A Conversation about Devil's Club

A personal journey into the world of natural remedies and devil's club in the Alaskan rainforest.

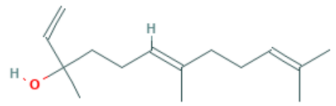
Native Uses

- ailments of the chest
- coughs and colds
- purgative and emetic
- general
- ulcer
- pregnancy and birth
- cancer
- dermatological uses and cuts
- abscesses
- tonic
- arthritis and rheumatism
- diabetes
- STD

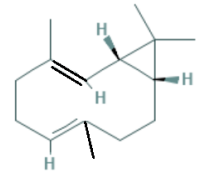
Chemical Profile of Devil's Club Essential Oil

Constituent	Branch bark (author's distillation)	Root bark (Garneau, 2006).
Trans-nerolidol	59.6%	54%
Bicyclogermacrene	10.5%	4%
Delta-cadinol (alpha-muurolol)	10.5%	-
Tau-cadinol	0.02	16.9%
Gamma-cadinene	2.7%	6%
Delta-cadinene	2.4%	4%
Spathulenol	2.2%	2.6%

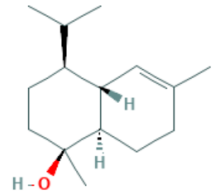
A comparison of the major constituents of the branch and root bark devil's club essential oils



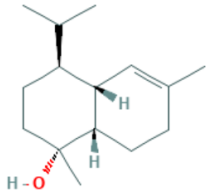
trans-nerolidol = (E)-nerolidol



bicyclogermacrene



tau-cadinol = cedrelanol = 10-epi-alpha-muurolol



delta-cadinol = torreyol = alpha-muurolol

Chemical Profile of Devil's Club Hydrosol

The hydrosol contains an estimated total of 51.8 mg/L of volatile compounds, of which the main ones were characterized as follows:

Constituent	mg/L	% of volatiles	Class	EO component?
(E)-Nerolidol	17.5	33.8	Sesquiterpenic alcohol	Yes
τ-Cadinol	6.7	12.96	Sesquiterpenic alcohol	Yes
4-Vinylguaiacol	5.8	11.13	Simple phenolic	No
Spathulenol	3.2	6.26	Sesquiterpenic alcohol	Yes
α-Cadinol	1.1	2.19	Sesquiterpenic alcohol	Yes
Isospathulenol	0.7	1.29	Sesquiterpenic alcohol	No

Full GC-MS profiles for the essential oil are available online at https://www.southeastdevilsclub.com/gc-ms-analysis

Full GC-FID profile for the hydrosol is available upon request.

Research on Therapeutic Actions

Primary constituent: trans-nerolidol

- Hydrophobic aliphatic sesquiterpene alcohol
- Reviewed in the paper entitled “Nerolidol: A Sesquiterpene Alcohol with Multi-Faceted Pharmacological and Biological Activities” (Chan,2016)

- anti-microbial
- anti-parasitic
- anti-biofilm
- antioxidant
- anti-nociceptive
- anti-inflammatory
- anti-ulcer
- skin penetration enhancer
- insect repellent
- anti-cancer

Many of these actions correspond to current Native uses of devil’s club

Therapeutic Actions of Nerolidol

Mechanisms

Pathways

Metabolites

Enzymes

DNA/RNA

Detailed information about the chemistry, biochemical interactions and cellular function, and the implications of secondary components is available on the Southeast Devilsclub website at https://southeastdevilsclub.com/research

General Pathology

Ailments can be caused by

- direct action of toxins, parasites, or viruses on cells and organs
- dnterruption of natural body processes by toxins, parasites, or viruses
  - Overproduction of normal enzymes, cells, and processes
  - Blocking pathways or receptors
  - Prevention of the production of essential compounds

Nerolidol potential

- counteract overproduction
- modulate critical chemical pathways.

Nrf-2 and LPS

Nrf-2 : Nuclear factor erythroid 2-related factor 2

- A **protein** that controls the rate of transcription of genetic information from DNA to messenger RNA
- **regulates** the production of cytoprotective phase II detoxification and antioxidant **enzymes**
- considered the master regulator of antioxidant defense molecules

LPS: Lipopolysaccharide

- Endotoxin and pyrogen
- structural component of the cell wall of gram-negative bacteria
- induces a strong immune response, inhalation airway inflammation, the progression of asthma, other forms of airway disease.
- Humans are the most susceptible species for immune response.

Nrf-2 Activation by Nerolidol

ALI (acute lung injury) (in vivo)

- a life-threatening disease that is characterized by the rapid onset of inflammatory responses.
- no effective therapeutic strategies are currently available
- nerolidol pretreatment inhibited LPS-induced alveolar-capillary barrier disruption, lung edema, and lipid peroxidation. LPS had interfered with the production of Nrf-2, but the Nrf-2 interference was remedied and enhanced by nerolidol in a dose-dependent manner
- protective effects of nerolidol in LPS-induced ALI by the activation of the AMPK/Nrf-2/HO-1 signaling pathway

Effects of Nrf-2 Activation by Nerolidol

Degenerative brain disease and Nrf-2 (in vivo)

- plays an important role in mouse models of neurodegenerative diseases such as Parkinson's disease and Huntington's disease.
- reported to be relevant to acute neurological disorders such as stroke.
- may contribute to the beneficial role of the neuroprotective Parkinson Protein.
- The protective results from nerolidol activation of Nrf2 in neurological disorders such as Parkinson's disease provide a rationale for additional disease model studies and the potential for human clinical trials in the future.

