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Neryl Acetate: A Natural Compound with Promising Therapeutic Benefits

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ABSTRACT

Neryl acetate, a naturally occurring monoterpene ester, has gained significant attention due to its diverse pharmacological properties, including anti-inflammatory, antimicrobial, and antioxidant effects. This review aims to provide a comprehensive overview of the chemical properties, biological activities, and potential therapeutic applications of neryl acetate. The compound has been identified in various essential oils and exhibits promising bioactivity in preclinical studies. Additionally, its molecular mechanisms and pharmacokinetic profile are discussed to highlight its potential in drug development. This review compiles data from peer-reviewed journal articles, patents, and scientific reports retrieved from databases such as PubMed, google scholar, and Web of Science. Studies were selected based on their relevance to the chemical properties, biological activities, and therapeutic potential of neryl acetate. By summarizing recent advancements in research, this review underscores the significance of neryl acetate as a bioactive compound with potential applications in medicine and industry.

Keywords: Antimicrobial; Neryl acetate; Monoterpene ester; PubMed.

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INTRODUCTION

Neryl acetate is oxygenated hydrocarbon monoterpene, contributing to plant fragrance. Neryl acetate is a monoterpene ester having monoterpene alcohol (nerol) which is esterified with acetic acid. Monoterpenes ($C_{10}H_{16}$) are terpenes and contain two linked isoprene units (C_5H_8). They are responsible for the unique aroma and flavour of the plant essential oil. As neryl acetate is lipophilic volatile compound confirms that it is monoterpene ester (Ma et al., 2021). Neryl acetate have floral and fruity odour impression providing sweet rose-orange blossom notes and apple notes (Butnariu, 2021).

Neryl acetate is classified by the European Commission as an artificial food flavouring that can be used in food without endangering human health. Therefore, neryl acetate due to its flavouring properties become a common component for food and beverage industry. Generally, neryl acetate is obtained from plants with the aid of vacuum distillation. However, this method is not usually preferred for its production at high scale due to tight supply and expensiveness of this procedure (Khan et al., 2024; Sha et al., 2022). Plant essential oils contain Npp from which the monoterpene derivative neryl acetate originates (Yang et al., 2024).

Neryl acetate impart rose and orange flower scent. At first, it is refreshing and sharp followed by sweet honey flavour with subtle raspberry notes (Merabet-Khelassi, 2023).In the pharmaceutical field, acne vulgaris treatment is positively effective by neryl acetate (Singh et al., 2022). In the feed industry, neryl acetate proved to be a safe fodder flavouring for animals by EU Food Safety Authority (on Additives et al., 2021). Moreover, *Sitophilus zeamais* is controlled by neryl acetate due to its insecticidal activity at certain concentrations (Wang et al., 2024). By broth microdilution assays, neryl acetate was identified as the main component with antimicrobial effects against *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Haemophilus parainfluenzae* (Goh et al., 2022).

METHOD OF PREPARATION

Neryl acetate is a natural compound and can be synthesised by various method.

Preparation of neryl acetate from nerol

Neryl acetate is synthesized from transesterification reaction of nerol and ethyl acetate, using Novozyme 435 as catalyst. High yield of 92.1% neryl acetate is obtained, making this enzyme catalysed reaction a reliable method. This solvent free system does not require any organic solvent therapy, thus reducing waste production. For optimization of reaction conditions, response surface methodology (RSM) is used (Jiang, 2020).

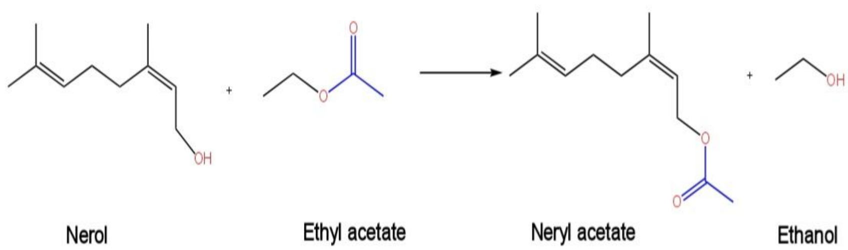

Figure 1: synthesis of neryl acetate from nerol and ethyl acetate.

Neryl acetate production by reacting nerol with acetic anhydride through esterification reaction in a solvent free system involving ion exchange resin namely Lewatit® GF 101 which heterogenously catalyze the reaction. This solid ion exchange resin is porous, which provides large surface area. Also, the presence of sulfonic groups facilitates this reaction (Zeferino et al., 2021). High conversion yield of nerol into neryl acetate and reusability of ion exchange resin makes this method valuable in industrial scale production of neryl acetate (Zeferino et al., 2022).

