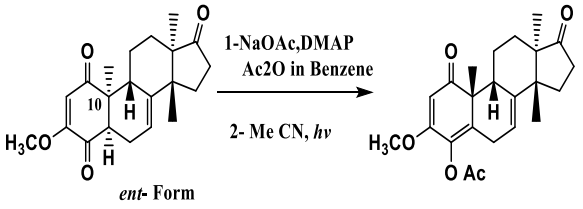
2) Recognizing that hydrindane could function as the CD-ring system in both lanostane and euphane tetracyclic systems, due to its two angular methyl groups being in an anti-orientation relative to each other.
3) The Reusch group focused on the selective functionalization of the carbonyl group on the six-membered ring of trans-hydrindane to produce a diene, which would then allow for the introduction of the AB-ring system.



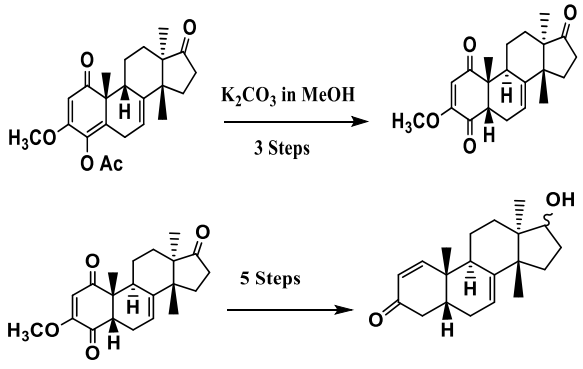
4) Lewis's acid-catalyzed Diels–Alder cycloaddition of diene with substituted benzoquinone then delivered the a-endo adduct a lanostane-like structure consisting of three quaternary centers at C10, C13 and C14 in the correct positions and relative stereochemistry typically seen in lanostane terpenoid natural products.

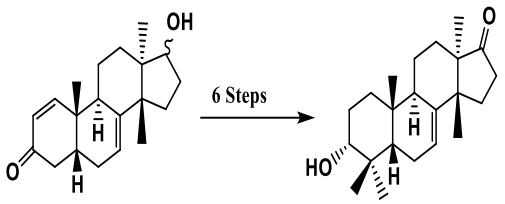


5) From this lanostane-like structure, the euphane system was accessed *via* photoisomerization of the quaternary center at C10 in the *ent*-form.



6) As a result, their efforts led to the synthesis of the 5-epi-euphane system, with its configuration confirmed by X-ray analysis.

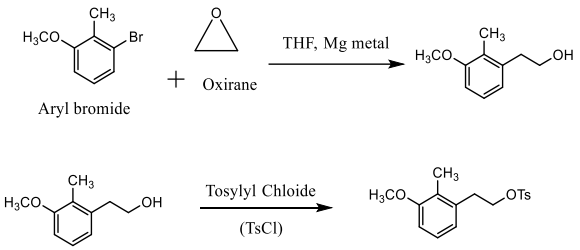




5-*epi*- Euphan System

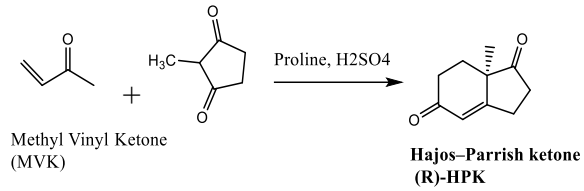
Third Method: [53]

1) Synthesis of tosylate: From aryl bromide as following:

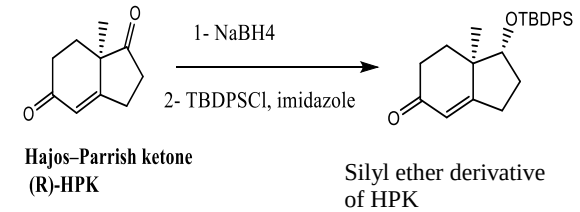


Tosylate

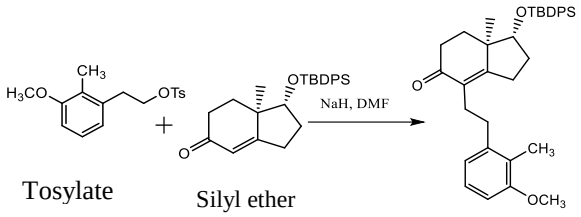
2) Synthesis of (R)-HPK:



