Figure 1. Graphical 3D representation of the binding modes of α -phellandrene with opioid receptors: A - Mu; B - Kappa; C - Delta

THU0452 ANTINOCICEPTIVE EFFECT OF α -PHELLANDRENE IN CHRONIC PAIN: IN SILICO PHARMACOKINETIC, MOLECULAR DOCKING AND IN VIVO EVALUATION

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Background: The pharmacological approaches of chronic pain are a challenge in the clinical context. Currently, only palliative treatments are performed. The α -phellandrene (α -phel) is a cyclic monoterpene found in essential oils of aromatic plants, which presents several biological activities, such as antinociceptive, antihyperalgesic and immunostimulant.^{1,2}

Objectives: This study aimed to investigate the action of α -phellandrene in chronic pain through *in silico* and *in vivo* approaches, aiming to develop a new therapeutic option for painful conditions, reducing analgesic doses and side effects.

Methods: The pharmacokinetic analysis of α -phel was performed by PreADMET online server. The software ACD/ChemSketch 14.0 was used to optimize the 3D structure of α -phel. Molecular docking was performed with the software AutoDock Tools 1.5.6 to evaluate the pharmacodynamics interactions of α -phel and opioid receptors.

The mechanism of action of α -phel in chronic pain was analyzed *in vivo*. Ethics Committee of UFPI approved this project (protocol nº 305/17). Female Swiss mice (25-30g) underwent partial sciatic nerve ligation surgery to induce neuropathy. The neuropathic mice (N=6) were pre-treated with Naloxone (2mg/kg, i.p.) or Saline (10mL/kg, p.o.). After 20 minutes, they were treated with α -phel (6,25mg/kg, p.o.) or morphine (5mg/kg, i.p.) and evaluated by Von Frey test.

Results: The predicted pharmacokinetic parameters (Table 1) suggest good intestinal absorption and good permeability. Plasma protein binding is elevated, however, it is reversible and technological alternatives, such as carrier systems, can improve it. The α -phel does not inhibit CYP3A4, it indicates a minimal possibility of interactions with others drugs and adverse reactions.

Table 1. Pharmacokinetic parameters of α -phel

ID	VALUE
BBB	7.17054
Buffer_solubility_mg_L	1227.08
Caco2	23.4164
CYP_2C19 and 2C9_inhibition	Inhibitor
CYP_2D6_inhibition_substrate	Non
CYP_3A4_inhibition	Non
CYP_3A4_substrate	Weakly
HIA	100.00000
MDCK	267.707
Pgp_inhibition	Non
Plasma_Protein_Binding	90.00000
Pure_water_solubility	141.466

The structure of α -phel binding opioid receptors is shown in Figure 1. The lowest ligand-receptor binding energies were, respectively: -6.0 kcal/mol, -6.6 kcal/mol and -7.4 kcal/mol for the interaction of α -phel with Mu, Kappa and Delta receptors. It indicates that α -phel has high affinity for all three opioid receptors, binding in a strong and stable way.

The analgesic potential of the substance was tested *in vivo* as well. It was observed that Naloxone, an opioid antagonist, significantly reversed the effect of α -phel, indicating that it displays antinociceptive and antihyperalgesic activity through opioid system.

Conclusion: The monoterpene α -phel presents antinociceptive activity and reduces the sensitivity in chronic pain through the activation of opioid receptors.

Thus, *in vivo* and *in silico* results indicate that α -phel is an analgesic opioid agonist. This work may guide further preclinical studies, since α -phel may be an important strategy to treat chronic pain, with fewer side effects, dependence and tolerance than conventional drugs.

References:

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- [2] Piccinelli AC, Santos JA, Konkiewitz EC, et al. Antihyperalgesic and antidepressive actions of (R)-(+)-limonene, α -phellandrene, and essential oil from *Schinusterebinthifolius* fruits in a neuropathic pain model. Nutritional neuroscience. 2015 Jul 1;18(5):217-24.

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THURSDAY, 04 JUNE 2020

Pain in rheumatic diseases, including fibromyalgia _

THU0453 THIRD OCCIPITAL NERVE RADIO-FREQUENCY UNDER FLUOROSCOPIC GUIDANCE IN MANAGEMENT OF CERVICOGENIC HEADACHE IN RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis is a common type of autoimmune arthritis characterized by chronic inflammation. Cervical spine is often affected specially in long lasting disease

Objectives: Evaluate efficacy of Third occipital nerve Radiofrequency under fluoroscopic guidance to treat refractory cervicogenic headache in RA patients.

Methods: The current study was revised and approved from the local ethical committee of Faculty of Medicine; Assiut University, then registered in the clinical trials under the number of NCT03852355. Inclusion criteria included, Patients who fulfilled the American College of Rheumatology (ACR) (2010) criteria for RA and suffering

from upper neck pain and/or headache due to bilateral 3rd occipital nerve involvement, excluding other local cervical spine pathologies was confirmed by MRI and previously failed conservative treatment for at least three months prior to enrollment. Sixty adult patients were randomly assigned to one of the two studied groups Group 1 (RF, n = 30), received bilateral Third occipital nerve Radiofrequency under fluoroscopic guidance or Group 2 (control group, n = 30), received oral prednisolone 10mg/day. The two groups were then followed-up with neck disability index (NDI), nocturnal neck pain VAS score and headache score every two weeks for three months. Sleep disturbance, sleep disability index were reassessed six months post intervention. Post interventional assessment was done by pain physician who were kept blind to the grouping process.