Effects of Nrf-2 Activation by Nerolidol

Neuroinflammation treatment (in vivo)

- protective effect of nerolidol against CP-induced
  - neuroinflammation,
  - oxidative stress
  - cognitive impairment
  - structural abnormalities in the hippocampus and cortex regions.
- findings suggested that nerolidol is a potential therapeutic molecule which can mitigate CP-induced neurotoxic manifestations via Nrf2 and NF-κB pathway. However, more detailed studies are needed to explain the mechanism underlying its neuroprotective effect.

Nerolidol vs LPS

Acute kidney injury (AKI) (in vivo)

- AKI is a critical care syndrome, resulting in acute reduction of renal function and up to 22% mortality of hospitalized patients.
- nerolidol dose-dependently reduced the pathological injuries of the kidneys and significantly decreased the levels of blood urea nitrogen and creatinine induced by LPS in rats.
- nerolidol had a critical anti-inflammatory effect through inhibition of enzyme signaling and protected against LPS-induced AKI.

Cyclophosphamide

Cyclophosphamide (CP)

- medication used as chemotherapy and also to suppress the immune system
- used to treat lymphoma, multiple myeloma, leukemia, ovarian cancer, breast cancer, small cell lung cancer, neuroblastoma, and sarcoma.
- severe side effects

Protective actions of Nerolidol

Cardioprotective (in vivo)

- an extensive test concluded that nerolidol acted as a potent cardioprotective molecule and attenuated CP-induced cardiotoxicity
- nerilodol reduces hypertension associated inflammation and oxidative stress and provides effective cardioprotection
- echocardiography analysis showed that nerolidol improved cardiac function
- demonstrates nerolidol as a cardio-protective agent against hypertension induced cardiac inflammation.

Gonadoprotective (in vivo)

- CP has a noticeable gonadotoxic profile.
- CP caused reduced sperm count, sperm motility and testosterone level
- conditions were reversed upon treatment with nerolidol in a dose-dependent manner.
- cerolidol acted as a gonadoprotective molecule and prevented the gonadotoxicity of CP

Nerolidol Actions -Hemaprotective

- Hemaprotective (in vivo)
- nerolidol exhibited potent antioxidant, anti-inflammatory, anti-apoptotic, and anti-fibrotic potential and thus acted as liver protecting agent.
- represents novel mechanisms of nerolidol against CP-induced liver toxicity.
- further studies are needed to use nerolidol as an adjuvant in chemotherapeutically treated patients.

Nerolidol Actions -Antibacterial

- Anti-bacterial (in vitro)
  - disrupts cell membranes in drug resistant bacteria
  - interferes with the genes that regulate pathogenicity
  - enhance susceptibility to antibiotics
  - Nerolidol binds with a key enzyme and showed potential antivirulent and biofilm inhibitory properties against clinical and drug resistant strains of MRSA
  - observations suggest that nerolidol provides an alternative therapeutic option for the development of drug combinations that may be more effective in controlling multi-drug resistant bacteria

- Anti-biofilm (in vitro)
  - biofilm is a film that is produced by bacteria and allows it to attach to surfaces.
  - trans-nerolidol inhibited biofilm formation by 45% at a concentration of .01% vs. MRSA

Nerolidol Actions –Antiparasitic and Antiviral

Anti-parasitic (in vitro)

- interferes with parasite-host cell interaction and chemical pathways in parasites
- shown to be a promising candidate for treating parasitic diseases.

Anti-viral

- SARS-CoV-2 Mpro (computer modeling)
  - when given alone and in a mixture nerolidol has the potential for inhibiting viral replication of SARS-CoV-2 Mpro.
  - showed the most potential for interfering with a protein required for viral replication and also preventing the spike proteins of the virus from attaching to cell walls. Data from well-established preclinical and clinical studies is required.
- HPV (in vivo)
  - Single treatment of 200 µl – change after 6 months, clearance at 2 and 6 months.
  - should be further evaluated for the role it may play in cervical cancer prevention.

Nerolidol Actions –Fungicidal and Antioxidant

Fungicidal (in vitro)

- nerolidol exhibits fungicidal activity against Candida albicans at a minimum concentration of .24%-1.26%
- could be a promising therapeutic alternatives for the treatment of candidiasis
- made all strains of Trichophyton fungus (causes dermaphytosis) sensitive to antifungal treatments and represents a potential antifungal agent

Antioxidant (in vitro)

- exhibits potent antioxidant properties
- counterbalances the effect of reactive oxygen species and free radicals.
- mediates a potent antioxidant activity by scavenging free radicals
- preventing lipid peroxidation
- enhances the production of antioxidant enzymes in cells for protection against oxidative stress.