3) Synthesis of silyl ether:

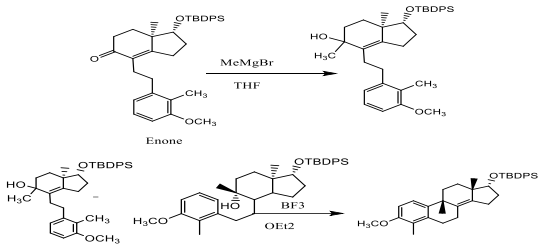


4) Synthesis of enone compound



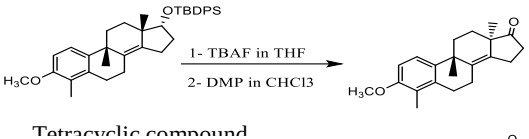
Tosylate Silyl ether derivative of HPK Enone

5) Synthesis of tetracyclic compound

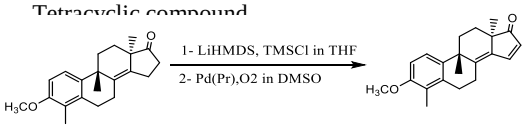


Tetracyclic compound

6) Synthesis of enone compound

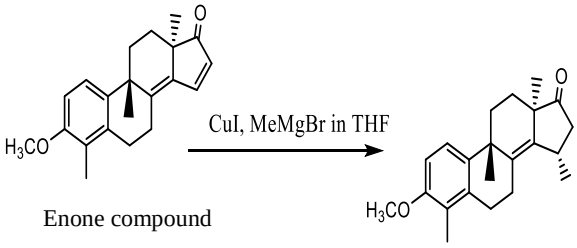


Tetracyclic compound



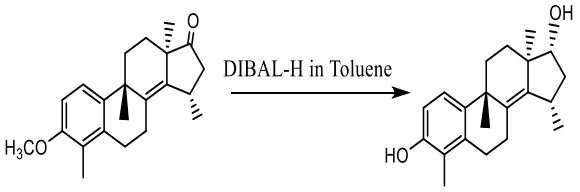
Enone compound

7) Synthesis of ketone:

