UTT BioPharma
Treating Chronic Pain

With Cannabis-Derived Compounds

Authors

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Chronic pain is defined as pain which persists for more than 12 months, arising from injury or illness (National Institute of Health).

There are two generalised sub-classifications for Chronic Pain, nociceptive and neuropathic pain.

- Nociceptive Pain: Caused by inflammation or tissue damage, which activate nociceptors (specialised pain receptors).
- Neuropathic Pain: Caused by malfunction or damage to Central Nervous System e.g. neuropathic injury or psychological injury.
• Chronic Pain affects ~20% European Population which is approximately 148 Million people! (van Hecke et al., 2013)

• WHO collaborative study estimates worldwide prevalence of ~22% (Gureje et al., 1998), which amounts to approximately 1.5 Billion People who suffer from chronic pain!

• The Market for Chronic Pain can be estimated at $7.5 Trillion and upwards (setting a baseline $5,000 per annum treatment cost per person)
Current pain treatments and their shortfalls

- Opioids e.g. morphine, codeine, fentanyl, oxycodone, hydrocodone have a market share of $12 Billion
  
  However they are riddled with side effects such as nausea, vomiting, constipation and respiratory depression. There are also the complications of tolerance and abuse associated with opioids (Compton and Volkow, 2006).

  Opioids are over and inappropriately prescribed. This is an epidemic in Australia, North America and Europe.

  There are also many pain conditions which are opioid resistant! (MacDonald, 1991)

- Gabapentenoids e.g. Gabapentin
  
  Only useful for neuropathic pain treatments

- NSAIDS e.g. Paracetamol, Ibuprofen, Aspirin
  
  Only efficacious in inflammatory conditions, often provide minimal relief in many chronic pain conditions
• Ancient Roman Physician Claudius Galen (ethnically Greek) mentioned the use of Cannabis for treating pain associated with various conditions

• William Brooke O'Shaughnessy brought the use of Cannabis into Western Medicine after his time in India, where it was frequently used. He was impressed by the favourable toxicology (after the toxicity experiments on goats and dogs) and cannabis preparations as analgesics in pain

• Queen Victoria’s personal Physician J. Russell Reynolds called “Indian hemp, when pure and administered carefully, is one of the most valuable medicines we possess” and reported hemp treatment to be the only successful treatment for a patient with “neuralgia of the lower branches of the nerve”(Reynolds, 1890).
• CB₁ receptor is prevalent in Central Nervous System.

• In the context of Pain, CB₁ is distributed in supraspinal (thalamus, amygdala, and periaqueductal grey matter), spinal (dorsolateral funiculus, in the surroundings of the central canal and in the superficial dorsal horn) and peripheral areas involved in the pain pathway.

• CB₁ activation attenuates primary nociceptive synaptic transmission (Manzanares et al., 2006) and increases the descending inhibitory pain modulation stemming from the Periaqueductal grey matter (Finn et al., 2003).

• CB₁ upregulation in chronic neuropathic pain pathologies (Siegling et al., 2001)-scope for increased analgesic effect!
• CB₂ receptors are majorly present on inflammatory cells

• In inflammatory states, immune cells are activated and release inflammatory mediators that sensitize nociceptors.

• CB₂ activation causes the decrease in pro-inflammatory cytokines (Rice et al.) and subsequently the suppression of persistent pain states which arise from inflammation.

Source: Corbus Pharmaceuticals
• Cannabinoids can activate or block many other receptors and ion channels
  • $\text{Ca}^{2+}$ Channels: L-type, N-type, P/Q type, T-type
  • $\text{Na}^{2+}$ Channels: Nav1.1, Nav1.2, Nav1.5
  • Serotonin: 1a, 2a and 3
  • $K^+$ Channels: K-ATP, TASK-1, TASK-3, TREK-1, Kv1.2, Kv1.5, Kv3.1, Kv4.3
  • Nuclear: PPAR$\alpha$, PPAR$\beta$/δ, PPAR$\gamma$
  • TRPs: TRPV1-4, TRPA1, TRPM8
  • Opioid Receptors: $\mu$, δ