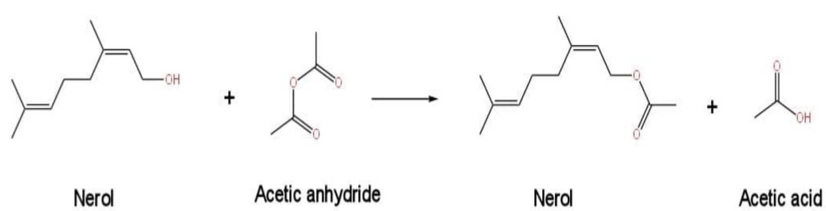

Figure 2: synthesis of neryl acetate by the reaction of nerol and acetic anhydride.

Production of neryl acetate from the transesterification reaction of vinyl acetate and nerol, using immobilized *Candida albicans* lipaseas catalyst in non-aqueous phase. Vinyl acetate is a solvent that behaves as an acyl donor. The conclusions show that this reaction follows a ping-pong bi-bi mechanism, which includes the sequential manner binding of enzyme to the substrate(Abdelgawad et al., 2022; Liaquat et al., 2024). For optimization of reaction conditions, RSM is used. 98% of high yield neryl acetate is obtained, making this method valuable in industrial-scale production of neryl acetate(Sun et al., 2022).

Preparation of neryl acetate From *E. coli*

Escherichia coli is genetically engineered to produce neryl acetate. First, genes involved in mevalonate pathway are introduced in *E. coli* for the synthesis of isoprenoid precursor of neryl acetate. Second, the introduction of the nerol synthase gene in *E. coli* favours the production of nerol from the isoprenoid precursor of neryl acetate (Lei et al., 2021).

Third, the introduction of acetyltransferases gene into *E. coli*, expressing alcohol acetyltransferases (ATF1) from Saccharomyces *cerevisiae*, which enables the synthesis of neryl acetate from nerol via acetyl CoA (Wang et al., 2023).

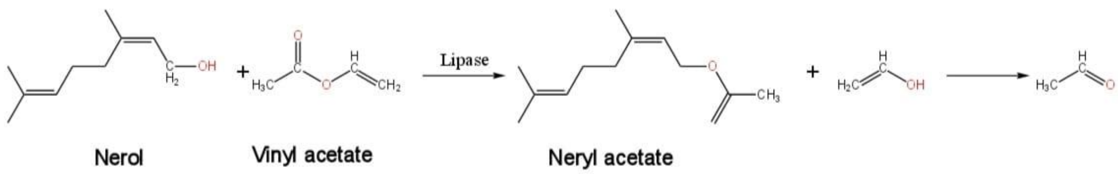

Figure 3: Neryl acetate synthesis from nerol and vinyl acetate.

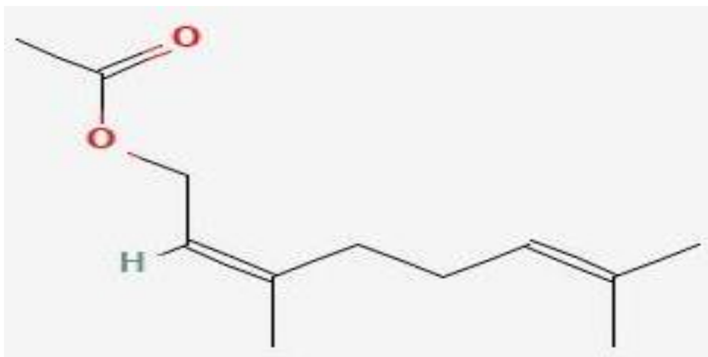

Figure 4: IUPAC name: (2E)-3,7-dimethylocta-2,6-dienyl] neryl acetate.

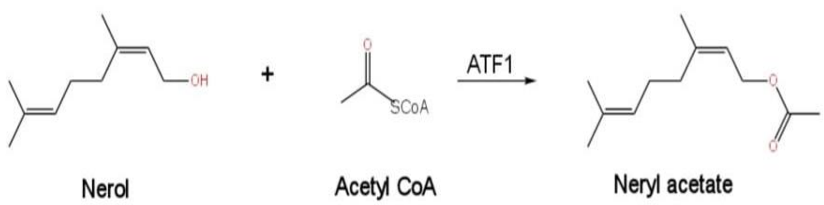

Figure 5: Neryl acetate synthesis from nerol-biosynthesizing E. coli strain.

Preparation of neryl acetate from nerol from plants

Neryl acetate is a natural compound found in various plant species and can be isolated through different methods. Some of them are following.