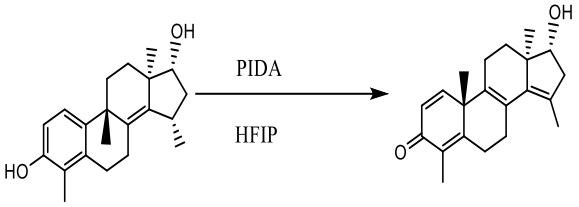


Enone compound

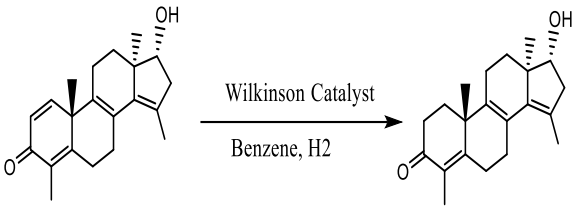
8) Synthesis of phenol



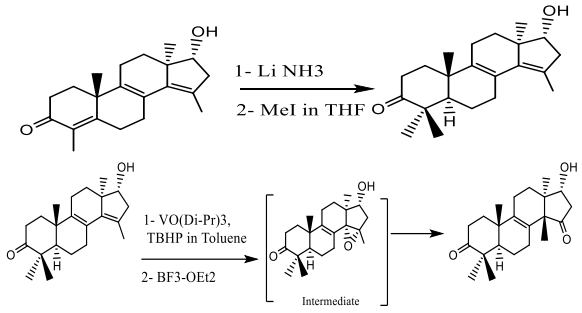
9) Synthesis of dienone



10) Synthesis of enone

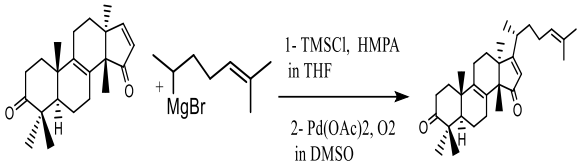


11) Synthesis of ketone

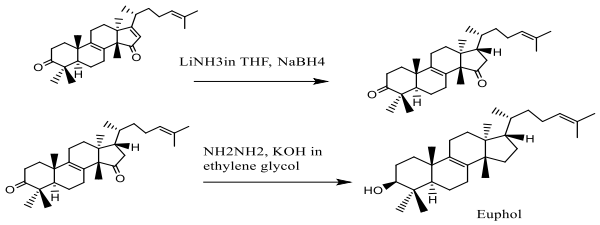


12) Synthesis of enone

13) Synthesis of enone:



14) Synthesis of alcohol (Euphol)



Biological Activities of Euphol

Euphol exhibits a broad spectrum of biological activities, making it a compound of interest for therapeutic applications. These biological activities include anticancer, anti-inflammatory, analgesic, antiviral, antioxidant, immunomodulatory activity, hypotensive and molluscicide activity.

Anticancer Properties

Cancer remains one of the leading causes of death worldwide. Nature offers a rich reservoir of bioactive compounds with significant anticancer properties. Numerous studies have highlighted the anti-cancer effects of euphol, which can be summarized as follows:

Cytotoxic activity of euphol in the smoke and stem extracts of *E. damarana*, was evaluated using the sulfo-rhodamine-B (SRB) assay on eight human cell lines: A549 (adenocarcinoma human alveolar basal epithelial cells), PC-3 (human prostate cancer cell line), HeLa (immortalized cell line), HepG2 (human liver cancer cell line), breast carcinoma MCF7 (human breast cancer cell line with estrogen, progesterone and glucocorticoid receptors), MCF-12A (non-tumorigenic mammary epithelial cells), MRC-5 (human diploid lung fibroblast cell line), and HaCaT (spontaneously immortalized human keratinocyte cell line derived from a distant periphery of a malignant melanoma).The study found significant cytotoxic activity from the purified euphol, stem and smoke extracts, with IC^{50} values ranging from 1.99 to 3.99 mg/mL, 5.00 to 20.00 mg/mL, and 11.75 to 40.00 mg/mL, respectively, across all tested human cell lines [54]. Furthermore, it exhibited cytotoxic effects against several human cancer cell lines, including colon cancer (SW-480), hepatocellular carcinoma (SMMC-7721), lung cancer (A549) and myeloid leukemia (HL-60) cells [37].

Euphol inhibits breast cancer growth by regulating the expression of key cell cycle proteins, including cyclin D1, CDK2 inhibitors p21 and p27[55, 56]. Additionally, euphol triggers apoptosis specifically in gastric cancer cells through the modulation of ERK signaling pathways [57].

Gastric cancer ranks among the most prevalent malignancies globally. Euphol exhibits significant anticancer effects against human gastric cancer cells and demonstrated higher cytotoxicity towards human gastric cancer cells (CS12) compared to noncancerous cells (CSN). Euphol enhances the expression of the pro-apoptotic protein BAX (Bcl-2-associated X protein) and reduces the levels of the pro-survival protein Bcl-2 (B-cell lymphoma 2), leading to mitochondrial dysfunction. This dysfunction is likely mediated through the activation of caspase 3, a critical enzyme in the apoptosis pathway. Euphol's anti-proliferative effects are further linked to increased levels of the cell cycle inhibitor p27^kip1 and decreased levels of cyclin B1, a protein essential for cell division. Moreover, the inhibition of ERK1/2 (extra-cellular signal-regulated kinase ½) activation using PD98059, a specific inhibitor, was able to reverse the euphol-induced expression of pro-apoptotic proteins and subsequent cell death. This indicates that euphol pro-apoptotic effects in gastric cancer cells are closely tied to the modulation of the ERK signaling pathway [58].