Nerolidol Actions – Skin Penetration Enhancer

Skin Penetration Enhancer (in vitro)

- transdermal delivery is limited by poor drug permeability
- testing of human epidermal membranes shows that nerolidol increased the diffusion rate by over 20-fold for drug delivery
- the most effective percutaneous permeation enhancer for 4 model drugs including hydrocortisone
- shows promise as clinically-acceptable skin penetration enhancer.

Nerolidol Actions – Anti-cancer

Anti-cancer (in vitro)

- strong cytotoxicity against cell lines of mouse melanoma, human liver carcinoma, human leukemia, and human chronic leukemia
- no toxicity effect on non-tumor cells
- authors suggest that nerolidol is a good candidate for the development of anticancer agent that selectively targets specific cancerous cells with no cytotoxicity towards non-tumor cells.

- colon and breast
  - (in vitro) showed potential anticancer activities on human breast cancer and colon cancer cells.
  - Inductive cancer cell apoptosis and destruction
  - arrested effects on cell cycle
  - results provide promising baseline information for the potential use of devil's club in the treatment of cancer
- leukemia and ovarian (in vitro)
  - ethanol extract of devil's club root showed that solutions as weak as 1/8000 had a strong anti-proliferative action against human leukemia cell lines and ovarian cancer lines. Nerolidol is also the primary constituent in devil's club root.

Nerolidol Actions – Anti-cancer, Antiemetic, Analgesic

- anti-tumor (in vivo)
  - showed an inhibitory effect on carcinogenesis of the large bowel of rats
  - proposed as an anti-cancer agent and a synergist for cancer treatments.

Anti-emetic (in vivo)

- Chemotherapy-induced nausea and vomiting (or CINV) are significant side effects for cancer patients.
- Nerolidol exerted antiemitic effects in animal tests and have promising potency in therapy-resistant CINV.

Analgesic (in vivo)

- shown to demonstrate promising analgesic and anti-inflammatory activities in mice studies. This is attributed to the suppression of proinflammatory cytokines.

Nerolidol Actions – Anti-inflammatory

Anti-inflammatory

- Arthritis (in vivo)
  - nerolidol inhibited neutrophils migration into joints
  - nanoencapsulation of nerolidol improved its anti-inflammatory effect on arthritis.
- Colon (in vivo)
  - supplementation attenuates colon inflammation through its potent antioxidant and anti-inflammatory activity
- Keratitis (in vitro)
  - directly inhibits the growth of the fungus Aspergillus fumigatus which causes keratitis

Nerolidol Actions – Anti-ulcer and diseases

Anti-ulcer (in vivo)

- showed significant inhibition of the formation of ulcers
- reduced the severity of the lesions

Endometriosis reversal (in vivo)

- nerolidol and hesperidin caused a significant endometriosis.
- Hesperidin and nerolidol treatment improved hemorrhage, vascular congestion, necrosis, and inflammatory cell infiltration in the endometriotic foci.

Nerolidol Actions – Neurological

Alzheimer's (in vitro)

- Cholinesterase inhibitors are routinely applied in the treatment of Alzheimer's disease
- nerolidol was identified as an effective cholinesterase inhibitor.

Parkinson's disease (in vivo)

- improved Parkinson's disease symptoms
  - reversing neuroinflammation and cerebral oxidative stress
  - increasing levels of the antioxidant enzymes SOD, CAT, GSH
  - decreases lipid peroxidation and MDA levels
  - decreases glial cell activation
  - decreases dopaminergic neuron loss.

Nerolidol Actions – Anxiolytic, Epilepsy

Anxiolytic (in vivo)

- nerolidol exerts an anxiolytic effect without altering motor coordination.

Epilepsy (in vivo)

- nerolidol treatment has a **protective** effect against
  - induced seizures
  - associated oxidative stress
  - behavioral comorbidities.
- decrease in oxidative stress and favorable neurochemical changes in both the cortex and the hippocampus
  - increased levels of noradrenaline
  - Increased levels of dopamine
  - Increased levels of serotonin
- Nerolidol also improved depression and memory loss in animals with epilepsy.

Cytochrome inhibition

Alosetron (Lotronex)
Caffeine
Clozapine (Clozaril)
Flutamide (Eulexin)
Frovatriptan (Frova)
Melatonin
Mexiletine (Mexitil)
Mirtazapine (Remeron)
Olanzapine (Zyprexa)
Ramelteon (Rozerem)
Rasagiline (Azilect)
Ropinirole (Requip)
Tacrine (Cognex)
Theophylline
Tizanidine (Zanaflex)
Triamterene (Dyrenium)
Zolmitriptan (Zomig)

Nerolidol might affect the function of catalyst cytochromes to metabolize drugs and other xenobiotics. These catalysts are called CYP1A2, CYP2B6, CYP3A4, and CYP3A5 cytochromes.

