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Toward the use of nanotechnology to enhance the therapeutic effect of nerolidol.

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ABSTRACT

Research and development in pharmaceutical chemistry have been ongoing for several decades, but the poor solubility of lipophilic compounds in aqueous media is a persistent barrier to their absorption, bioavailability, and effectiveness. Nanotechnology is highly emerging nowadays in different fields ranging from medicine to engineering. Using nanotechnology in drug delivery is a highly promising strategy to overcome such limitations and enhance the therapeutic effect of natural and chemical agents. Nerolidol which is a natural sesquiterpene is highly potent active ingredient, but its hydrophobicity is limiting its duration of action as well as its therapeutic effect. Using nanotechnology to enhance nerolidol activity was studied recently. Using different nanoparticles in encapsulating nerolidol or in functionalizing it was shown to improve its activity. Agents with similar chemical structures were successfully delivered using different carriers but were not implemented to deliver nerolidol. This review aims to compare between different nano formulations that were previously studied to deliver nerolidol and suggest other nano formulations to be developed in the future.

Keywords: Nerolidol, Nanotechnology, Drug delivery, Hydrophopbic.

I. BACKGROUND

The knowledge and use of materials at dimensions between 1 and 100 nm are known as nanotechnology. Materials at the nanoscale can be devices, systems, structures, complexes, or composites. In fact, the physical and chemical properties of materials can change as their size is down scaled into smallerclusters which results in higher surface area to volume ratio and enormous percentage of atoms on the surface when compared their bulk origin. This have opened exciting new possibilities to solve great challenges in several areas, such as energy, environment, medicine and biology(1,2). Nanosized carriers overcome the limitations of traditional DD methods, leading to improved therapies for various diseases (3).

Hydrophobicity and oral drug delivery

Hydrophobic drugs are drugs having poor water solubility. Those drugs are not easy to be formulated using traditional known formulating approaches due to their problems including slow onset of action, bioavailability is poor following oral administration, lack of achieving steady state plasma concentration, and even unwanted side effects. Such drugs will result in higher or lower dose of the drug reaching the blood and poor patient compliance(4).

Nerolidol

Nerolidol (3,7,11–trimethyl-1, 6, 10-dodecatrien-3-ol), which is also called peruviol, is a sesquiterpene alcohol that occurs naturally in the essential oils of several plants with floral odors including Baccharis dracunculifolia(5,6). has methyl groups at the carbon positions 3, 7 and 11 and a hydroxy group at position 3 as shown below in **Error! Reference source not found.**. Chemically, twogeometric isomers of NR are available, trans and cis forms. It is a farnesane sesquiterpenoid, a tertiary allylic alcohol and a volatile organic compound(5–7).

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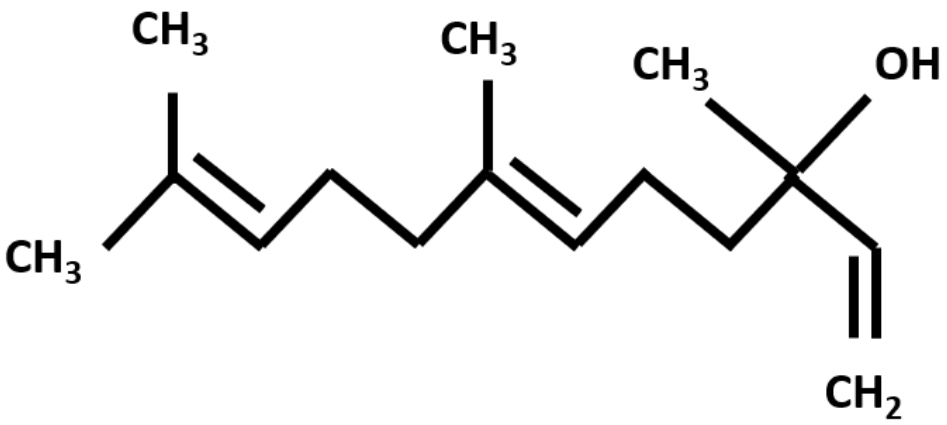

Figure 1: chemical structure of trans-Nerolidol

NR is still being explored by researchers, yet there is no definite dose of NR to be used, but up to 500 mg/kg of NR was proven to be safe during research on animals but to most common dose used is 200 mg/kg. NR was successfully given orally and intra-peritoneally in animals (8,9).

