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TRANSLATION OF BERGAMOT ESSENTIAL OIL IN CLINICAL TRIAL FOR CONTROL OF BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

D. Scuteri[1,2], L. Rombolà[3], L. A. Morrone[3], S. Sakurada[4], T. Sakurada[5], P. Tonin[2], G. Bagetta[1], M. T. Corasaniti[6]

[1] Department of Pharmacy, Health and Nutritional Sciences, Pharmacotechnology Documentation and Transfer Unit, Preclinical and Translational Pharmacology, University of Calabria, Rende, Italy
[2] Regional Center for Serious Brain Injuries, S. Anna Institute, Crotone, Italy
[3] Department of Pharmacy, Health and Nutritional Sciences, Preclinical and Translational Pharmacology, University of Calabria, Rende, Italy
[4] Department of Physiology and Anatomy, Tohoku Pharmaceutical University, Sendai, Japan
[5] Department of Pharmacology, Daiichi University of Pharmacy, Fukuoka, Japan
[6] Department of Health Sciences, Magna Graecia University of Catanzaro, Catanzaro, Italy

E.mail: giacinto.bagetta@unical.it. **ORCID:** 0000-0001-8540-6218

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SUMMARY

The essential oil of bergamot (BEO; *Citrus bergamia Risso et Poiteau*) is endowed with analgesic activity in inflammatory and neuropathic pain models. Modulation of endogenous peripheral and central opioid system and morphine dose rescue are among the main pharmacological activities of the phytocomplex. Due to the tight link between undertreated pain and agitation in patients suffering from severe dementia, aromatherapy can turn out to be a useful approach if an essential oil with powerful analgesic activity is used. Methodological limitations of most aromatherapy trials hamper any conclusion about its effectiveness in dementia. Based on the strong preclinically proven antinociceptive and anti-allodynic activity of BEO, a nanotechnology-based delivery system consisting of odorless alpha-tocoferyl stearate solid lipid nanoparticles loaded with BEO deprived of furocoumarins (NanoBEO; patent EP 4003294), has been engineered and tested, confirming the previously demonstrated efficacy of the phytocomplex. Thus, the actually active BRAINAID (NCT04321889) double-blind, randomized, placebo-controlled, clinical trial has been designed to 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.

Key words
Bergamot essential oil; agitation; pain; dementia.

Impact statement
BEO is the first essential oil to be deviced in a nanotechonology delivery system (NanoBEO) to allow double-blind, randomized, clinical trial (NCT04321889) for the control of agitation in patients with severe dementia.

INTRODUCTION

Bergamot is a citrus fruit classified as *Citrus bergamia*, Risso belonging to the *Rutacee* family, genus *Citrus*. The essential oil of bergamot (BEO) is obtained by cold pressing of the epicarp and, partly, of the mesocarp of the fresh

fruit, according to what is reported in the *Farmacopea Ufficiale Italiana* (1). It is world widely known for its great demand by perfumery and cosmetic industries but also employed by pharmaceutical, food and confectionery industries. BEO is composed of a volatile (93-96% of total) and a non-volatile (4-7% of total) fraction. Among these, the volatile contains oxygenated compounds, as linalool and linalyl acetate, and monoterpenes and sesquiterpenes, as limonene, mainly responsible for its pharmacological activity (2). On the other hand, the non-volatile contains coumarins and psoralens (3), within which bergapten is responsible for phototoxicity (4). Essential oils extracted from different organs of aromatic plants, have been extensively used in aromatherapy for mood disturbances for inhalation or massage, although their effectiveness remains controversial due to the lack of adequate methodology in preclinic and clinic studies originating poor quality evidence, mainly in dementia (5). In fact, insufficient methodological quality of clinical trials has been highlighted already two decades ago (6); indeed, despite the increased amount of clinical trials (**figure 1**) the critical appraisal cannot be considered remarkably improved, as demonstrated by Cochrane analyses concerned with aromatherapy confirming conduct or reporting problems in half of the studies or inconsistent results, preventing from drawing any convincing evidence (5, 7).

