



Editorial: Application of Plant Secondary Metabolites to Pain Neuromodulation

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Editorial on the Research Topic

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Pain is a highly unpleasant and intolerable condition, which is associated with multiple diseases and disorders, including but not limited to cancer, diabetes, infectious diseases, neurological and dysfunctional disorders, etc (Li et al., 2019; Yang, 2019; Singla et al., 2020). Further, tissue damage or chronic disease of the somatosensory nervous system cause neuropathic pain, which impacts and disturbs life to a higher extent (Pu et al., 2019; Finnerup et al., 2020). Natural resources especially plants have served and contributed several potential drugs for the alleviation and treatment of pain, either directly or in the derived form (Singla et al., 2018; Santos et al., 2019). For instance, the standard drugs like morphine, cannabidiol, acetylsalicylic acid are some of the key examples gifted by the nature. Even regular and healthy dietary food contains many phenolic compounds that elicit the potential to be anti-inflammatory (Laganà et al., 2019). Thus, in the present research topic, we further emphasized and collected the articles which fill the knowledge gap in this domain.

Brugnatelli et al. (2020) in their article “Irritable Bowel Syndrome: Manipulating the Endocannabinoid System as First-Line Treatment” described the role of the endocannabinoid system (ECS) in irritable bowel syndrome as ECS controls the gut homeostasis and explained how it is an efficient target to do the first-line treatment (Russo, 2016; Zhang et al., 2020). They briefed about the endocannabinoids like anandamide, 2-arachidonoyl glycerol, etc where the former was regulating the appetite and energy balancing while the latter was more involved in the general hunger signal (Di Marzo and Matias, 2005; Acharya et al., 2017). Further, they have also elaborated why menthol, an important phytoconstituent of peppermint oil is effective in IBS treatment.

Uddin et al. (2020) have reviewed the potential of flavonoids for the treatment of neuropathic pain and covered it in their article “Exploring the Promise of Flavonoids to Combat Neuropathic Pain: From Molecular Mechanisms to Therapeutic Implications”. They have comprehensively reviewed and documented how various flavonoids carries the potential to decrease and alleviate various neuropathic pain like that of diabetic neuropathy, chemotherapy-induced peripheral neuropathy, spared nerve injury, thermal hyperalgesia, sciatic nerve ligation-induced neuropathic pain, and sciatic nerve chronic constriction injury. They cited that flavonoids are multimodal and act by different mechanisms viz. inhibiting the reduction of antioxidant defense, decreasing oxidative stress, inhibiting PARP over-activation, inhibiting cellular injury and mitochondrial dysfunction processes, and inhibiting glial cells activation and neuroinflammation.

Jin et al. (2020) in their research article “Lipoxin A4 Inhibits NLRP3 Inflammasome Activation in Rats With Non-compressive Disc Herniation Through the JNK1/Beclin-1/PI3KC3 Pathway” have

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studied the lipoxin modulated molecular mechanisms associated with inflammation in female Sprague-Dawley rats having non-compressive disc herniation. The test analog of lipoxin, LXA4 was compared with standard LY294002 (phosphoinositide-3 kinase (PI3K) inhibitor) alone or in combination with the test drug. Results indicated that LXA4 was a potential agent leading to an increase in the pain threshold, decrease in the proinflammatory cytokines like TNF- α , IL-1 β , and IL-18, while increasing the anti-inflammatory mediators like IL-4, IL-10, and TGF- β as well as autophagy-related proteins like MAP1LC3B, Beclin-1, and PI3KC3.

Boccella et al. in their research article “Treatment With 2-Pentadecyl-2-Oxazoline Restores Mild Traumatic Brain Injury-Induced Sensorial and Neuropsychiatric Dysfunctions” evaluated the effect of 2-pentadecyl-2-oxazoline (PEA-OXA) which is a natural product, on the mild traumatic brain injury (mTBI) induced in the male C57BL/6J mice. PEA-OXA was found to be the adrenergic α -2 antagonist, with the potential to restore and reverse all the effects of mTBI i.e. behavioral changes like depression, the cortical GABA levels, and neuronal activity.