Effects of nerolidol

The effect of NR has been investigated and it was shown to have protective effects in different conditions and organs such as the heart and kidneys(10–12). Moreover, NR was shown to have anti-ulcer (7), anti-inflammatory (13,14), anti-Trypanosoma(15,16), anti-fungal (17,18), anti-malarial (19,20), anti-tumor (21,22) and skin permeation enhancing effects (23,24). Nerolidol was shown to have an antinociceptive activity with possible involvement of the GABAergic system, and anti-inflammatory activity, which attributed to the suppression of tumor necrosis factor-alpha (TNF-α) and interlukin-1β (IL-1β) proinflammatory cytokines in peritoneal inflammation (25). Nerolidol was also shown to have an antimicrobial activity against Staphylococcus Aureus, Candida Albicans and Escherichia Coli (26). Nerolidol was found to have an antioxidant effect via free radicals scavenging and lipid peroxidation inhibition which were effective in neuroprotection against Parkinson's disease(27,28). Moreover, nerolidol was shown to attenuate the loss of cardiac functions following hypertension-induced inflammation in acute cases(10). Nerolidol also was reported to have a reno protective effect in lipopolysaccharide (LPS)-induced AKI, it reduced the pathological injury, blood urea nitrogen (BUN) and creatinine (Cr) and inhibited the increase of TNF-α and IL-1β in LPS treated rats (11). In a thioacetamide induced kidney injury, nerolidol was shown to ameliorate oxidative damage in kidney tissue (12). Although nerolidol was found to be therapeutically effective in all previously mentioned areas, this effect was not with the full potency of nerolidol. This is due to the water in-solubility which leads to low plasma concentration and short circulation time.

Advantages of nanoscale drug delivery systems

The aim of nanotechnology in targeted DD and CR is to manage drug pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity and biorecognition of systems in the quest for improved efficacy in an improved manner. Nanoscale DD systems are considered powerful tools for imaging, diagnosis, and therapy due to their intrinsic properties (24). The intrinsic properties of nanomaterials include (26): ability to go through tiny capillary vessels due to their nano volume thus avoiding rapid clearance by phagocytes in the body and prolonging their availability in the blood stream, easily penetrate cells and tissue gaps to arrive at target organs such as the liver, kidneys, spleen, lungs, spinal cord and lymph glands, ability to demonstrate controlled-release properties using biodegradability, pH, ion and temperature sensibility of materials, and the ability to improve the utility of drugs and reduce undesired side effects.

Nano-formulations of nerolidol

NR functionalized gold nano particles (NR-AuNPs) by the reduction of chloroauric acid was successfully synthesized by Y. Jing, et al, and the results have shown an enhanced diabetic wound healing within a time of 14 days when compared to control group which took longer wound healing time upon topical application. This synthesis

process is considered environment friendly, this is due to the use of natural products as reducing agents(29). Baldissera et al has synthesized NSs loaded with NR using Eudragit polymer, the NSs was prepared according to the interfacial deposition of preformed polymer. These NPs were evaluated for their antimicrobial effect against T. evansi infected mice for oxidative stress, Na+, K+-ATPase and acetyl- cholinesterase (AChE) activities in brain tissue and S. agalactiae in the brain tissue of fish. Oral administration of NR-loaded NSs was able to reverse memory impairment, to prevent increased ROS and TBARS levels due to amelioration of Na+, K+-ATPase and AChE activities,protect the liver from the oxidative stress caused by T. evansi, activate the antioxidant enzymes, and increase the survival rates after T. evansi infection due to the enhanced therapeutic effect.

Therefore, nanoencapsulation increased the therapeutic efficacy of NR against T. evansi and can be used as an alternative treatment for T. evansi infection.The treatment also had potent bactericidal effects in terms of augmentation of fish longevity and survival, and reduction of brain microbial loads and against S. agalactiae-induced brain oxidative damage that contributed to disease pathogenesis(26,30–32).

El-hammadi et al, has successfully encapsulated NR in PLGA NPs using the nanoprecipitation and emulsion-solvent evaporation method, the formed NPs encapsulation efficiency was 55% and the therapeutic effect was enhanced (33). Nano-encapsulated NR inhibited neutrophils migration into joint cavity more efficiently compared with pure NR and control group by Barros silva et al. This was histological proved to have an improved anti-inflammatory effect on arthritis in mice by the quantification of pro-inflammatory and anti-inflammatory cytokines (34). Iqbal et al has developed nano-lipid carrier loaded NR dosage form which exerted significant neuroprotection compared to free NR. Due to its reduced particle size, it effectively crossed the blood brain barrier, increased its availability in the hippocampus and cortex and thus displayed neuroprotection treatment in a cyclophosphamide injury model in mice (35).

Future recommendations

Using biodegradable polysaccharides for the encapsulation of nerolidol was not previously investigated. Chitosan is a promising polysaccharide that was successfully used to encapsulate insulin for oral drug delivery(36). Therefore, using such a delivery system seems to be effective.

II. CONCLUSION

In conclusion, nerolidol is a natural product with high potency of different therapeutic effects. Unfortunately, due to the hydrophobicity of nerolidol, its therapeutic effect was short acting and with low potency. The encapsulation of nerolidol in nanoparticles, or the functionalizationof nerolidol with different nanoparticles is a promising approach for targeting sites of action, extending residence and release time, and increasing its bioavailability which in turn increases its therapeutic effect. Thus, the therapeutic effect of the drug is enhanced, and the side effects are minimized.

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