Interactions should be verified during *in-vivo* tests on animals

Inhibiting CYP1A2 enzymes will increase plasma concentrations of these medications

General Toxicity with CYP3A4 enzyme inhibitors			
Alfentanil (Alfenta)	Docetaxel (Taxotere)	Ketoconazole (Nizoral)	Quinine
Alfuzosin (Uroxatral)	Donepezil (Aricept)	Lapatinib (Tykerb)	Ranolazine (Ranexa)
Almotriptan (Axert)	Doxorubicin (Adriamycin)	Levomethadyl (Orlaam)	Repaglinide (Prandin)
Alprazolam (Xanax)	Droperidol	Loperamide (Imodium)	Rifabutin (Rimactane)
Amiodarone (Cordarone)	Dutasteride (Avodart)	Lopinavir (Kaletra)	Ritonavir (Norvir)
Amlodipine (Norvasc)	Ebastine (Kestine)	Loratadine (Claritin)	Saquinavir (Invirase)
Aprepitant (Emend)	Efavirenz (Sustiva)	Lovastatin (Mevacor)	Sibutramine (Meridia)
Atazanavir (Reyataz)	Eletriptan (Relpax)	Maraviroc (Selzentry)	Sildenafil (Viagra)
Atorvastatin (Lipitor)	Eplerenone (Inspra)	Mefloquine (Lariam)	Simvastatin (Zocor)
Bepridil (Vascor)	Ergotamine (Ergomar)	Methylprednisolone	Sirolimus (Rapamune)
Bexarotene (Targretin)	Erlotinib (Tarceva)	Midazolam (Versed)	Solifenacin (Vesicare)
Bosentan (Tracleer)	Erythromycin	Mifepristone (Mifeprex)	Sufentanil (Sufenta)
Bromocriptine (Parlodel)	Estazolam (ProSom)	Modafinil (Provigil)	Sunitinib (Sutent)
Budesonide (Entocort)	Eszopiclone (Lunesta)	Nefazodone	Tacrolimus (Prograf)
Buprenorphine (Subutex)	Ethinyl Estradiol	Nevirapine (Viramune)	Tadalafil (Cialis)
Bupropion (Zyban, Wellbutrin, Voxra)	Ethosuximide (Zarontin)	Nicardipine (Cardene)	Tamoxifen (Nolvadex)

Carbamazepine (eg, Tegretol)	Etoposide (Vepesid)	Nifedipine (Adalat)	Tamsulosin (Flomax)
Cevimeline (Evoxac)	Exemestane (Aromasin)	Nimodipine (Nimotop)	Teniposide (Vumon)
Cilostazol (Pletal)	Felodipine (Plendil)	Nisoldipine (Sular)	Testosterone
Cisapride (Propulsid)	Fentanyl (Sublimaze)	Nitrendipine (Baypress)	Tiagabine (Gabitril)
Clarithromycin (Biaxin)	Finasteride (Proscar)	Oxybutynin (Ditropan)	Tinidazole (Tindamax)
Clonazepam (Klonopin)	Flurazepam (Dalmane)	Oxycodone (Percodan)	Tipranavir (Aptivus)
Clopidogrel (Plavix)	Fosamprenavir (Lexiva)	Paclitaxel (Taxol)	Topiramate (Topamax)
Colchicine	Galantamine (Reminyl)	Paricalcitol (Zemplar)	Triazolam (Halcion)
Cyclophosphamide (Cytoxan)	Gefitinib (Iressa)	Pimozide (Orap)	Vardenafil (Levitra)
Cyclosporine (Neoral)	Granisetron (Kytril)	Pioglitazone	Verapamil (Calan)
Dapsone (Avlosulfon)	Halofantrine (Halfan)	Praziquantel (Biltricide)	Vinblastine (Velbane)
Darunavir (Prezista)	Ifosfamide (Ifex)	Prednisolone	Vincristine (Oncovin)
Dasatinib (Sprycel)	Imatinib (Gleevec)	Prednisone	Ziprasidone (Geodon)
Delavirdine (Rescriptor)	Indinavir (Crixivan)	Propoxyphene (Darvon)	Zolpidem (Ambien)
Dexamethasone (Decadron)	Irinotecan (Camptosar)	Quazepam (Doral)	Zonisamide (Zonegran)
Dihydroergotamine	Isradipine (DynaCirc)	Quetiapine (Seroquel)	Zopiclone (Imovane)
Diltiazem (Cardizem)	Itraconazole (Sporanox)	Quinacrine	
Disopyramide (Norpace)	Ixabepilone (Ixempra)	Quinidine	

References

ALI (acute lung injury) (Ni,2019) in vivo

Ni YL, Shen HT, Su CH, Chen WY, Huang-Liu R, Chen CJ, Chen SP, Kuan YH. Nerolidol Suppresses the Inflammatory Response during Lipopolysaccharide-Induced Acute Lung Injury via the Modulation of Antioxidant Enzymes and the AMPK/Nrf-2/HO-1 Pathway. Oxid Med Cell Longev. 2019 Nov 16;2019:9605980. doi: 10.1155/2019/9605980. PMID: 31827712; PMCID: PMC6885193.

degenerative brain disease (Gao,2014) in vivo

Gao B, Doan A, Hybertson B. The clinical potential of influencing Nrf2 signaling in degenerative and immunological disorders. Clin Pharmacol. 2014;6:19-34.https://doi.org/10.2147/CPAA.S35078

neuroinflammation treatment (Iqubal,2019); (Iqubal,2020) in vivo

Iqubal A, Sharma S, Najmi AK, Syed MA, Ali J, Alam MM, Haque SE. Nerolidol ameliorates cyclophosphamide-induced oxidative stress, neuroinflammation and cognitive dysfunction: Plausible role of Nrf2 and NF- κB. Life Sci. 2019 Nov 1;236:116867. doi: 10.1016/j.lfs.2019.116867. Epub 2019 Sep 11. PMID: 31520598.