Table 1: Method of isolation of neryl acetate from selected plants.

Method of isolation	Plant
Hydrodistillation	*Helichrysum italicum* (Lemaire et al., 2023).
Steam distillation	*Salvia sclarea* (Acimovic et al., 2022).
Supercritical Fluid Extraction	*Dracocephalum moldavica* (Morshedloo et al., 2021).
Solvent Extraction	*Jasminum sambac* (Makeri and Salihu, 2023).
Headspace solid phase microextraction	*Rosa damascene* (Erbas and Baydar, 2016).
Vacuum distillation	*Citrus bergamia Risso* (Bozova et al., 2024).

Pharmacological activity

Fragrance and flavor

Neryl acetate is the major constituent contributing to the floral fragrance of *Rosa rugosa*, present majorly in petals of these plants. Neryl acetate fragrance here play role in pollination (Singh et al., 2023). Neryl acetate also contributes in the floral fragrance of *Rosa hybrida* (Feng et al., 2022).

Neryl acetate is one of the main component present in genus *Chaenomeles* and involved in their fruity, sweet, and floral aroma and flavour (Moneva et al., 2023). Neryl acetate is safe for flavouring food, and also considered a safe flavour in perfumery and other personal care products (Pierson et al., 2021).

Table 2: Chemical Composition, Concentrations, and Pharmacological Effects of Selected Medicinal Plants containing neryl acetate.

Plants	Concentration of NA	Pharmacological effects
Helichrysum italicum	33.80%	Improve skin barrier function and retain moisture in various conditions of skin (Lemaire et al., 2023) and show Antimicrobial activity (Mollova et al., 2020).
Pastinaca hirsuta	28.41%	Biofungicide (Semerdjieva et al., 2024).
Helichrysum amorginum	17.5%	Antimicrobial Activities (STAVROPOULOS et al., 2024).
Pelargonium graveolens	10.5%	Antiviral effect (Senthil Kumar et al., 2020).
Eupatorium cannabinum leaf	9.4%	Antioxidant and toxic activities (КІНІЧЕНКО).
Lavandula angustifolia	6.1%	Inhibition of glucosidase (Najibullah et al., 2021).
Abis holophylla	6.08%	Antibacterial activity (Ham et al., 2020).
Dracocephalum moldavica	2.75% 5.1-8.82%	In flavours and perfumery, it is used to impart floral and fruity aromas (Rezaei-Chiyaneh et al., 2021).
Murraya koenigii	3.45%	antibacterial and antioxidant activity (Abuga et al., 2020).
Citrus medica	2.51%	Anti-oxidant effect (Husni et al., 2024).
Coriandrum sativum	2.3-14.2%	Antioxidative and antimicrobial effect (Mahleyuddin et al., 2021).
Toddalia asiatica	1.8%	Antioxidant effect (Lobine et al., 2021).
Cananga odorata	1.31%	Antidepressant activity (Borgonetti et al., 2022).
Ocimum basilicum	1.24%	Antibacterial activity (Dhama et al., 2023).
Citrus reticulata	1.1%	Antimicrobial (Ali et al., 2021) and antiatherogenic agent (Castro et al., 2020).
Citrus aurantium	0.13%(flower) 0.10% (leaf)	Antianxiety and Antispasmodic effect(Zakerimehr et al., 2023).
Citrus limon	0.08%(flower) 0.93%(leaf) 0.43%	Mild inhibitory effect on tyrosinase leading to mild prevention of hyperpigmentation (Capetti et al., 2021). Protective and antioxidant on aspirin induced toxicity (Lokuge, 2020).
Rosa damascena	0.1%	Antioxidant and effective in the treatment of face Pigmentation (Hadipour et al., 2023).
Eupatorium fortunei Turcz	0.132%	Anti-influenza activity (Nan et al., 2021).

Effect in skin

Neryl acetate is the major component of Corsican Helichrysum italicum essential oil (HIEO). Corsican HIEO is known to enhance skin barrier functions by increasing the expression of differential gene complex including involucrin, skin proline rich proteins, late cornified envelope, S100 protein family. The effect of neryl acetate and Corsican HIEO were separately tested on skin explant model for 24 hours and 5 days to determine how much neryl acetate contribute in HIEO for enhancing skin barrier functions. Results were analysed by various methods. According to transcriptomic analysis, neryl acetate contribute 41.5% in HIEO regulated genes and quantitative reverse transcription PCR analysis was used to confirm the selected panel of genes involved in enhancing skin function. Skin barrier protein immunofluorescence showed the upregulation of involucrin, a protein precursor for the formation of cornified envelope. Lipid chromatography-mass spectroscopy used for lipid staining and ceramide analysis showed that total lipid and ceramide content was increased at the end of experiment. In conclusion, neryl acetate contribute the major part in HIEO for skin barrier formation (Lemaire et al., 2023).