Euphol has significant cytotoxicity against esophageal squamous cell carcinoma (11.08 μM) and pancreatic carcinoma cells (6.84 μM), prostate, melanoma, and colon cancer cells [59].

Autophagy induction in Glioblastoma: The antitumor effects of euphol was investigated on 12 different human glioma and glioblastoma multiforme (GBM) cell lines [59]. The study demonstrated that euphol has significant cytotoxic effects on glioma cells, both *in vitro* and *in vivo*, by targeting multiple cancer pathways. These results suggest that euphol has potential

as a new therapeutic option for treating GBM and warrant further research into its development. In *Euphorbia tirucalli*, Euphol induces autophagy and enhances the cytotoxicity of temozolomide in glioblastoma cells.

Selective Cytotoxicity Against Leukemia: Euphol displays selective cytotoxic effects against various cancer cell lines, particularly leukemia, potentially through apoptosis induction [15].

Euphol has demonstrated promising antitumor activity, presenting a potential alternative for cancer therapy. However, its application might require advanced drug delivery methods as adsorbed into ZIF-8 (zeolitic imidazolate framework), to reduce toxicity, enhance stability and system's efficacy against cancer cells [60].

Anti-inflammatory activity

Euphol exhibits strong anti-inflammatory activity, which can be summarized in the following points:

Euphol inhibited the activation of TPA-induced extracellular signal-regulated kinase (ERK) and the upregulation of cyclooxygenase-2 (COX-2) [5]

Anti-Inflammatory Effects in skin conditions:

Euphol has demonstrated significant anti-inflammatory effects through several mechanisms:

a. NF-κB Pathway Modulation: Euphol inhibits the activation of NF-κB, a protein complex that plays a crucial role in regulating inflammatory responses and cytokine production.
b. Cytokine Inhibition: It reduces the levels of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, thereby alleviating inflammation.

Inflammation plays a crucial role in the onset and progression of various skin conditions, such as psoriasis, atopic dermatitis, and cancer. Therefore, finding new anti-inflammatory agents is of significant clinical interest for both the prevention and treatment of these disorders.

The anti-inflammatory effects of euphol, derived from the sap of *Euphorbia tirucalli*, in a mouse model of skin inflammation induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) as decreased levels of keratinocyte-derived chemokine (CXCL1/KC) and macrophage inflammatory protein (MIP)-2. Intracellularly, euphol was found to attenuate TPA-induced activation of ERK and the upregulation of cyclooxygenase-2 (COX-2). In addition, euphol inhibits the activation of protein kinase C (PKC), specifically the PKCα and PKCδ isozymes, which are key players in the inflammatory signaling pathways triggered by TPA [61]. Also, it exhibits inhibitory activity on TPA-induced inflammation in mice, with an ID_{50} of 0.2 mg/ear [15].

Anti-inflammatory effect in colitis management:

Euphol has shown significant promise in mitigating experimental colitis in mice through both preventive and therapeutic treatments. The treatment with euphol led to a notable reduction in several key inflammatory markers in colon tissue. Specifically, euphol inhibited the levels and expression of pro-inflammatory cytokines and chemokines, including IL-1β, CXCL1/KC, MCP-1, MIP-2, TNF-α, and IL-6. Additionally, it reduced the expression of inducible nitric oxide synthase (NOS2), vascular endothelial growth factor (VEGF), and Antigen Kiel 67 (Ki67) in colonic tissue, suggesting a broad anti-inflammatory and anti-proliferative action. This broad-spectrum anti-inflammatory effect is likely associated with the inhibition of nuclear factor-κB (NF-κB) activation, a key regulator in the inflammatory response. [62]