Iqubal A, Syed MA, Najmi AK, Azam F, Barreto GE, Iqubal MK, Ali J, Haque SE. Nano-engineered nerolidol loaded lipid carrier delivery system attenuates cyclophosphamide neurotoxicity - Probable role of NLRP3 inflammasome and caspase-1. Exp Neurol. 2020 Dec;334:113464. doi: 10.1016/j.expneurol.2020.113464. Epub 2020 Sep 15. PMID: 32941795.

AKI treatment (acute kidney injury) (Zhang,2017) in vivo

Zhang L, Sun D, Bao Y, Shi Y, Cui Y, Guo M. Nerolidol Protects Against LPS-induced Acute Kidney Injury via Inhibiting TLR4/NF-κB Signaling. Phytother Res. 2017 Mar;31(3):459-465. doi: 10.1002/ptr.5770. Epub 2017 Jan 17. PMID: 28093813.

cardioprotectant vs chemotherapy (Iqubal,2019) in vivo

Iqubal A, Sharma S, Ansari MA, Najmi AK, Syed MA, Ali J, Alam MM, Ahmad S, Haque SE. Nerolidol attenuates cyclophosphamide-induced cardiac inflammation, apoptosis and fibrosis in Swiss Albino mice. Eur J Pharmacol. 2019 Nov 15;863:172666. doi: 10.1016/j.ejphar.2019.172666. Epub 2019 Sep 18. PMID: 31541628.

cardioprotectant vs hypertension (Lin,2020) in vivo

Lin YM, Badrealam KF, Kuo WW, Lai PF, Shao-Tsu Chen W, Hsuan Day C, Ho TJ, Viswanadha VP, Shibu MA, Huang CY. Nerolidol improves cardiac function in spontaneously hypertensive rats by inhibiting cardiac inflammation and remodelling associated TLR4/ NF-κB signalling cascade. Food Chem Toxicol. 2020 Nov 17:111837. doi: 10.1016/j.fct.2020.111837. Epub ahead of print. PMID: 33212213.

gonadoprotective (Iqubal,2020) in vivo

Iqubal A, Syed MA, Najmi AK, Ali J, Haque SE. Ameliorative effect of nerolidol on cyclophosphamide-induced gonadal toxicity in Swiss Albino mice: Biochemical-, histological- and immunohistochemical-based evidences. Andrologia. 2020 May;52(4):e13535. doi: 10.1111/and.13535. Epub 2020 Feb 12. PMID: 32048763.

Hemaprotective (Iqubal,2020) in vivo

Iqubal A, Syed MA, Ali J, Najmi AK, Haque MM, Haque SE. Nerolidol protects the liver against cyclophosphamide-induced hepatic inflammation, apoptosis, and fibrosis via modulation of Nrf2, NF-κB p65, and caspase-3 signaling molecules in Swiss albino mice. Biofactors. 2020 Nov;46(6):963-973. doi: 10.1002/biof.1679. Epub 2020 Sep 17. PMID: 32941697.

anti-bacterial (Chan,2016) in vitro

Chan WK, Tan LT, Chan KG, Lee LH, Goh BH. Nerolidol: A Sesquiterpene Alcohol with Multi-Faceted Pharmacological and Biological Activities. Molecules. 2016 Apr 28;21(5):529. doi: 10.3390/molecules21050529. PMID: 27136520; PMCID: PMC6272852.

anti-biofilm (Chan,2016) in vitro

Chan WK, Tan LT, Chan KG, Lee LH, Goh BH. Nerolidol: A Sesquiterpene Alcohol with Multi-Faceted Pharmacological and Biological Activities. Molecules. 2016 Apr 28;21(5):529. doi: 10.3390/molecules21050529. PMID: 27136520; PMCID: PMC6272852.

vs MRSA (Rubini,2018) in vitro

Rubini D, Banu SF, Nisha P, Murugan R, Thamotharan S, Percino MJ, Subramani P, Nithyanand P. Essential oils from unexplored aromatic plants quench biofilm formation and virulence of Methicillin resistant Staphylococcus aureus. Microb Pathog. 2018 Sep;122:162-173. doi: 10.1016/j.micpath.2018.06.028. Epub 2018 Jun 18. PMID: 29920307.

anti-parasitic: schistosomal, leishmanial, other (Chan,2016) in vitro

Chan WK, Tan LT, Chan KG, Lee LH, Goh BH. Nerolidol: A Sesquiterpene Alcohol with Multi-Faceted Pharmacological and Biological Activities. Molecules. 2016 Apr 28;21(5):529. doi: 10.3390/molecules21050529. PMID: 27136520; PMCID: PMC6272852.

