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Review

Pharmacotechnological Advances for Clinical Translation of Essential Oils for the Treatment of Pain and Agitation in Severe Dementia

Damiana Scuteri [1,2,*], Chizuko Watanabe [3], Shinobu Sakurada [3], Kengo Hamamura [4], Tsukasa Sakurada [5], Paolo Tonin [2], Giacinto Bagetta [1,*] and Maria Tiziana Corasaniti [6]

1 Pharmacotechnology Documentation and Transfer Unit, Preclinical and Translational Pharmacology, Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, 87036 Rende, Italy
2 Regional Center for Serious Brain Injuries, S. Anna Institute, 88900 Crotone, Italy; patonin18@gmail.com
3 Department of Physiology and Anatomy, Faculty of Pharmaceutical Sciences, Tohoku Medical and Pharmaceutical University, Sendai 981-8558, Japan; w-chizu@tohoku-mpu.ac.jp (C.W.); s-sakura@tohoku-mpu.ac.jp (S.S.)
4 Center for Clinical Pharmacology and Pharmaceutics, Nihon Pharmaceutical University, Saitama 362-0806, Japan; k-hamamura@daiichi-cps.ac.jp
5 Center for Supporting Pharmaceutical Education, Faculty of Pharmaceutical sciences, Daiichi University of Pharmacy, Fukuoka 815-8511, Japan; tsukasa@daiichi-cps.ac.jp
6 Department of Health Sciences, University "Magna Graecia" of Catanzaro, 88100 Catanzaro, Italy; mtcorasa@unicz.it
* Correspondence: damiana.scuteri@unical.it (D.S.); giacinto.bagetta@unical.it (G.B.)

Abstract: The demand for natural products is steadily increasing, and pharmacotechnological engineering is needed to allow rigorous investigation of their efficacy and safety in clinical conditions representing still unmet needs. Among aged patients affected by dementia, up to 80% of residents in nursing homes suffer from chronic pain and 97% from fluctuant neuropsychiatric symptoms (NPS), of which the most challenging is agitation. It is, at least in part, due to undertreated pain and treated with antipsychotics almost doubling the risk of death. In the frame of a scoping review assessing the existence of essential oils undergoing engineering pharmacotechnological processes using solid lipid nanoparticle delivery systems for clinical translation in pain and/or neuropsychiatric symptoms of dementia following the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR), here we identified that the sole essential oil engineered to overcome the criticisms of aromatherapy clinical trials in pain and dementia is the essential oil of bergamot (BEO). Therefore, we present the process leading to the actually ongoing randomized, double-blind, placebo-controlled NCT04321889 clinical trial to assess the efficacy and safety of intervention with bergamot in the management of agitation and pain in severe dementia to be followed also for the proof of concept of efficacy and safety of other essential oils.

Keywords: bergamot essential oil; NanoBEO; SLN; severe dementia; pain; agitation; I-MOBID-2; CONSORT

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1. Natural Products from Traditional Medicine to Pharmacotechnological Innovation

The demand for natural products is constantly growing and the global market of essential oils, used in traditional medicine for centuries [1] (Table 1), is expected to grow by 7.5% from 2020 to 2027 [2]. In fact, the World Health Organization developed a global traditional medicine strategy for 2014-23 for safe and effective access to traditional and complementary medicine, which is the main source of health care for several populations. Within complementary, alternative and integrative medicine using officinal plant products along with validated treatments, aromatherapy consists in the administration of essential oils via massage or inhalation to improve well-being with an increase in the expenditure of the global market up to 5 trillion dollars by 2050 [3].

Table 1. Traditional medicinal uses of plant-based products examined throughout the periods up to the 1960's. The first find is represented by the earliest systematic medical text recording more than 800 plant medicines, Papyrus Ebers, arriving to The Divine Farmer's Materia Medica, the first text of Chinese Traditional Medicine, representing the first form of combinatorial medicine. The most recent finds include the antiseptic use of essential oils by Gattefossé and the aromatherapy books by Jean Valnet, Shirley Price and Marguerite Maury. Modified, integrated and reproduced with permission from [4].