With all the above in mind, over the last two decades a series of controlled preclinical researches have led to the characterization of the pharmacological profile of BEO, that now provides the rationale for its clinical translation. BEO has been proven to interfere with basic mechanisms finely tuning synaptic communication, modulating excitatory amino-acids release and affording neuroprotection (**figure 2**). In particular, brain microdialysis and synaptosomes superfusion have demonstrated that BEO modulates hippocampal synaptic amino acid neurotransmitters: at low concentrations it causes exocytosis of glutamate from presynaptic nerve endings, while at high concentrations it may induce glutamate release *via* a Ca2+-independent, carrier mediated, process (9). Moreover, it induces neuroprotection in focal cerebral ischemia preventing glutamate accumulation (10), along with blockade of spinal Extracellular Signal-Regulated Protein Kinase

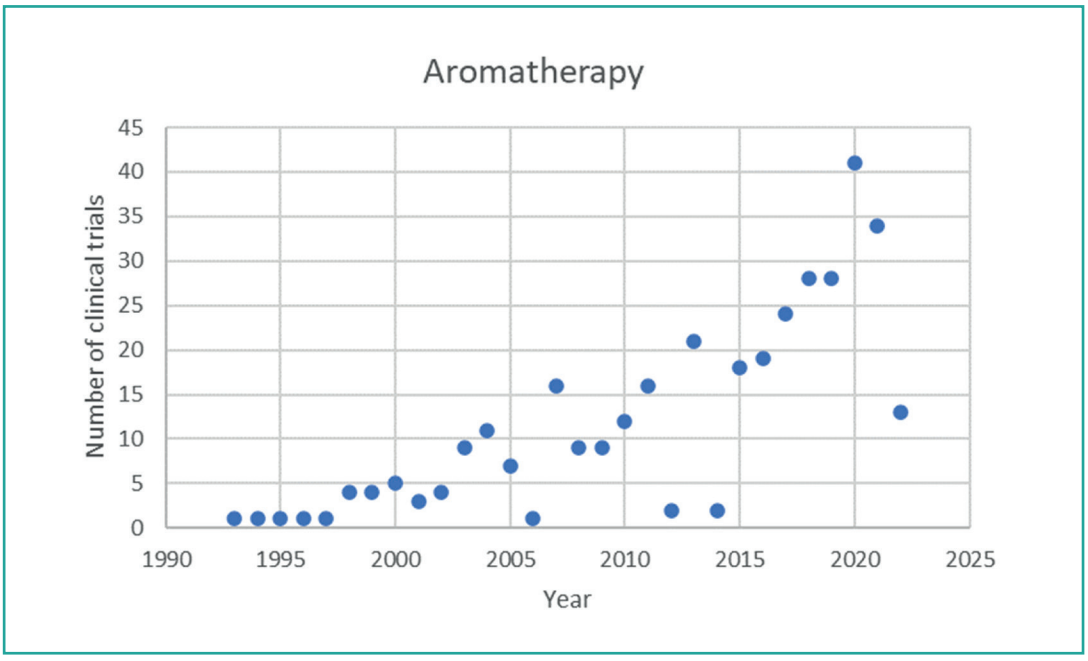

Figure 1. Studies concerned with aromatherapy clinical trials since PubMed/MEDLINE inception (date of last search May 16th, 2022).