Moreover, *in vitro* studies showed that euphol decreased the secretion of MCP-1, TNF-α, IL-6, and IFN-γ induced by lipopolysaccharide (LPS) in bone marrow-derived macrophages while increasing the secretion of the anti-inflammatory cytokine IL-10. Notably, euphol treatment also significantly inhibited the expression of adhesion molecules such as selectins (P- and E-selectin) and integrins (ICAM-1, VCAM-1, and LFA-1) in colonic tissue. These molecules are crucial for the recruitment of inflammatory cells to sites of inflammation, suggesting that euphol may help to limit the infiltration of immune cells into inflamed tissues. These findings collectively demonstrate that oral administration of euphol, whether used as a preventive or therapeutic measure, effectively reduces the severity of colitis in two models of chemically induced mouse colitis. These results highlight euphol's potential as a therapeutic agent for managing inflammatory bowel diseases (IBD), suggesting it could be developed into a novel treatment to alleviate inflammation and promote healing in conditions like colitis [62]

Analgesic (Pain-Relieving):

Persistent pain from inflammatory and neuropathic conditions is a common and debilitating issue that often lacks safe and effective treatments. Oral administration of euphol reduced carrageenan-induced mechanical hyperalgesia. Similarly, when administered *via* spinal or intracerebroventricular routes, euphol effectively prevented carrageenan-induced hyperalgesia. Euphol also mitigated mechanical hyperalgesia caused by complete Freund's adjuvant, keratinocyte-derived chemokine, interleukin-1b, interleukin-6, and tumor necrosis factor-alpha, accompanied by decreased myeloperoxidase activity in the mouse paw. Additionally, euphol effectively prevented mechanical nociceptive responses following sciatic nerve ligation and significantly lowered cytokine/chemokine levels and mRNA in paw and spinal cord tissues post-injection with complete Freund's adjuvant. Notably, the antinociceptive effects of euphol were reversed by pre-treatment with CB1R and CB2R antagonists and the gene knockdown of CB1R and CB2R, highlighting the involvement of these receptors in euphol's action. Euphol is a promising candidate for managing inflammatory and neuropathic pain [63]

Euphol exhibits several key actions that inhibit persistent inflammatory and neuropathic pain:

a. Modulation of the PKCε Pathway: Euphol intervenes in the protein kinase C epsilon (PKCε) signaling pathway, which plays a crucial role in the development and maintenance of chronic pain. By modulating this pathway, euphol helps reduce persistent pain.
b. Inhibition of Transcription Factors: Euphol suppresses the activation of critical transcription factors like NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and CREB (cAMP response element-binding protein). These transcription factors are involved in the expression of genes that promote inflammation and pain.
c. Reduction in algesic Proteins and Pain Mediators: Euphol decreases the release of algesic proteins and other mediators that contribute to pain and inflammation. This leads to a significant reduction in persistent hypersensitivity, a common feature of chronic pain conditions.

Central and Peripheral Pain Modulation

Euphol reduces pain perception by influencing both central and peripheral mechanisms involved in pain signaling.

Given these multifaceted mechanisms, euphol holds significant promise as a molecule for the development of novel analgesic drugs aimed at treating chronic pain conditions, particularly those stemming from inflammation. Its ability to target and modulate various pain pathways and mediators highlights its potential in advancing pain management therapies. [64].

Monoacylglycerol Lipase Inhibition:(Anti-inflammatory, *in vitro*)

Euphol identified as a potent and reversible inhibitor of monoacylglycerol lipase in HeLa cell lysates genetically modified or infected with 2-arachidonoyl-sn-glycerol ABHD6 hydrolase, targeting recombinant 2-arachidonoyl-sn-glycerol ABHD6 hydrolase [7]

Antiviral Activity

Euphol shows cytotoxic and antiviral properties in compounds derived from *Euphorbia kansui* [32].