anti-viral vs SARS-CoV-2 (Asif,2020) computer modeling

Asif, M., Saleem, M., Saadullah, M. et al. COVID-19 and therapy with essential oils having antiviral, anti-inflammatory, and immunomodulatory properties. Inflammopharmacol 28, 1153–1161 (2020). https://doi.org/10.1007/s10787-020-00744-0

anti-viral vs HPV (Mutombo,2019) in vivo – human

Baleka Mutombo A, Tozin R, Kanyiki H, Van Geertruyden JP, Jacquemyn Y. Impact of antiviral AV2 in the topical treatment of HPV-associated lesions of the cervix: Results of a phase III randomized placebo-controlled trial. Contemp Clin Trials Commun. 2019 May 16;15:100377. doi: 10.1016/j.conctc.2019.100377. PMID: 31193477; PMCID: PMC6529824.

fungicidal (Chan,2016; de Oliveira,2020; Fonseca,2020) in vitro

Chan WK, Tan LT, Chan KG, Lee LH, Goh BH. Nerolidol: A Sesquiterpene Alcohol with Multi-Faceted Pharmacological and Biological Activities. Molecules. 2016 Apr 28;21(5):529. doi: 10.3390/molecules21050529. PMID: 27136520; PMCID: PMC6272852.

de Oliveira JC, de Vasconcelos Pinto Â, de Medeiros CAC, Ponte HAS, Pereira FO. The Sensitivity Modifying Activity of Nerolidol and α-Bisabolol Against Trichophyton spp. Indian J Microbiol. 2020 Dec;60(4):505-510. doi: 10.1007/s12088-020-00895-2. Epub 2020 Jun 13. PMID: 33088000; PMCID: PMC7539253.

Fonseca Bezerra C, de Alencar Júnior JG, de Lima Honorato R, Dos Santos ATL, Pereira da Silva JC, Silva TGD, Leal ALAB, de Freitas TS, Vieira TAT, Esmeraldo Rocha J, Lima Sales D, Barbosa Filho JM, Ribeiro de Sousa G, Pinheiro AP, Ribeiro-Filho J, Coutinho HDM, Bezerra Morais-Braga MF, da Silva TG. Antifungal Properties of Nerolidol-Containing Liposomes in Association with Fluconazole. Membranes (Basel). 2020 Aug 20;10(9):194. doi: 10.3390/membranes10090194. PMID: 32825411; PMCID: PMC7558210.

anti-oxidant (Chan,2016) in vitro

Chan WK, Tan LT, Chan KG, Lee LH, Goh BH. Nerolidol: A Sesquiterpene Alcohol with Multi-Faceted Pharmacological and Biological Activities. Molecules. 2016 Apr 28;21(5):529. doi: 10.3390/molecules21050529. PMID: 27136520; PMCID: PMC6272852.

skin penetration enhancer (Chan,2016)(Cornwell,1994) in vivo

Chan WK, Tan LT, Chan KG, Lee LH, Goh BH. Nerolidol: A Sesquiterpene Alcohol with Multi-Faceted Pharmacological and Biological Activities. Molecules. 2016 Apr 28;21(5):529. doi: 10.3390/molecules21050529. PMID: 27136520; PMCID: PMC6272852.

CORNWELL, P.A. and BARRY, B.W. (1994), Sesquiterpene Components of Volatile Oils as Skin Penetration Enhancers for the Hydrophilic Permeant 5-Fluorouracil. Journal of Pharmacy and Pharmacology, 46: 261-269. https://doi.org/10.1111/j.2042-7158.1994.tb03791.x

anti-cancer: general (Chan,2016) in vitro, in vivo

Chan WK, Tan LT, Chan KG, Lee LH, Goh BH. Nerolidol: A Sesquiterpene Alcohol with Multi-Faceted Pharmacological and Biological Activities. Molecules. 2016 Apr 28;21(5):529. doi: 10.3390/molecules21050529. PMID: 27136520; PMCID: PMC6272852.

anti-cancer: colon and breast (Sun,2010) in vitro

Sun S, Du GJ, Qi LW, Williams S, Wang CZ, Yuan CS. Hydrophobic constituents and their potential anticancer activities from Devil's Club (Oplopanax horridus Miq.). J Ethnopharmacol. 2010 Oct 28;132(1):280-5. doi: 10.1016/j.jep.2010.08.026. Epub 2010 Aug 17. PMID: 20723598; PMCID: PMC3050531.

anti-cancer: leukemia and ovarian (Tai,2006) in vitro

Tai J, Cheung S, Chan E, Hasman D. Inhibition of human ovarian cancer cell lines by devil's club Oplopanax horridus. J Ethnopharmacol. 2010 Feb 3;127(2):478-85. doi: 10.1016/j.jep.2009.10.010. Epub 2009 Oct 14. PMID: 19835944.

anti-cancer: anti-tumor (Chan,2016; Wattenberg,1991) in vivo

Chan WK, Tan LT, Chan KG, Lee LH, Goh BH. Nerolidol: A Sesquiterpene Alcohol with Multi-Faceted Pharmacological and Biological Activities. Molecules. 2016 Apr 28;21(5):529. doi: 10.3390/molecules21050529. PMID: 27136520; PMCID: PMC6272852.

