Essential oils-induced analgesia and related translation for the management of agitation in dementia

Damiana Scuteri[1,2], Paolo Tonin[2], Giacinto Bagetta[1] and Maria Tiziana Corasaniti[3]*

[1]Pharmacotechnology Documentation and Transfer Unit, Preclinical and Translational Pharmacology, Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende, Italy - E-mail: damiana.scuteri@unical.it; [2]Regional Center for Serious Brain Injuries, S. Anna Institute, Crotone, Italy; [3]Department of Health Sciences, University "Magna Graecia" of Catanzaro, Catanzaro, Italy.

Abstract. Alzheimer's Disease (AD) accounts for approximately 50% of dementia cases worldwide and the linked agitation, the most challenging neuropsychiatric symptom, is tightly associated with under-treated pain states. Essential oils able to provide analgesia are needed to afford a safe treatment of pain with consequent efficacy on agitation. The essential oil of bergamot (BEO) proved effective in preclinical models of nociceptive and neuropathic pain. The aim of the present study is to review the pharmacological properties of BEO accounting for its translational activity in chronic pain and in agitation due to dementia.

Keywords: pain, essential oils, NanoBEO, Alzheimer's disease, agitation.

Pain and dementia

Chronic pain is widespread, affecting some 30–50% people worldwide, including pain from different etiology and pathogenesis: low back pain (1) due to a lesion or disease of the somatosensory system (2), stroke (3) or neuropathies (4) often related to comorbidities during aging, that impacts on pain modulation and response to treatment (5); rheumatic conditions (6-8), often experienced by the elderly. Up to 80% of nursing home residents is affected by dementia, of which Alzheimer's disease (AD) is the first cause and no disease-modifying drugs are available (9). Some 97% AD patients develops neuropsychiatric symptoms (NPS) (10), among which agitation (11) is the most challenging, with noteworthy burden on quality of life. It is treated with atypical antipsychotics and risperidone is the sole approved for this use for no longer than 6-12 weeks since this class of drugs almost doubles the risk of death due to serious cerebrovascular adverse events (CVAEs) in this fragile population. Over 80% of patients suffering from AD in long-term facilities is affected by chronic pain usually without taking advantage from analgesia even more in the community setting, because pain assessment is complicated by the impaired communication skills (12). The role of analgesia has been demonstrated to be a priority in the treatment of agitation (13), managing to reduce it without neuroleptics.

Essential oils and analgesia

The demand for essential oils of the global market is constantly growing (14), because of the important pharmacological actions of some of their components on several neurotransmissions, *via* a synergic mechanism widely known as entourage effect (15): it has been hypothesized that linalool, limonene, and pinene are involved in anxiolytic and antidepressant properties (16) and that some natural components are endowed with analgesic action (17) in a preclinical setting (18). Limonene is involved also in motor activity and in transdermal analgesic effect (19, 20). Among the essential oils most investigated for their anti-nociceptive properties, it is necesssary to quote the essential oil of croton and of bergamot (BEO).

Croton

The essential oil of Croton conduplicatus Kunth (Euphorbiaceae) displays anti-nociceptive properties in the acute pain models of acetic acid test and hot-plate test and on the formalin test biphasic model including central sensitization, through mechanisms involving ATP-sensitive K+ channels, opioid and cholinergic systems (21, 22). Croton cordiifolius Baill. (Euphorbiaceae) exerts efficacy in acetic acid and glutamate tests, without effect in the capsaicin test of acute pain; it shows efficacy in the formalin test, but its mechanism of action seems independent on opioid modulation (23). However, Croton adamantinus Müll. Arg. is more effective than morphine on licking behavior (24). Therefore, these effects are not fully elucidated and no neuropathic pain model was investigated.

BEO

BEO proves rigorous, preclinical evidence of anti-nociceptive and anti-allodynic effects in pain models relevant to chronic and neuropathic pain in clinic (25), based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) criteria (26, 27). In fact, it is effective in the acute pain model of the capsaicin test, but also in models resembling chronic pain in clinic as the formalin test, the spinal nerve ligation and the partial sciatic nerve ligation, also after continuous administration (25). Moreover, it is characterized by benzodiazepine-unrelated anxiolytic-like effects on a serotonergic basis important in the management of agitation (28, 29), thus devoid of sedation that could worsen cognitive decline (28). Importantly, BEO defurocoumarinized to avoid phototoxicity (30), is already available in the nanotechnology delivery system NanoBEO based on anti-oxidants enriched solid lipid nanoparticles entrapping aroma to allow the clinical confirm of its efficacy in agitation and chronic pain in AD (31) (patent EP 4003294) in a randomized, double-blind, placebo-controlled trial (BRAINAID, NCT04321889) (32).

Discussion and future perspectives

The elderly, mainly if affected by cognitive impairment, are generally excluded from clinical trials for pain and migraine treatment (33-36). Furthermore, trials are underpowered and not specifically designed for this population with poor or absent self-reporting capabilities (3, 33). However, research assessing the efficacy and safety of essential oils with analgesic properties on agitation and pain in non communicative patients affected by AD is necessary, along with the evaluation of herbal-drug pharmacokinetic interactions (37). NanoBEO can pave the way for a novel safer and effective treatment to reduce the use of neuroleptics and analgesics in patients suffering from severe AD, decreasing the risk of severe adverse reactions, also due to polypharmacy and drug-to-drug interactions, and improving their quality of life.

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