Anti-Epstein-Barr Virus Activity:

Euphol strongly inhibits Epstein-Barr virus early antigen activation induced by the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) [26].

Venom Protection:

Euphol provides protective effects against the lethal action of the venom from the jararaca snake (*Bothrops jararaca*) [65]

Antioxidant Properties

Euphol exhibits antioxidant activity by scavenging free radicals and donating hydrogen, comparable to α-tocopherol, as tested using DPPH, hydroxyl radical, reducing power, and superoxide radical scavenging assays [66]

Immunomodulatory Activity

Euphol modulates immune responses and demonstrates cytotoxicity, suggesting potential for treating complement-related inflammatory diseases and supporting complement-dependent cytotoxicity in monoclonal antibody-based cancer therapies [66]

Euphol's Potential in Treating Multiple Sclerosis (MS)

Multiple sclerosis (MS) is a debilitating, chronic autoimmune disorder characterized by T cell-mediated inflammation in the central nervous system (CNS). Current therapies for MS often provide only partial relief and can be accompanied by significant side effects. Recent research has explored the therapeutic potential of euphol, a natural compound, in managing this disease. Euphol treatment notably attenuated the neurological symptoms associated with EAE (experimental autoimmune encephalomyelitis). The beneficial effects of euphol appear to be linked to its ability to down-regulate the mRNA and protein expression of key pro-inflammatory mediators within the CNS. These include tumor necrosis factor-alpha (TNF-α), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2). By reducing these inflammatory markers, euphol helps to mitigate the damaging inflammatory processes in MS. [67]

In vitro studies further demonstrated that euphol effectively inhibits T cell-mediated immune responses. Specifically, it reduced the production of TH1 and TH17 cytokines in spleen cells from untreated EAE animals. TH1 and TH17 cells are critical drivers of the autoimmune response in MS and their cytokines play a significant role in sustaining inflammation and damage in the CNS. [67]

Moreover, oral administration of euphol significantly inhibited the infiltration of TH17 myelin-specific cells into the CNS. This effect is mediated through the suppression of the adhesion molecule lymphocyte function-associated antigen 1 (LFA-1), which is crucial for the migration of immune cells into the CNS. By blocking this pathway, euphol helps to prevent the accumulation of inflammatory cells in the CNS, thereby reducing the severity of the disease. [67]

Overall, the consistent reduction and limitation of EAE severity by euphol suggest that it holds promise as a potential therapeutic agent for MS and other TH17 cell-mediated inflammatory diseases. Euphol's ability to modulate immune responses and down-regulate inflammatory mediators positions it as a compelling candidate for further research and development in the treatment of MS, offering hope for a more effective and better-tolerated therapy.[67]

Hypotensive activity of euphol

When administered intravenously, euphol demonstrated hypotensive effects in normotensive anesthetized dogs and rats, with the degree of blood pressure reduction varying from slight to significant depending on the dose. Euphol was found to inhibit various autonomic responses that regulate blood pressure, both those that increase (pressor) and those that decrease (depressor) it. [68]

The hypotensive action of euphol remained consistent even in dogs that were pretreated with atropine, antihistamines, and β-blockers, as well as in those that underwent bilateral vagotomy and carotid sinus denervation. Interestingly, the blood pressure-lowering effect was more pronounced in spinally transected and eviscerated dogs and after ganglion blockade with hexamethonium, suggesting that its action might be enhanced under these conditions. [68]

Despite the significant impact on blood pressure, direct application of euphol to central cardiovascular centers did not alter blood pressure, indicating that its hypotensive effects are likely mediated peripherally rather than centrally. [68]

Molluscicide Activity

Euphol demonstrates effectiveness in killing mollusks. [28]

Perspective on Future Directions

Exploration euphol as nutraceutical and cosmeceutical agents, along with their industrial applications, is gaining momentum. These compounds, derived from natural sources, exhibit a wide range of biological activities. Notably, their potential cytotoxic properties make them promising candidates for the control and treatment of cancer. Given their broad spectrum of activity, future research should also consider their potential against COVID-19.