Wattenberg LW. Inhibition of azoxymethane-induced neoplasia of the large bowel by 3-hydroxy-3,7,11-trimethyl-1,6,10-dodecatriene (nerolidol). Carcinogenesis. 1991 Jan;12(1):151-2. doi: 10.1093/carcin/12.1.151. PMID: 1988176.

antiemetic (treats nausea, vomiting, motion sickness) (Lee,2018) in vivo

Lee G, Yang E, Kim S, Park CS, Park YS, Jin YH. Parapheromones Suppress Chemotherapy Side Effects. J Pharmacol Exp Ther. 2018 Nov;367(2):215-221. doi: 10.1124/jpet.118.251363. Epub 2018 Aug 22. PMID: 30135179.

analgesic (anti-nociceptive/chronic pain) (Chan,2016; Fonsêca,2016) in vivo

Chan WK, Tan LT, Chan KG, Lee LH, Goh BH. Nerolidol: A Sesquiterpene Alcohol with Multi-Faceted Pharmacological and Biological Activities. Molecules. 2016 Apr 28;21(5):529. doi: 10.3390/molecules21050529. PMID: 27136520; PMCID: PMC6272852.

Fonsêca DV, Salgado PR, de Carvalho FL, Salvadori MG, Penha AR, Leite FC, Borges CJ, Piuvezam MR, Pordeus LC, Sousa DP, Almeida RN. Nerolidol exhibits antinociceptive and anti-inflammatory activity: involvement of the GABAergic system and proinflammatory cytokines. Fundam Clin Pharmacol. 2016 Feb;30(1):14-22. doi: 10.1111/fcp.12166. Epub 2015 Nov 22. PMID: 26791997.

anti-inflammatory vs arthritis (Barros,2019) in vivo

Barros Silva Soares de Souza EP, Trindade GDGG, Lins Dantas Gomes MV, Santos Silva LA, Grespan R, Quintans Junior LJ, Cavalcanti de Albuquerque Júnior RL, Shanmugan S, Antunes de Souza Araújo A. Anti-inflammatory effect of nano-encapsulated nerolidol on zymosan-induced arthritis in mice. Food Chem Toxicol. 2020 Jan;135:110958. doi: 10.1016/j.fct.2019.110958. Epub 2019 Nov 9. PMID: 31715307.

anti-inflammatory vs colon (Raj,2020) in vtro, in vivo

Raj V, Venkataraman B, Almarzooqi S, Chandran S, Ojha SK, Attoub S, Adrian TE, Subramanya SB. Nerolidol Mitigates Colonic Inflammation: An Experimental Study Using both In Vivo and In Vitro Models. Nutrients. 2020 Jul 8;12(7):2032. doi: 10.3390/nu12072032. PMID: 32650602; PMCID: PMC7400891.

anti-inflammatory vs keratitis prevention (Yang,2020) in vivo, in vitro

Yang H, Wang Q, Han L, Yang X, Zhao W, Lyu L, Wang L, Yan H, Che C. Nerolidol inhibits the LOX-1 / IL-1β signaling to protect against the Aspergillus fumigatus keratitis inflammation damage to the cornea. Int Immunopharmacol. 2020 Mar;80:106118. doi: 10.1016/j.intimp.2019.106118. Epub 2020 Jan 9. PMID: 31926445.

anti-ulcer (Chan,2016) in vivo

Chan WK, Tan LT, Chan KG, Lee LH, Goh BH. Nerolidol: A Sesquiterpene Alcohol with Multi-Faceted Pharmacological and Biological Activities. Molecules. 2016 Apr 28;21(5):529. doi: 10.3390/molecules21050529. PMID: 27136520; PMCID: PMC6272852.

endometriosis reversal (Rauf,2018) in vivo

Rauf Melekoglu, Osman Ciftci, Sevil Eraslan, Aslı Cetin & Nese Basak (2018) The beneficial effects of nerolidol and hesperidin on surgically induced endometriosis in a rat model, Gynecological Endocrinology, 34:11, 975-980, DOI: 10.1080/09513590.2018.1469611

Neurological: Alzheimer's (Szwajgier,2019) in vitro

Szwajgier D, Baranowska-Wójcik E. Terpenes and Phenylpropanoids as Acetyl- and Butyrylcholinesterase Inhibitors: A Comparative Study. Curr Alzheimer Res. 2019;16(10):963-973. doi: 10.2174/1567205016666191010105115. PMID: 31660828.

Neurological: Parkinson's (Javed,2016) in vivo

Javed H, Azimullah S, Abul Khair SB, Ojha S, Haque ME. Neuroprotective effect of nerolidol against neuroinflammation and oxidative stress induced by rotenone. BMC Neurosci. 2016 Aug 22;17(1):58. doi: 10.1186/s12868-016-0293-4. PMID: 27549180; PMCID: PMC4994214.

Neurological: anxiolytic (De Carvalho,2018)(Goel, 2016) in vivo

De Carvalho RBF, De Almeida AAC, Campelo NB, Lellis DROD, Nunes LCC. Nerolidol and its Pharmacological Application in Treating Neurodegenerative Diseases: A Review. Recent Pat Biotechnol. 2018;12(3):158-168. doi: 10.2174/1872208312666171206123805. PMID: 29210667.