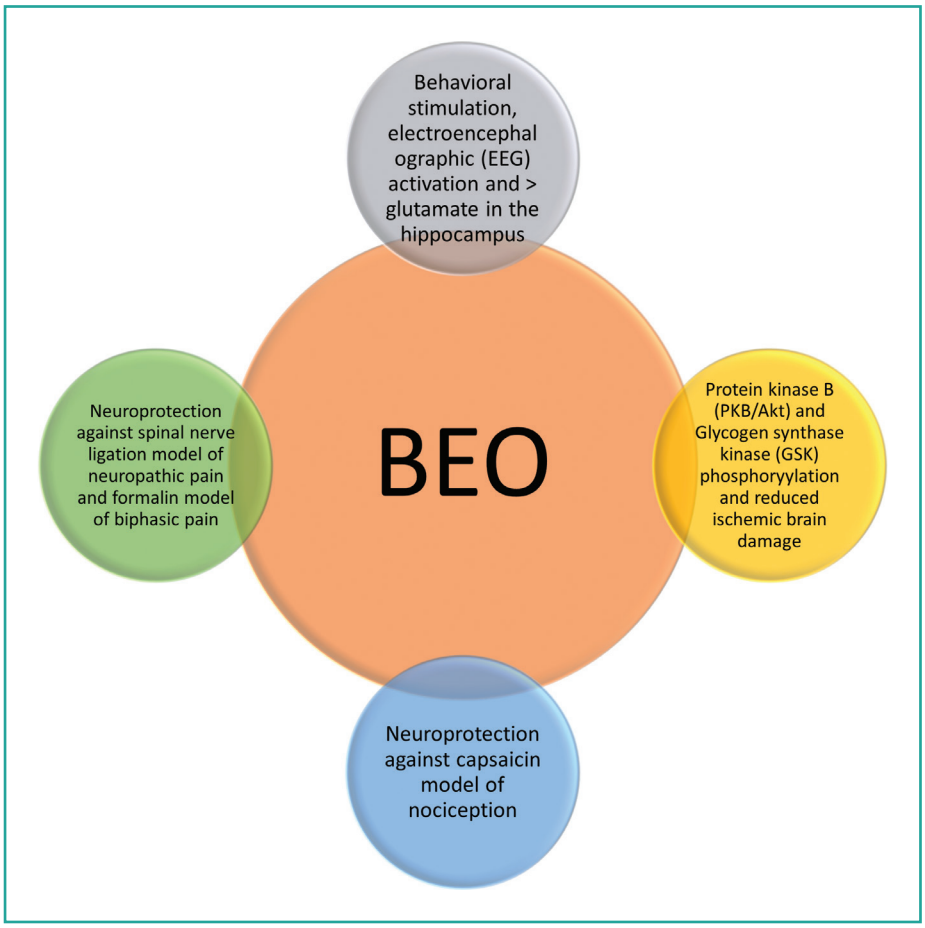

Figure 2. Neuropharmacological and behavioral effects of BEO (adapted with permission from (8)).
EEG = electroencephalography; Akt = Protein kinase B, PKB; GSK = Glycogen synthase kinase).

(ERK) activation, and it enhances autophagy (11), an evolutionarily conserved process undergoing derangement in chronic pain (12). Finally, BEO exerted anxiolytic-like effects, not superimposable to those of diazepam, thus devoid of sedative action, and involving serotonergic neurotransmission in the animal behavioural tasks Open Field Test, Elevated Plus Maze Test and Forced Swimming Test (13).

PHARMACOLOGICAL ACTION OF BEO IN PAIN

The potential for analgesic efficacy of BEO has been investigated in models of inflammatory (capsaicin model in mice), neuropathic [mice subjected to spinal nerve ligation (SNL) or partial sciatic nerve ligation (PSNL)] and biphasic pain (formalin test in mice). In particular, BEO has proven to reduce the time spent in licking/biting induced by the intraplantar (i.pl.) administration of capsaicin, an acute inflammatory algogen input (14, 15). Interestingly, BEO resulted effective also in the formalin test, reputed relevant to clinic conditions due to its biphasic nature (16), characterized by: 1) an early phase of about 5-10 minutes since formalin injection, resulting from the direct activation of nociceptive primary afferents; 2) a late phase, following the recovery interphase and up to 30 min following the administration of formalin, produced by sensitization of the dorsal horn neurons (17). In particular, BEO exerts analgesia in both phases of the formalin test (18), also when adminis-