• Orphan Receptors: GPR55, GPR119, GPR18, GPR30

• More research with Cannabinoids could help to characterize orphan receptors
• CB₁ and CB₂ partial agonist
• Synthetic preparations of Δ⁹-THC (Nabilone and Dronabinol) have been tried for chronic pain.
• Nabilone produced significant analgesic effects in spinal pain, fibromyalgia and spasticity related pain. (Lynch and Campbell, 2011)
• Dronabinol led to significant reduction in central pain in Multiple Sclerosis (Lynch and Campbell, 2011)
• However due the risks of cognitive impairment in administering pure Δ⁹-THC (debatable), Nabilone and Dronabinol have very restricted access (mainly for anorexia treatment in HIV/AIDS patients)
Cannabidiol (CBD) has shown to reverse the cognitive affects of Δ⁹-THC (Bhattacharyya et al., 2010)

Cannabidiol also has anti oxidant and anti-inflammatory properties which are valuable properties to treat pain (Booz, 2011).

Sativex: a 1:1 formulation produced by GW Pharmaceuticals, approved in Canada for the treatment of Neuropathic Pain. It is Phase II and III for some other pain conditions

Sativex has shown favourable efficacy in various chronic pain conditions (Russo et al., 2007), and Δ⁹-THC and CBD compliment therapy.
Currently 105 phytocannabinoids have been isolated from Cannabis, many with different affinities to the Cannabinoid receptors. In total there are 545 compounds that have been isolated from Cannabis.

Examples of the pharmacological actions of other compounds:

- **CBDA**: TRPA1 partial agonist, TRPV1 partial agonist, TRPM8 antagonist
- **CBG**: CB1 and CB2 partial agonism, TRPA1 agonist, TRPV1α, TRPM8 antagonist
- **THCA**: TRPA1 partial agonist, TRPM8 antagonist
- **THCV**: CB1 antagonist, CB2 partial agonist
- **CBC**: TRPA1 agonist
- **CBN**: CB₁, CB₂ and possibly more

There is a need to study the actions of each compound in more depth, particularly in experimental models of chronic pain.
• Other than the cannabinoids, active Terpenes and Flavonoids are present in Cannabis.

• These compounds are also present in other plants, and are often used in other herbal remedies and medicines.

• **Beta-Myrcene** is a compound also present basil essential oil, with anti-inflammatory properties and analgesic properties.

• **Limonene** is a compound present in lemon extracts, shown to have anti-inflammatory and gastro-protective properties.

• **Alpha-pinene** is a compound present in ginseng plants from China, has anti-inflammatory and antioxidant properties.

• There is anecdotal evidence suggesting Terpenoids enhance central Cannabinoid action, possibly by facilitating greater Blood Brain Barrier intrusion of Cannabinoids

**Cannabinoids and Terpenoids in could be used in synergic therapies to provide therapeutic relief to many various diseases and disorders, particularly chronic pain**
Investigation of Anecdotes, Herbal Remedies and Historical Medical Uses

Pharmacological, pre-clinical and clinical rationale

Registered therapies with controlled dosage and administrative properties
Future Directions

- Throughput analysis of Cannabis, the various strains and the omnipresent active compounds present in the plant
- Screening of each potential compound (affinity to the right receptors) within various experimental models of pain, examining synergic affects as well
- Cell based assays (GPCRs, TRPs etc) as well as pain assays to evaluate components.
- Large Scale clinical trials? Possibly using Cannabis-derived therapeutics as conjunctive or replacement drugs.
- Favourable interactions have been seen with opioids, with increases in efficacy (Abrams et al., 2011) More investigation is required in the form of large scale clinical trials


• REYNOLDS, J. R. 1890. ON THE THERAPEUTICAL USES AND TOXIC EFFECTS OF CANNABIS INDICA. *The Lancet*, 135, 637-638.