As the prevalence of severe bacterial and viral infections rises, along with the growing issue of resistance to current treatments, there is a critical need for novel compounds to combat these challenges. euphol, with its low toxicity and demonstrated biological activity, stands out as a candidate for further investigation. The hepatoprotective and gastroprotective properties of triterpenes also suggest that they could play a valuable role in future therapeutic regimens.

Moving forward, research should focus on enhancing the efficiency of these terpenes while preserving their bioactivity and bioavailability. Ensuring stability through storage, preparation and consumption is also crucial. Innovative drug delivery methods, such as nano formulations or encapsulation, should be explored to improve both the stability and the biological efficacy of these compounds. This approach will not only optimize their therapeutic potential but also broaden their application in modern medicine.

Research and Therapeutic Potential

Due to its potent biological activities, euphol is a candidate for developing new therapeutic agents. Current research focuses on:

a. Drug Development: Exploring euphol potential as a lead compound for developing anti-inflammatory, anti-cancer and analgesic drugs.
b. Synergistic Effects: Studying its use in combination with other compounds to enhance therapeutic efficacy.
c. Mechanistic Studies: Understanding the detailed molecular mechanisms underlying its biological activities to optimize its application in medicine.

4. Conclusion

Euphol is a captivating molecule, celebrated for their natural origin and notable therapeutic potential, as evidenced by a broad range of studies conducted *in silico*, *in vitro*, and *in vivo*. The journey of drug discovery from natural sources, though arduous and complex, is exceptionally rewarding, particularly when it taps into the ethnopharmacological knowledge and empirical use of plants.

The rich presence of euphol in various plants has made it a focal point of extensive research. This compound has demonstrated significant biological activities in various studies, including anti-inflammatory, analgesic, antipyretic, antimicrobial, antiviral, hypolipidemic, gastroprotective, antioxidant, and antihyperglycemic effects. These diverse and beneficial properties underscore its potential as a key candidate for drug development.

Despite the broad spectrum of biological activities, many findings on the cytotoxicity of euphol suggest it may have limited or selective activity in this area. This highlights the critical need for establishing a detailed structure-activity relationship (SAR). Understanding SAR is essential to elucidate how euphol interacts effectively with specific biological targets and why it may fail to engage with others. While the process of identifying and harnessing active compounds from natural sources is challenging, the promising results associated with euphol make it a compelling subject for future research. Continued exploration and analysis could lead to significant advancements in its application across various therapeutic areas, potentially contributing to the development of new and effective drugs.

List of abbreviations

Abbreviation	stands for
12-C NMR	Carbon-13 nuclear magnetic resonance
2-AG	Endocannabinoid 2-arachidonoyl-sn-glycerol
A549	Adenocarcinoma human alveolar basal epithelial cells
ABHD6	Alpha/beta-Hydrolase domain containing 6
B16F10	A murine melanoma cell line from a C57BL/6J mouse
BAX	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma 2
BF3	Boron trifluoride
BF3OEt2	Boron trifluoride etherate
C57BL/6	"C57 black 6", a common inbred strain of laboratory mouse
CB1 and CB2	Cannabinoid receptors 1 and 2
CDK2	Cyclin-dependent kinase 2
CH2Cl2	Dichloromethane
CHCl3	Chloroform
COX-2	Cyclooxygenase-2
CREB	cAMP response element-binding protein
CXCL1	Chemokine (C-X-C motif) ligand 1
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane (methylene chloride)
DIPEA	N, N-Diisopropylethylamine
DIBAL.H	Diisobutylaluminium hydride (reducing agent)
DMAP	4-Dimethylaminopyridine
DME	Dimethyl Ether
DMF	Dimethyl Formamide
DMAPP	Dimethylallyl diphosphate
DMP	Dess-Martin Periodinane (Chemical Reagent used as Oxidizing agent)
EAE	Experimental autoimmune encephalomyelitis
ERK	Extracellular signal-regulated kinase
ERK1/2	Extra-cellular signal-regulated kinase 1/2
EtOAc	Ethyl acetate
FPP	Farnesyl diphosphate
FPPS	Farnesyl diphosphate synthase
GBM	Glioblastoma multiforme
GPPS	Geranyl diphosphate synthase
HaCaT	Spontaneously immortalized human keratinocyte cell line derived from melanoma
HeLa	Immortalized cell line
HepG2	Human liver cancer cell line
HFIP	Hexafluoro isopropanol used as solvent (Green Solvent)
HL-60	Myeloid leukemia cells
HMPA	Oxide tris (dimethylamino phosphine)
I-Prp(PH)3I	Isopropyltriphenylphosphonium iodide
IC50	50% inhibitory concentration
ICAM-1	Intercellular adhesion molecule
ID50	The median infective dose
IFN-γ	Interferon-gamma

