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Nanocarriers for Natural Therapeutics in the Management of Neuropathic Pain

Dhage Shivraj Sopan[1] and Dr. Pramod V Burakle[2]
[1]Research Scholar, Department of Pharmaceutics
[2]Research Guide, Department of Pharmaceutics
Sunrise University Alwar (Raj.) India

Abstract: *Neuropathic pain is defined by the International Association for the Study of Pain as "pain caused by a lesion or disease of the somato-sensory nervous system, which causes unpleasant and abnormal sensation, an increased response to painful stimuli (hyperalgesia), and pain in response to a stimulus that does not normally provoke pain (allodynia)." By limiting its scope to the somatosensory nerve system, this definition of neuropathic pain sets it apart from other forms of pain, such as musculoskeletal pain. It has been noted that intense and incapacitating pain is a common feature of documented neurodegenerative pain cases.*

Keywords: Nanocarriers, Neurotherapy, Natural Products, Pain Management, Euro Inflammation, Biodegradable.

I. INTRODUCTION

Neuropathic pain is defined as any injury or lesions in the somatosensory system (Jensen 2011). Neuropathic pain may result from a variety of disorders, including spinal cord injuries, brain injuries of any kind, and pain linked with many diseases, including diabetes, AIDS, multiple sclerosis, and cancer (Fig. 16.1) (Treede 2008). According to a study, 6.9–10.0% of the general population experiences neuropathic pain, and this percentage is expected to rise in the future due to a number of factors, including rising obesity rates, a growing geriatric population, and improved survival rates for cancer patients receiving advanced medical treatments (VanHecke 2014). One may refer to neuropathic pain as a chronic ailment.

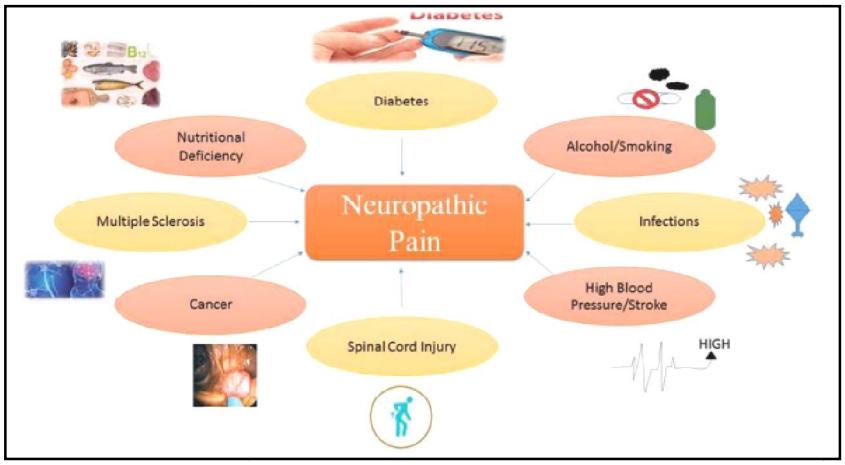

Fig. 1. Few listed conditions leading to neuropathic pain conditions

This strains healthcare institutions, people, and society (Smith and Torrance 2012). Managing neuro-pathic pain is challenging and tough because it demands a different therapeutic approach than nociceptive pain (Finnerup 2015). The Canadian Pain Society (CPS), the European Federation of Neurological Societies (EFNS), the National Institute for Health and Care Excellence and the International Association for the Study of Pain have published clinical practice guidelines to help diagnose and treat neuropathic pain.

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OPD treatment has three phases depending on pain severity. The first-line therapy includes calcium channel alpha-2-delta ligands like pregabalin and gabapentin, tricyclic antidepressants like amitriptyline, and SNRIs like duloxetine. According to Chris (2017), opioid and SNRI Tramadol is usually used as a second-line therapy for neuropathic pain. Tramadol withdrawal rates are higher than other drugs due to side effects, hence NICE recommends using it in rescue treatment. Strong opioids, anti-epileptics (excluding gabapentinoids), and cannabinoids are recommended for third and fourth-line neuropathic pain treatment. Pregabalin and carbamazepine are popular trigeminal neuralgia treatments (Cruccu and Truini 2017; Colloca 2017).