Goel RK, Kaur D, Pahwa P. Assessment of anxiolytic effect of nerolidol in mice. Indian J Pharmacol. 2016 Jul-Aug;48(4):450-452. doi: 10.4103/0253-7613.186188. PMID: 27756960; PMCID: PMC4980937.

Neurological: epilepsy treatment (De Carvalho,2018)(Kaur, 2016) in vivo

De Carvalho RBF, De Almeida AAC, Campelo NB, Lellis DROD, Nunes LCC. Nerolidol and its Pharmacological Application in Treating Neurodegenerative Diseases: A Review. Recent Pat Biotechnol. 2018;12(3):158-168. doi: 10.2174/1872208312666171206123805. PMID: 29210667.

Kaur D, Pahwa P, Goel RK. Protective Effect of Nerolidol Against Pentylenetetrazol-Induced Kindling, Oxidative Stress and Associated Behavioral Comorbidities in Mice. Neurochem Res. 2016 Nov;41(11):2859-2867. doi: 10.1007/s11064-016-2001-2. Epub 2016 Jul 14. PMID: 27418279.

Cytochrome inhibitors:

CYP1A2: https://www.pharmacytimes.com/publications/issue/2007/2007-11/2007-11-8279

CYP3A4: https://www.pharmacytimes.com/publications/issue/2008/2008-09/2008-09-8687

https://www.pharmacytimes.com/publications/issue/2015/december2015/drug-interactions-with-cyp3a4-an-update

Anecdotes:

Some anecdotes about friends and family who have used the essential oil and hydrosol:

- In early November of 2019, we flew south for a family vacation and caught what seemed like the flu at an amusement park. But it was much worse than any flu I'd had before. My chest was tight and could barely breath. Chills and fever. I had taken some DC essential oil with me and used 3 drops in a large cup of coffee twice a day for several days. After that, I was doing well with no symptoms. Later, I had to wonder if that was covid due to the severity.

- During a conversation about devil's club, one of my friends mentioned that he had painful arthritis on his hand with swelling and very limited mobility. I suggested soaking it in hydrosol a little while to help with the pain. He decided to put an exam glove on his hand and a tablespoon of hydrosol to soak overnight for 5 nights. The swelling and pain went away for about 30 days. He also found that a single drop of essential oil in coffee relieved anxiety and he would use it whenever he was feeling out of sorts.

- The manager of a local store has anxiety. She put a drop of essential oil in a quart of water (I told her it wouldn't mix with the water) and reported that it evened out her mood- not like a high, just mellowed.

- A family friend has severe arthritis that caused continual pain and his hands had begun to swell. A 2% dilution of the EO in olive oil applied topically reduced the pain immediately and reduced the swelling overnight.

- An elderly friend of my mother's is on a pain pump for severe chronic pain. A 3% dilution in olive oil applied topically immediately stopped the pain and the relief lasted 6 hours. He reports that the devil's club essential oil is as effective as CBD oil, but takes effect much more quickly.
- A friend of the family had swelling on his hands. 3% dilution in olive oil applied once daily for 3 days completely reduced the swelling.
- An elderly friend had chronic stabbing foot pain that caused her to lose sleep. A 3% dilution in olive oil relieved the pain. She reports that each time the pain returned, it was less severe- and that the essential oil seemed to be healing it. She also reports that nothing else she had tried would help the pain.
- A coworker was smelling the essential oil and inadvertently rubbed the top of the jar on her wrist. She reported that just that small amount of neat oil took away her carpal tunnel pain for 3 weeks. She is an executive assistant who does a large amount of typing. She also uses a couple drops of a devil's club tincture made by local artisans internally as a part of her daily regimen. She began putting one drop of the essential oil in a bottle of tincture and reports that she feels more alert and als that she and her siblings who have also been taking it haven't had any ailments in 9 months.
- A very elderly friend reported that whenever she cut her skin, it would take 2 weeks to heal. A single treatment of one drop of neat essential oil on a cut on the hand healed in 3 days. She routinely reported that a 3% dilution applied topically would help the swelling in her knee and legs allowing her to walk.
- A friend reported a benign growth, which he treated with 3% dilution topically for 3 weeks. The size of the growth after treatments was half its original size.

- A coworker reports that her mother had fallen last spring and tried different medications for chronic pain relief and swelling over a period of 6 months. After 3 days of massage using 3% dilution of essential oil, she reports no swelling and no pain.
- One of my sons reported that a topical application of 3% dilution to the temples, forehead, and neck relieved his migraine headache after an hour.
- My wife has used the hydrosol in a foot soak and also in a bath for high blood sugar and has used the essential oil topically for headaches, sinus infections, chest congestion, anxiety, muscle pain, uterine cramps, and lowering glucose levels. Taking it internally makes her nauseated.
- I had the beginnings of a sinus infection resulting from mold exposure. 2 sessions of 10 slow deep breaths of the essential oil vapor spaced one minute apart stopped the infection and all symptoms after 10 minutes.