Results: Neck disability index (1ry outcome), Nocturnal pain VAS, and severity of headache showed significant differences during the whole post-interventional study period. The patients in RF group demonstrated significant improvement of pain in comparison to baseline value over the whole six months with p-value < 0.001 as regard to the fore-mentioned three parameters. On the other aspect, the control group patients showed significant improvement in comparison to its baseline value after the 2nd, 12th and 24th weeks only as follows: (0.001, 0.003, 0.003 for the NDI) (p values of 0.02, 0.01, 0.01 for the nocturnal pain VAS), (0.001, 0.009, 0.005 for the headache VAS severity).

Conclusion: Radiofrequency of 3rd occipital nerve is effective in treatment of refractory cervicogenic headache in RA.

Disclosure of Interests: : None declared

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THU0454 SOMATIC SYMPTOMS IN FIBROMYALGIA AND THEIR CORRELATION WITH DRUG TREATMENT

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Background: Drug treatment in fibromyalgia (FM) is often disappointingly ineffective, and there are currently very few data to support therapeutic choices towards a personalized medicine approach.

Objectives: To evaluate the prevalence of selected somatic symptoms in FM, and to study their relationship with drug treatments.

Methods: The study population consisted of 526 patients (471 F 55 M, mean age 47.31±11.33 yrs) affected by FM not associated with other rheumatic diseases. All patients were required to compile a questionnaire reporting the presence of 42 somatic symptoms -as suggested (1) – in the last 7 days. Drug usage was assessed by interview.

Results: On average, patients reported the presence of 17.04±6.68 symptoms (range 4-35), with ample variations in the prevalence of different symptoms (Fig. 1), ranging from over 95% (fatigue and muscle pain) to less than 10 %, seizures being reported by only 2 patients (0.4%). 31.1% of patients were not taking any drug for their FM. The most frequently used drugs were analgesics (ANA, 41.7%) followed by benzodiazepines (BD, 29.1%), SSRIs (16%), gabapentinoids (GABA, 14.4%), and NSRI (14.3%) (Fig. 2). Different drugs were associated with a different spectrum of somatic symptoms: as compared to non users, BD users reported a significantly higher (p< 0.05 by chi-square test) prevalence of irritable bowel (65.4% vs 52.3%), fatigue (98.7% vs 94.9%), thinking difficulties (78.4% vs 68.5%), muscle weakness (94.1% vs 81.7%), abdominal pain (55.6% vs 43.9%), insomnia (73.9% vs 56.6%), depression (63.4 % vs 37.2%), constipation (60.1% vs 42.9%), pain in upper abdomen (50.3% vs 40.2%), nausea (53.6% vs 38.3%), nervousness (71.9% vs 61.5%), chest pain (49.0 vs 37.75), blurred vision (65.4% vs 53.6%), dry mouth (72.5% vs 52.3%), itching (56.2% vs 44.5%), vomiting (13.7% vs 7.8%), taste change (22.2% vs 12.7%), dry eyes (55.6% vs 41.0%), breath shortness (56.9% vs 47.7%), appetite loss (33.3% vs 19.7%), painful urination (15.0% vs 8.4%), and bladder spasms (18.3% vs 8.6%). NSRI users reported a significantly higher prevalence of thinking difficulties, constipation, blurred vision, dry mouth, wheezing, dry eyes, easy bruising. Among GABA users, there was a higher prevalence of thinking difficulties, numbness, insomnia, constipation, nausea, dry mouth, dry eyes, appetite loss, sun sensitivity, easy bruising, and bladder spasms. In no cases a higher prevalence of symptoms was recorded in drug non users vs users.

Conclusion: The usage of different drugs in FM is associated with different somatic symptoms. The higher prevalence of symptoms in drug users as compared to non users raises serious questions concerning the opportunity or the appropriateness of drug selection in FM.

Figure 1. Prevalence of Somatic Symptoms in The Population (%)

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Figure 2. Drug Usage in The Population

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THU0455 DIFFERENCES IN PSYCHIATRIC COMORBIDITIES AND LIFE ADVERSITIES BETWEEN PATIENTS WITH RHEUMATOID ARTHRITIS ASSOCIATED WITH FIBROMYALGIA AND PATIENTS WITH PRIMARY FIBROMYALGIA

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Background: Patients with rheumatic arthritis (RA) continue to report significant pain despite apparent disease control by immunosuppressive drugs (1), leading to the hypothesis that central sensitisation (CS) plays a role in the chronic musculo-skeletal pain defining fibromyalgia (FM).

Objectives: The aim of our study was to evaluate the differences in psychiatric comorbidities and life adversities between patients with RA+FM and patients with primary FM (PFM).

Methods: In a observational cross-sectional study patients with PFM and RA+FM were consecutively recruited. The inclusion criteria were an age of 18-70 years; a diagnosis of RA according to the 2010 ACR classification criteria and FM according to the 1990 ACR criteria and 2016 ACR criteria. Lifetime diagnoses of major depression disorder (MDD), panic disorder (PD) and post-traumatic stress disorder (PTSD), three of the most frequently described psychiatric disorders among FM patients, were made with the Structured Clinical Interview for DSM-5. Depressive symptoms were measured using the Zung Self-rating Depression Scale (ZSDS). Childhood trauma was measured using the short form of the Childhood Trauma Questionnaire (CTQ) and stressful events were assessed