Chia et al. in their research article “Zerumbone Modulates α 2A-Adrenergic, TRPV1, and NMDA NR2B Receptors Plasticity in CCI-Induced Neuropathic Pain *In Vivo* and LPS-Induced SH-SY5Y Neuroblastoma *In Vitro* Models”, have studied the neuropathic pain-alleviating effects of zerumbone which is a bioactive compound obtained from the rhizome of *Zingiber zerumbet* (family Zingiberaceae). They reported that zerumbone is a multimodal molecule that elicits its anti-allodynic and antihyperalgesic effects by acting on various receptors viz. TRPV1, NMDA, α -1 adrenoceptor, α -2 adrenoceptor, β -1 adrenoceptor, β -2 adrenoceptor, and NR2B. They previously documented and validated the zerumbone involvement in the serotonergic system also.

Argueta et al. in their article “A Balanced Approach for Cannabidiol Use in Chronic Pain” briefly documented the use of cannabidiol in the treatment of chronic pain. Cannabidiol, contrary to the tetrahydrocannabinol which was another major metabolite of *Cannabis sativa*, is a non-psychoactive molecule and evidently recorded its potential use in intractable chronic pain. As the cannabidiol also possessed teratogenic effects proven through the preclinical studies as well as devoid of any long-term studies, authors recommended that the public should use a balanced approach while dealing with cannabidiol and should avoid any sort of drug abuse.

Assis et al. in their article “Antinociceptive Activity of Chemical Components of Essential Oils That Involves Docking Studies: A Review”, have systemically reviewed the computational studies which had been conducted on essential oil's chemicals for their detailed analysis of antinociceptive potential. The data was extracted from Science Direct and PubMed. They have categorized the various antinociceptive chemicals, software used for evaluation, as well as the

molecular targets and their interacting amino acids for eliciting the antinociceptive potential.

Uddin et al. have contributed another review article “Emerging Promise of Cannabinoids for the Management of Pain and Associated Neuropathological Alterations in Alzheimer's Disease” where they have comprehensively reviewed the potential and applications of various cannabinoids for pain management especially in case of Alzheimer's disease (AD). They cited in their article how pain via cascade pathways initiated at the locus coeruleus-noradrenergic system can lead to neuronal death and Alzheimer's disease. Further, they have well elaborated on how cannabinoids are functional in tackling various pathological conditions of AD.

Muñoz-Montesino et al. in their research article “Inhibition of the Glycine Receptor α 3 Function by Colchicine” have studied the potential inhibitory effect of colchicine and its mechanism involved while inhibiting the ion channel, α 3 subunit based glycine receptor (α 3GlyRs) which is primarily involved in the chronic inflammatory pain. They found that the orthosteric site of the α 3GlyR's closed state is the main binding site for this colchicine which was found to be the competitive antagonist for the target receptor.

Alberto et al. in the article “Molecular Modeling Applied to the Discovery of New Lead Compounds for P2 Receptors Based on Natural Sources” have comprehensively covered various natural products against P2Y and P2X classes of P2 purinergic receptors as well as elaboratively explained the potential role of various *in silico* tools in achieving the goals.

Singla et al. in their research article “Regulation of Pain Genes-Capsaicin vs Resiniferatoxin: Reassessment of Transcriptomic Data”, have bioinformatically reassessed the transcriptomic data covering the gene regulatory information of two natural products, capsaicin and resiniferatoxin which was earlier published by Isensee et al., (2014). They have found that resiniferatoxin was regulating more non-pain associated genes as compared to capsaicin when the filtering of the genes was done by two pain gene databases.

This research topic, thus covered one brief research report, one mini-review, one opinion, four original research, three reviews, and one systematic review article. In conclusion, it is indeed very clear that plant secondary metabolites are highly efficient in neuromodulating pain via multimodal pathways. Exhaustive exploration in the next step can lead to the development of more potent drugs with the least or minimal side effects.

AUTHORS CONTRIBUTIONS

RS, AG, and GZ have collectively conceived and wrote the text. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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