Traditional Medicine	Plant-Based Products
Egypt	Papyrus Ebers, the earliest systematic medical text recording more than 800 plant medicines (1500 BC).
Iraq	Skeleton found 30,000 years ago with concentration of extracted plant essential oils.
India	Ayurveda natural system of medicine.
China	Shen Nung's manuscript listed 350 plants in 2800 BC; The Divine Farmer's Materia Medica, the first text of Chinese Traditional Medicine, representing a form of combinatorial medicine (200 AD).
Greece	Pedanius Dioscorides wrote De Materia Medica covering 700 plants, including aromatics.
Arabia	Medical aromatherapy emerged in the third century.
German	Hieronymus Braunschweig a surgeon and botanist, wrote a book on distillation of oils from plants that included 25 oils.
France	In 1919, Gattefossé, a famous chemist, was burned in an explosion in his laboratory. The wounds became infected. Wound rinsing with essential oils eradicated the infection. He coined the term, aromatherapy, and was known for the medical use of essential oils with their antibacterial and healing properties of essential oils. Jean Valnet, an army physician, wrote the first aromatherapy book by a doctor. Shirley Price authored Aromatherapy for Healthcare Professionals. She is known for clinical use of essential oils. In 1961, Marguerite Maury, a nurse, published Le Capital "Jeunesse". This book classified clinical departments' use of essential oils, such as surgery and spa treatment. Maury won 2 international awards for her research.

The Food and Drug Administration (FDA) approved new molecular entities (NMEs) from natural sources, e.g., morphine, paclitaxel, vinblastine and vincristine, since natural products contribute more than one third to all the NMEs [5]. However, the FDA classification includes essential oils for aromatherapy in cosmetic formulations. Therefore, studies assessing the efficacy and safety of these natural products in diseases are few and poor in methodological rigor. Scarce quality of preclinical research contributes to the latter poor methodological quality of the clinical findings. Novel technological approach is needed for the clinical development and accurate investigation of essential oil formulations in human diseases representing still unmet needs (Figure 1). In fact, progresses occur in pharmacotechnology as well as in the field of artificial intelligence and machine learning in the most different fields [6], in the modernization of productions for sustainable development and renewable energy [7,8], and in the use of artificial neural networks algorithm based on Levenberg-Marquardt [9]. Innovative technological processes are of the utmost importance, in particular in the field of analgesia and of neurodegenerative diseases, for which disease-modifying drugs are not available yet and the evidence of the efficacy of aromatherapy is debated [10–12]. To find out more about the body of evidence dealing with the pharmacotechnological engineering processes dealing with essential oils encapsulated in solid lipid nanoparticles (SLN) for the treatment of pain and/or neuropsychiatric symptoms of dementia, the execution of a scoping review, thus not eligible for registration in

the National Institute for Health Research International prospective register of systematic reviews (PROSPERO), is the aim of the present study. In fact, scoping reviews analyze a new field including different types of evidence, hence not assessing the risk of bias and additional analysis, and it is conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [13], developed according to published guidance by the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network for the development of reporting guidelines [14].