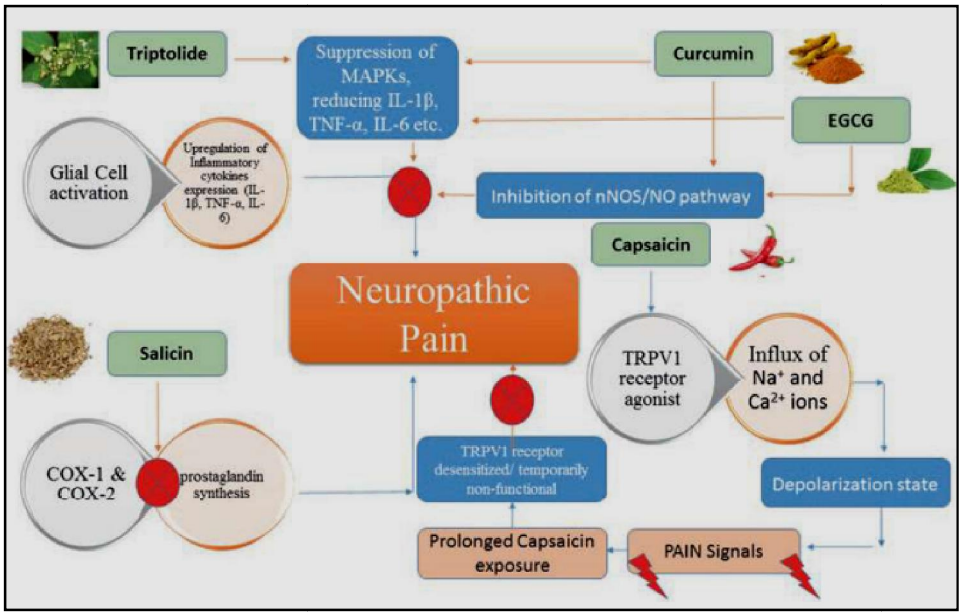

Fig. 2. Flowchart explaining the role of multiple phytotherapeutics in pain management

Globally, pain is rising (Garg and Adams 2012; Forouzanfar and Hosseinzadeh 2018). Plant-based compounds are being studied to alleviate neuropathic pain, such as capsaicin (Derry and Moore 2012). Acorus calamus, Artemisia dracunculus, Butea monosperma, Citrullus colocynthis, Curcuma longa, Crocus sativus, Elaeagnus angustifolia, Ginkgo biloba, Mitragyna speciose, Momordica charantia, and Antioxidant, anti-inflammatory, antiapoptotic, neuroprotective, and calcium inhibitory properties of herbal medications reduce pain (Fig. 16.2). Natural substances and nano-formulations for neuropathic pain are the focus of this chapter. Table 16.1 lists many phytocompound patents while Table 16.2 lists several commercially commercialized products.

II. MECHANISM OF ACTION

Transmembrane receptos-ion channel complex TRPV1 is the pain receptor that capsaicin agonistically activates. As a ligand molecule, capsaicin opens the TRPVI receptor, generating a rapid influx of Ca and No ions and depolarization. In A-delta and C nerve fibers, depolarization causes action potentials that send impulses to the brain and spinal cord as pain signals. TRPV1 is commonly expressed. Heat, tingling, itching, stinging, or burning are the early inflammatory symptoms. Capsaicin causes pain and analgesia. High and repeated capsaicin stimulation temporarily disables TRPV1 receptors, making them reffractory or insensitive. Harmful chemical, mechanical, or thermal stresses may impair receptor activity. Based on the data, the process is thought to be caused by the depletion of neuropeptides (Substance Px, particularly in nerve fibras that express TRPVI receptors) and the inhibition of both HVA and type calcium channels, which raises intracellular calcium ions. The delayed effect of rapid calcium influx in the tum desensitizes TRPV1 and activates many calcium-dependent proteins (Fattori 2016).

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PHARMACOKINETICS OF CAPSAICIN

The stomach and intestinal system absorb most of capsaicin, with absorption rates ranging from 50% to 90%, according to many studies. Within an hour of oral administration, Cor mean plasma concentration is achieved. The liver metabolizes capsaicin into three main metabolites: 16-hydroxycapsaicin, 17-hydroxycapsaicin, and 16.17-hydroxycapsaicin, with vanillin as a minor metabolite. Capsaicin is metabolized in the liver by P450 enzymes, according to research. The kidneys eliminate most capsaicin, however some is excreted in the feces as unchanged and glucuronide (O'Neill 2012). Intravenously or subcutaneously given capsaicin increases brain concentrations by five times and liver concentrations by three times. Capsaicin absorbs fast when applied topically. A clinical investigation found that capsaicin administered topically had a mean peak plasma concentration of 1.86 ng/ml and a maximum of 17.8. This shows that capsaicin given topically is unlikely to enter the circulation (Sayanlar 20123).

III. NANO-FORMULATIONS OF CAPSAICIN

Nagoth (2015) produced capsaicin-capped silver nanoparticles, 20–30 m in size, that were highly compatible with ABO blood types in the haemagglutination test, indicating therapeutic potential. Kaiser (2015) designed a capsaicin-loaded chito-san nanocapsule to increase paracellular transport by reversibly opening cellular tight junctions across an epithelial cell monolayer. Physiochemical properties of capsaicin-louded chitosan nanocapsules and free capsaicin were compared. Cytotoxicity to epithelial MDCK-C7 cells, tight junction integrity, membrane permeability, and cellular uptake were assessed. MDCK-C7 cells absorbed nanocapsules and regulated capsaicin-tight junction interaction. Mradhula (2017) synthesized PLGA-coated capsaicin magnetic nanoparticles (PCMN) and observed their characteristics in vitro using solvent evaporation/co-precipitation. The 10–20 am nanoparticles had 89.15% encapsulation efficiency (EE) and 9.29% drug loading. In vitro dissolution tests revealed increased capsaicin solubility (20 a 3% for pure capsaicin, 83 ± 4.15% release after 50 h for PLGA-coated capsaicin magnetic nanoparticles) due to their nanosize. Mei (2015) constructed a capsaicin-coded nanoparticle gel using hot-solvent high-pressure homogenization and optimized it using Bo-Behnken Design in vitro and in vivo.