Insecticidal activity

Neryl acetate along with other monoterpenes was tested against Sitophilus zeamais Motschulsky for showing insecticidal activity. These monoterpenes were obtained from essential oils of different plants. Neryl acetate was tested at 10µ, 20µ and 30µ against 33 individuals of Sitophilus zeamais Motschulsky. The mean mortality rate was observed after 24, 48, 72 and 96 hours. After 24 hours, neryl acetate showed 0%, 14.14% and 22.22% at 10µ, 20µ and 30µ, respectively. After 48 hours, neryl acetate showed 14.14%, 41.41% and 55.56% at 10µ, 20µ and 30µ, respectively. After 72 hours, neryl acetate showed 55.56%, 81.82% and 92.93% at 10µ, 20µ and 30µ, respectively. After 96 hours, neryl acetate showed 72.73%, 96.97% and 100%, respectively. In conclusion, neryl acetate is considered to be strong insecticidal agent (Langsi et al., 2020). The insecticidal activity of neryl activity was also supported by its larvicidal and adulticidal activity against West Nile vector Culex pipiens (Yezli et al., 2024). Also, neryl acetate show some fumigant toxicity against the peach aphid (Myzus persicae Sulzer) (Zhou et al., 2021). Also, Neryl acetate show noticeable toxicity in in vitro assays against brine shrimp larvae (Judzentiene et al., 2022).

Antiatherogenic effect

The antiatherogenic effect of Citrus reticulata peel oil containing neryl acetate was studied HepG2 human-hepatoma and RAW 264.7 cells. By molecular Docking Analysis, neryl acetate along with other compounds was found to inhibit lanosterol synthase, which is an important enzyme involved in pathway of cholesterol biosynthesis. This inhibition leads to hypo lipogenic effects due to reduced cholesterol synthesis in hepatic cells. Neryl acetate synergize with other compounds to reduce the expression of receptor involved in lipid uptake known as CD36. This reduces the accumulation of lipid in RAW 264.7 macrophage-derived foam cells which contributes to atherosclerotic plaque formation. Neryl acetate also prevent the peroxidation of Low-Density Lipoprotein (LDL), contributing to antioxidant and antiatherogenic effect of peel oil as oxidized LDL is involved in the development of atherosclerosis. Reduced LDL in body highly reduces the chance of development of atherosclerosis, promoting cardiovascular health (Castro et al., 2020).

Antimicrobial effects

Antimicrobial effects of terpenes and terpenoids isolated from Helichrysum italicum essential oil was studied against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Candida albicans. Disc diffusion test and minimum inhibitory concentrations against microbes were observed in this experiment. The results stated that Helichrysum italicum essential oil show antimicrobial effect due to the synergistic effect of oxygen containing monoterpenes including neryl acetate and other multiple constituents. The combined effect of various compounds including neryl acetate show high antimicrobial efficacy against above microbial strains (Mollova et al., 2020; Węglarz et al., 2022). By broth microdilution assays, neryl acetate was identified as the main component with antimicrobial effects against Pseudomonas aeruginosa, Streptococcus pneumoniae, Haemophilus influenzae, and Haemophilus parainfluenzae (Goh et al., 2022).

Essential oils which have neryl acetate in high amount have antimicrobial activity, specially against Staphylococcus aureus and Candida albicans. They are also effective against both gram-positive and gram-negative bacteria but comparatively more effective against gram positive bacteria. For instance, Helichrysum italicum essential oil having neryl acetate exhibit antimicrobial activity (Aćimović, 2023). Moreover, Neryl acetate together with borneol and carveol from essential oils of Abies holophylla and Pinus thunbergii leaves have strong antimicrobial activity against gram negative fish pathogens (Ham et al., 2020). Neryl acetate has been observed to show antifungal properties against Rhizoctonia solanii (Achimón et al., 2022).

Cytoprotective effect

The protective effect of essential oil Citrus limon was studied against aspirin-induced toxicity in small intestine epithelial cells IEC-6 in rats. Aspirin is non-steroidal anti-inflammatory, which interferes with prostaglandin synthesis resulting in increased permeability of intestinal epithelial cells by causing mucosal damage and increasing acid release. Neryl acetate being one of the major components of Citrus limon essential oil synergize with other components in maintaining cellular integrity and function of IEC-6 cells leading to cytoprotective activity. They also play a role as antioxidant by neutralising free radicals and reducing oxidative stress induced by aspirin. Moreover, they reduce the activity of enzymes Superoxide Dismutase (SOD) and Catalase (CAT) which were increased by aspirin. Thus, neryl acetate as a part of Citrus limon essential oil plays role in cytoprotective and antioxidative activity (Lokuge, 2020).