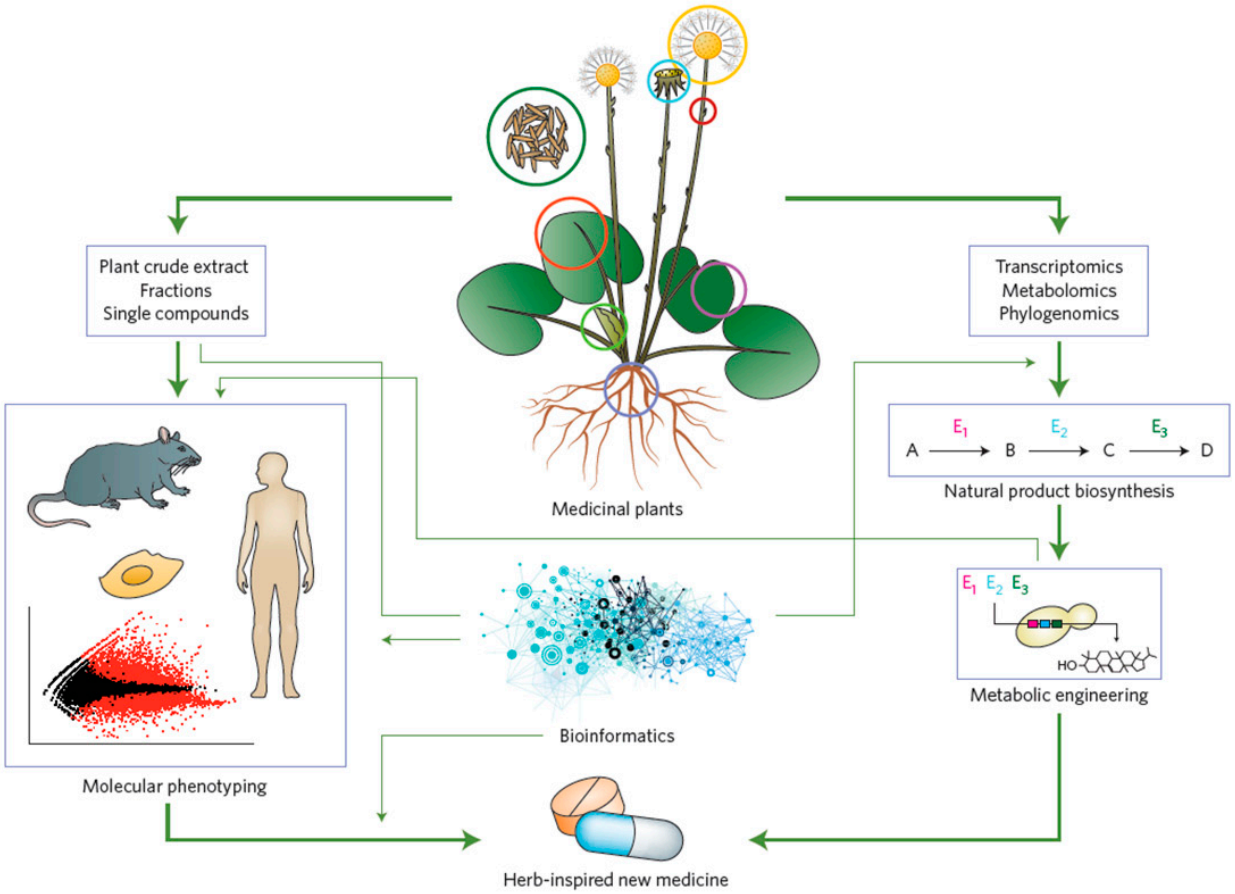

Figure 1. Technological advances in the fields of medicinal properties of plants in the post-omics era for developing new medicine to aid future drug development. Reproduced with permission from [1].

2. Materials and Methods

The PRISMA-ScR [13] recommendations are followed to answer to the participants/population, interventions, comparisons, outcomes, and study design (PICOS) question based on the working hypothesis investigating the existence of essential oils subjected to pharmacotechnological modification and engineering processes leading to encapsulation in SLN for clinical translation in the treatment of pain and/or neuropsychiatric symptoms of dementia. The search is conducted on PubMed/MEDLINE up to 7th July 2022 using the following strings: "essential oils" AND "solid lipid nanoparticles"AND "pain"; "essential oils" AND "solid lipid nanoparticles"AND "dementia"; "essential oils" AND "solid lipid nanoparticles" AND "neuropsychiatric symptoms". Duplicate records are removed using reference manager software (EndNote X7, Clarivate, Camelot UK Bidco Limited). Two review committee members screen titles and abstracts independently. Subsequently, the full text of the retrieved studies is assessed for inclusion in the scoping review in agreement with the a priori established eligibility criteria including original studies available in English and in full text. The reference list of relevant papers is inspected to avoid missing of additional

studies in the database search. Any disagreement is planned to be solved by consensus or by consulting a third team member.

3. Results: Essential Oil of Bergamot as a Paradigm to Follow

According to the results obtained, summarized in the PRISMA flow diagram in Figure 2, one original study [15] produced a SLN-based delivery system of an essential oil for the treatment of pain and agitation in course of dementia; this is the essential oil of bergamot. The sole other original study retrieved from the search is the study by Saporito and coworkers, that is excluded because it regards the development of SLN to be loaded with eucalyptus or rosemary essential oils to enhance healing of skin wounds [16]. Therefore, deeper insight into the preclinic research in favor of clinical translation of BEO is needed to understand the reasons for its loading in SLN through a pharmacotechnological engineering process.