IV. SALICIN

Salicin is a member of the glycoside class and serves as a building block for the production of ace-tylsalicylic acid. Willow (Sales) barks are a common source of salicin, which has been shown to have anti-inflammatory effects on humans. Salicin is also present in the leaves of willows and other poplars, as well as in the bark of popular species. In addition, it has antipyretic, antiseptic, analgesic, and disinfecting properties. It works in a manner somewhat similar to aspirin. Willow bark is used to relieve back pain and persistent headaches instead of aspirin. Singh (2003) and Art (2009)

V. MECHANISM OF ACTION

Salicylic acid's mode of action is same to that of aspirin molecules. The substance prevents the production of prostaglandins by inhibiting the cyclooxygenase enzymes (COX-1 and COX-2) (Rao and Knaus 2008: Raju 2015). Both direct and peripheral actions on the central nervous system cause the analgesic effect. According to reports, salicylicin works centrally on the hypothalamus to provide analgesia, while in the periphery it inhibits the production and release of prostaglandins. Natural salicin has an advantage over aspirin since white willow doesn't affect coagulation. This is the main disadvantage of using aspirin (Dissanayake 2017; Vase and Botting 2003).

VI. PHARMACOKINETICS OF SALICIN

When taken orally, salicin is rapidly and highly absorbed. After being quickly absorbed into the bloodstream and transported to the liver, where it is first hydrolyzed into salicylic acid, then into salicyluric acid (after conjugation with the glycine moiety), and finally to glucuronic acid, the intestinal flora converts sali-cin to saligenin. The primary excretion occurs in the kidneys as glucuronic acid or salicylic acid (Maclagan 1879; Schmid 2001; Wagner and Heide

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2003). The precise dose form, the salicylate utilized, and other variables like the tablet's rate of dissolution and the intraluminal or gastric pH may all affect its pharmacokinetic characteristics. Salicin has a 99.5% plasma protein binding rate (with albumin) and a T or plasma half-life of around 15 minutes, which increases when dosage is raised (300–650 mg have a Tof of approximately 3.1 hours, while 1-2 g of daily dosages have a Ta of approximately 5 hours, respectively, in the form of salicylate). Willow typically has a dosage of 60–120 mg (total salicin) per day, with a later start of effect and a longer duration of activity (Lewis and Johnson 2006).

VII. NANO-FORMULATIONS OF SALICIN

Delivery methods using nanoparticles have the potential to prolong the duration of the therapeutic action and improve medication stability. Shang (2018) used the interpolymer complexation approach to create chitosan (CS)-acetylsalicylic acid (ASA) nanoparticles. The produced nanoparticles were shown to have a pH-dependent, prolonged drug release. Furthermore, compared to crude acetylsalicylic acid, the produced nanoparticles had a better bioavailability and a longer circulation, according to early pharmacokinetic studies. Woo (2014) employed the melt emulsification method in conjunction with the ultrasonication approach to create salicylic acid-loaded stearic acid-oleic acid nanoparticles (SONs) in a cream-kused formulation for topical application. In vitro release tests revealed that SONs integrated with crean exhibited a consistent release for a whole day, indicating the incorporation of salicylic acid into the solid SON matrix and prolonging the in vitro release. Taghizadeh and Juvan (2010) used the emulsion approach to create chitosan nanoparticles that contained salicylic acid (SA). The drug concentration varied from 20% to 35%, and the nanoparticles were spherical with an average size of 300 mm.

IX. CONCLUSION

Several phytocompounds have been utilized to alleviate neuropathic pain. Any nerve injury causes neuropathic pain, a dangerous chronic condition that is hard to treat. Current analgesics include opioids and non-steroidal anti-inflammatory drugs, which are ineffective in reducing neuropathic pain. Opioids may cause addiction, seizures, and respiratory depression. Tricyclic antidepressants and anticonvulsants reduce allodynia in neuropathic pain. However, these medications have several adverse effects, limiting their effectiveness in neuropathic pain therapy. Therefore, it's necessary to study alternative medications that may alleviate neuropathic pain without side effects. This helped researchers find a natural medication. Neuropathic pain may be treated using Creama longa, Camellia sinensis, Tripterygian um, and Capsicue species and their active compounds. We need further research to develop an effective natural neuropathic pain reliever.

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