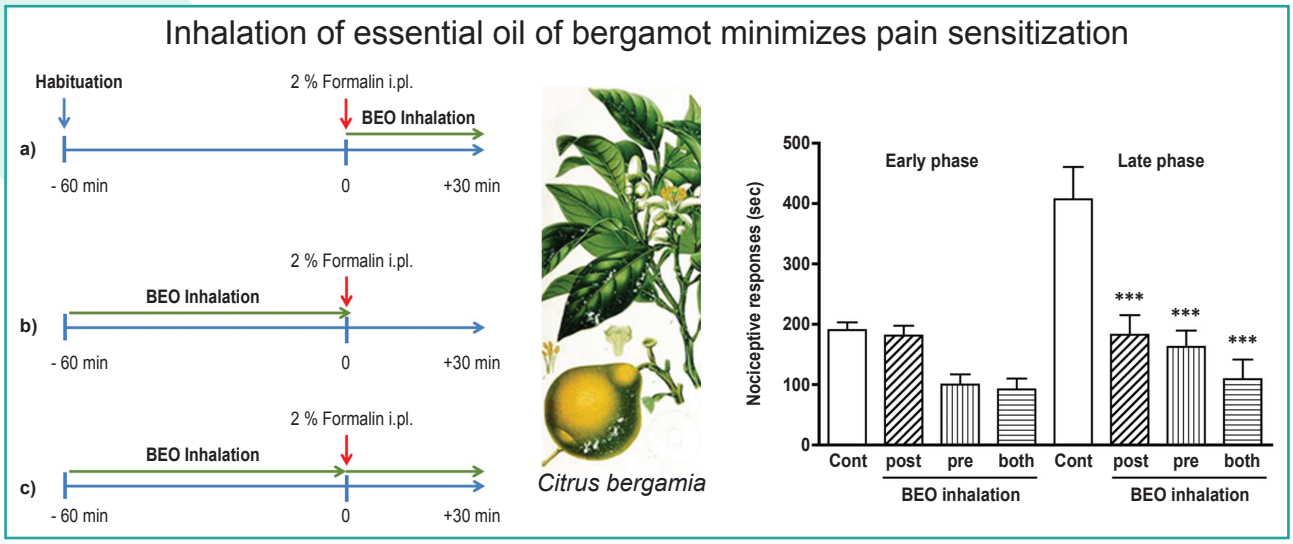

Figure 3. Analgesic efficacy BEO after inhalation in formalin test as pre-, post- or pre + post treatment (reproduced with permission from (19)).

tered *via* inhalatory (19) (**figure 3**) or transdermal route, as it occurs in aromatherapy (20, 21). Pretreatment with the opioid receptor antagonist naloxone methiodide decreases the antinociceptive effect of BEO, supporting the involvement of opioid system together with the evidence of enhancement of morphine-induced antiallodynic effect in the partial sciatic nerve ligation (PSNL) model of neuropathic pain (22); under the latter experimental conditions, BEO is also active by means of continuous administration through an osmotic pump mimicking chronic pain treatment (23). Moreover, the subcutaneous (s.c.) administration of BEO for 7 days attenuates long-lasting tactile allodynia induced by spinal nerve ligation (SNL) of the spinal nerve L5 (8). The first systematic review and meta-analysis investigating the preclinical evidence in favor of the working hypothesis of analgesic properties of the essential oils (24), following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) criteria, highlighted that: 1) studies present different experimental design and rise serious concerns in terms of selection, performance and detection biases, not following the Animal Research: Reporting In Vivo Experiments (ARRIVE) guidelines for accurate *in vivo* preclinical research (25); 2) BEO is the most suitable candidate for clinic translation since proving strong analgesic properties in the most reliable models of pain relevant to clinic in a methodologically rigorous manner. Accordingly, the preclinically demonstrated antinociceptive and antiallodynic properties of BEO provide a robust rational basis for its translation in clinical settings in which pain has a pivotal role.