List of abbreviations (continued…)

IL-1β	Interleukin 1β
IL-6	Interleukin 6
IL-10	Interleukin 10
IPP	Isopentenyl diphosphate
KC	Keratinocyte-derived chemokine
Ki67	Antigen Kiel 67
LFA-1	Lymphocyte function associated antigen 1
LI NH3	Reduction reaction of alkyne to form the trans alkene
LIHMDS	Lithium bis (trimethylsilyl) amide
LPS	Lipopolysaccharide
MCL-12A	Non-tumorigenic mammary epithelial cells
MGL	Monoacylglycerol lipase
MIP-2	Macrophagic inflammatory protein 2
MRC-5	Human diploid lung fibroblast cell line
MS	Multiple sclerosis
MSCL	Methanesulfonyl chloride CH3SO2Cl
MVA	Mevalonate
NF-κB	Nuclear factor kappa B
NOS2	Nitric oxide synthase
NSL	Nonsaponifiable lipid fractions
Oregano Silicon	Strong non-nucleophilic base for Enolization, Metal Complexation, Alkylation
OSC	Oxidosqualene cyclase
Pd(OAC)2	Palladium acetate
PE	Petroleum ether
PCC	Pyridinium Chlorochromate
PIDA	Poly(diiodoacetylene)
PKC	Protein kinase C
PKCα	Protein kinase C alpha isozyme
PKCδ	Protein kinase C delta isozyme
PKCε	Protein kinase C epsilon type
PPTS	Pyridinium-p-toluene Sulphonate (Catalyst)
SAR	Structure-activity relationship
SE	Squalene epoxidase
SMMC-7721	Hepatocellular carcinoma cells
SRB	Sulfo-rhodamine-B
SW-480	Colon cancer cells
TBHP	tert-Butyl hydroperoxide (Used in a variety of Oxidation Process)
TBAF	Tetra-n-butylammonium fluoride (Deprotective Group)
TBDPSCL	t-Butyl dimethylsilyl chloride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TNF-α	Tissue necrotizing factor
TOSYL Chloride	Toluene Sulphonyl Chloride (TSCl)
TPA	12-O-tetradecanoylphorbol-13-acetate
TMSCL	Trimethylsilyl chloride (Silylating agent)
TSCl	Tosyl Chloride (Toluene Sulphonyl Chloride)

List of abbreviations (continued…)

VEGF	Vascular endothelial growth factor
VCAM-1	Vascular cell adhesion protein 1
VO(Oi-Pr)3	Vanadium(V) oxytriisopropoxide
Wilkinson's catalyst	A coordination complex of rhodium with the formula [RhCl(P(C6H5)3]
ZIF-8	Zeolitic imidazolate framework

5. Conflicts of interest

There are no conflicts to declare.

6. Formatting of funding sources

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8. References

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