Effect on anxiety induced facial spots

Patients with anxiety disorder often have the problem of facial spots at the same time. These facial spots are associated with high melanin synthesis promoted by anxious and nervous mood. Neryl acetate by acting on PI3K containing PIK3CA and PIK3CD genes lead to work against skin pigmentation, as they are the main targets against facial spots. Thus, neryl acetate is an effective compound against anxiety induced facial spots (Xin et al., 2022).

Antidepressant Effect

3D-ALMOND-QSAR Models was built to study the antidepressant and neuroleptic effect of neryl acetate and nine other compounds. Three receptors namely serotonin transporter (SERT) and 5-hydroxytryptamine receptor 1A (5-HT1A) for determining anti-depressant efficacy and dopamine D2 receptor for determining neuroleptic effect, were the main targets of this study. This Models predicted neryl acetate to be a ligand for SERT and D2 receptors while it did not show the predicted effect on 5-HT1A receptor. In addition, neryl acetate showed favourable ADME features including high membrane permeability leading to good intestinal absorption and CNS permeability. Also, it was found to be having no predicted toxicity. The predicted effects were then compared with the effect of drugs available clinically. These results indicate that neryl acetate is a safe anti-depressant and neuroleptic agent which can be prescribed to pregnant females and patients with comorbidities as an alternate treatment therapy against depression (Avram et al., 2021).

Effect on acne vulgaris

Neryl acetate is an effective compound for acne vulgaris treatment by targeting lipase. The study was conducted to show the effect of natural inhibitors including neryl acetate against acne vulgaris lipase which is involved in the growth of acne vulgaris by converting sebum lipid into fatty acids. In this study, the inhibitory effect was analysed by Molecular docking, MD simulations, and binding affinity analysis. By molecular Docking test, neryl acetate showed showed strong interaction with active site amino acids of lipase proteins. This high interaction stability was analysed by MD stimulation studies. This information was also supported by binding affinity analysis between active site of lipase and neryl acetate. Thus, neryl acetate is strongly recommended for the management of acne vulgaris clinically (Singh et al., 2022).

Antiviral effect

Neryl acetate, one of the major components of Geranium oil show antiviral activity against corona virus (SARS-COV-2). The study of Geranium and Citrus limon essential oil was done on Angiotensin-Converting Enzyme (ACE2) on epithelial cells. ACE2 enzyme is considered as an important target as it is the site of virus entry. Neryl acetate act by downregulating ACE2 enzyme expression without having cytotoxic effects on epithelial cells, thereby considerably reducing the viral entry into host. In conclusion, neryl acetate is ab important component useful in prevention and treatment of SARS-COV-2, a viral disease (Senthil Kumar et al., 2020).

Anti-neoplastic activity

A study explored the anti-neoplastic properties of Helichrysum Italicum essential oil, which was extracted via hydro distillation, focusing on its potential effect against B16F10 murine melanoma cells. Chemical analysis using Gas chromatography-mass spectrometry (GC-MS) showed bioactive components like neryl acetate, a-pinene and nerol where neryl acetate was present majorly about 33.97%. The essential oil exhibited significant anti-proliferative effects on B16F10 murine melanoma cells in a dose-and-time-dependent manner, with slightest cytotoxicity. Assessment of antioxidant activity by DPPH, ABTS, and FRAP assays was identified as a contributing factor to its bioactivity. These finding Helichrysum italicum as a promising source for developing anti-cancer therapies (Gismondi et al., 2020).

Antioxidant activity

The antioxidant activity of neryl acetate was analysed by using , cyclic voltammetry (CV) and square wave voltammetry (SWV) techniques (Judzentiene et al., 2022). Antioxidant activity was dominantly showed by neryl acetate acquired from Helichrysum italicum (Węglarz et al., 2022). Analysis of Salvia sclarea containing neryl acetate also showed antioxidant properties (Bhatia et al., 2023).

Anti-diabetic activity

Neryl acetate has been shown to inhibit the activity of a-glucosidase by binding to its active site (Najibullah et al., 2021). α - Glucosidase is an enzyme responsible for the breakdown of dietary sugars and enhances gastric emptying. Inhibition of α - glucosidase plays a key role in the management of type 2 diabetes by rapid glucose absorption from small intestine as well as regulate glucose spike in blood after meal (Hossain et al., 2020).

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