Translation of bergamot essential oil in clinical trial for control of behavioral and psychological symptoms of dementia (BPSD)

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The essential oil of bergamot, *Citrus bergamia* Risso et Poiteau (BEO), is endowed with analgesic activity in inflammatory and neuropathic pain models; it modulates endogenous peripheral and central opioid system and enhances morphine analgesic effect, both locally and systemically (see Scuteri et al., 2021, Pharmaceutics, doi.org/10.3390/pharmaceutics13030379). BEO can play a pivotal role in the modulation of synaptic glutamate, thus contributing to the processes of sensitization and autophagy (see Scuteri et al., 2021), known to be dysregulated in neuropathic pain. Due to the tight link between undertreated pain and agitation in dementia patients (Husebo et al., 2011, BMJ 2011, 343, d4065), aromatherapy can turn out to be a useful approach if an essential oil with powerful analgesic activity is used (see Scuteri et al., 2021). Methodological difficulties of most aromatherapy trials have not allowed any definitive conclusion about the effectiveness of aromatherapy in dementia (see Scuteri et al., 2021). Recently, a nanotechnology-based delivery system consisting of odorless alpha-tocoferyl stearate solid lipid nanoparticles (SLN) loaded with BEO deprived of furocoumarins (NanoBEO; WO2021019588), has been tested on acute and neuropathic pain models confirming the strong antinociceptive and anti-allodynic efficacy reported for BEO. In particular, after two and six months of light exposure, the content in the active ingredients declined by 10% and 18%, respectively with no further degradation at 12 months. The prolonged physicochemical stability and titration in its main components (linalool, linalyl acetate, and limonene) are remarkable advantages allowing reproducible antinociceptive and anti-itch responses to be measured. Added to this is the possibility to perform double-blind clinical trials, impossible so far because of the strong smell of essential oils used in aromatherapy. The diagnosis and treatment of pain in cognitively impaired patients is a neglected area, from chronic pain in dementia and migraine in aged patients often affected by concurrent cognitive impairment to post-stroke pain. Demented patients receive limited treatment for chronic pain, particularly neuropathic. The BRAINAID (NCT04321889) trial will assess the effectiveness of NanoBEO on agitation and pain in severely demented patients to offer a safe tool able to provide relief to this fragile population. It will enroll 134 patients aged >65 years with severe dementia (Mini-Mental State Examination <12) who will be randomized to NanoBEO or placebo cream in a 1:1 allocation ratio. The primary endpoint is the assessment of agitation through the Cohen-Mansfield Agitation Inventory over four weeks. This double-blind clinical trial will be the first to assess the efficacy and safety of an engineered essential oil and will provide the rationale for the safer treatment of BPSD and pain in clinic.

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