DEMENTIA AND PAIN-LINKED NEUROPSYCHIATRIC SYMPTOMS (NPS)

Patients suffering from severe dementia often receive insufficient treatment of pain, particularly neuropathic, (26, 27) and this undertreatment is associated with widespread use of antipsychotics and antidepressants (28), usually due to their lack of communication skills preventing self-reporting (29). In particular, age-related comorbidities are responsible for chronic pain in up to 80% demented patients living in nursing homes (30). A tight link between unrelieved pain and the development of agitation, one of the most challenging and resistant neuropsychiatric symptoms (NPS) of dementia, has been demonstrated (31, 32) pointing at the priority of analgesia in the management of agitation (33). In fact, the latter can be significantly reduced by adequate pain treatment

and regular review of therapy (34, 35). There is growing evidence in favor of the significant correlation of pain intensity with dementia severity, NPS and antipsychotic prescriptions (36). However, the treatment of agitation often consists in the off-label use of antidepressants and atypical antipsychotics, known to increase up to almost doubling the risk of death for cardiocerebrovascular accidents (37). Therefore, pain control plays a fundamental role to decrease the use of unnecessary and potentially harmful atypical antipsychotics (33, 38), often used without evidence of the benefits and even increasing mortality risk after initiation of treatment (39). In this complex frame, aromatherapy with the melissa and lavender has proven efficacy for agitation in dementia (34), but the quality of the evidence has been downgraded (5, 7), as for all clinical trials in aromatherapy, due to sources of methodological biases (5). One of the major causes of poor quality is linked to strong aroma of essential oils hampering adequate allocation masking and double-blinding and to the lack or reproducibility and active principle titration in inhalatory systems. Moreover, because of the link existing between pain and agitation (40) the essential oil investigated for clinic treatment of agitation needs to be endowed with analgesic activity (41), as it is the case for BEO.

ENGINEERING BEO FOR TRANSLATION IN CLINIC

The illustrated limitations leading to poor quality clinical research in the field of aromatherapy have been overcome by the production of a nanotechnology delivery system, *i.e.*, NanoBEO, consisting in solid lipid nanoparticles (SLN) encapsulating BEO-bergapten free to avoid phototoxicity (European Medicine Agency [EMA], September 13rd, 2011 EMA/HMPC/56155/2011 Committee on Herbal Medicinal Products [HMPC]), and developed in the pharmaceutical form of a cream for transdermal application (42). Quite importantly, the antinociceptive and antiallodynic properties of NanoBEO have been studied in the capsaicin, formalin and PSNL pain models, demonstrating that it keeps all the pharmacological activities of BEO. Nano-BEO shows efficacy on scratching behavior, a typical neuropsychiatric symptom associated to dementia. This nanotechnology delivery system prevents the content in the active ingredients from declining after two and six months of light exposure over 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 present invention has been recently patented (EP4003294) and this makes it possible to effectively test NanoBEO deprived of furocoumarins in clinical trials for the treatment of acute and chronic pain and the prevention or treatment of NPS. Furthermore, the presence of anxiolytic activity and the documented absence of sedative effects is very relevant for the use of NanoBEO in cognitively impaired patients (43). In fact, the actually ongoing clinical trial BRAINAID (NCT04321889) (44) has been designed with the purpose to study the effectiveness and safety of NanoBEO on the NPS agitation and on related pain in 134 patients (n = 67 per arm) over 65 affected by severe dementia (Mini-Mental State Examination ≤ 12) (44). The primary outcome is reduction of the Cohen-Mansfield Agitation Inventory (CMAI) (45), used to assess agitation. The secondary outcome is represented by decrease of the score of the recently translated, adaptated and validated scale in the Italian setting for the assessment of pain in non-verbal, severe demented patients Italian Mobilization–Observation–Behavior–Intensity–Dementia (I-MOBID2) (46). The latter is able to unravel even concealed musculoskeletal and visceral pain states by means of active guided movements

(47, 48). Incidentally, the clinical trial BRAIN-AID (NCT04321889) could provide rational basis for use in e-health setting, important during the pandemic (49-51).

ETHICS

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Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

All authors have contributed equally and they have read and agreed to the final version of the manuscript.

Availability of data and material

The data presented in this study are available within the article.

Ethical approval

N/A.

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