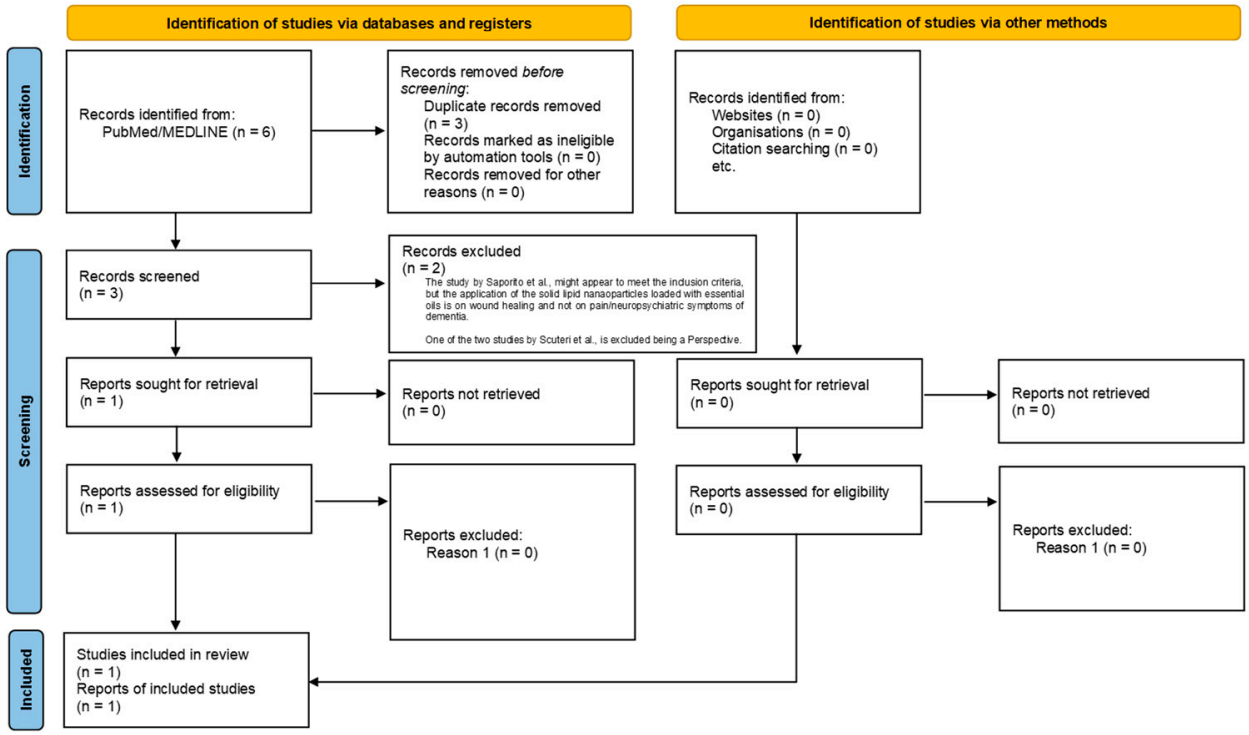

Figure 2. Process of search, selection and identification of the studies according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).

The first systematic review and meta-analysis aimed at assessing the quality of the body of evidence of preclinical analgesic efficacy of essential oils [2], following the Preferred Reporting Items for Systematic reviews and Meta-Analyses recommendations (PRISMA) [17,18], identifies only thirty studies meeting ethical standards; almost all (twenty-seven) study acute pain models not recapitulating clinical pain conditions. The meta-analysis conducted on the eight studies out of twenty-seven showing acceptable heterogeneity I^2 proves the efficacy of the treatment with essential oils respect to placebo (Mean difference -59.77; $p < 0.00001$). Among the most studied phytocomplexes for antinociceptive properties, there are the essential oil of croton [19–22] and of bergamot (BEO): the critical appraisal [23–25], along with the finding that BEO is the sole investigated in models of acute, [26] neuropathic pain [27,28], but also relevant to clinic due to central sensitization mechanisms [29], make BEO the best candidate for clinical translation in conditions characterized by painful syndromes. Bergamot is a citrus fruit classified as *Citrus bergamia*, Risso belonging to the Rutacee family, genus Citrus and BEO is obtained by cold pressing of the epicarp and, partly, of the mesocarp of the fresh fruit [30]. Oxygenated compounds

mainly responsible for its pharmacological activity are: linalool, linalyl acetate and the terpene limonene [31]. Its only documented adverse reaction is phototoxicity caused by bergapten [32]. Apart from having antinociceptive and antiallodynic properties, BEO is endowed with anxiolytic-like effects devoid of sedative action of benzodiazepines [33], linked to the modulation of serotonergic mechanisms in the animal behavioral tasks Open Field Test, Elevated Plus Maze Test and Forced Swimming Test [34]. Moreover, its fractions are active for inhalation [35] and transdermal [36] application, used in clinic as aromatherapy routes of administration. The analgesic properties of BEO are summarized together with representative studies in Table 2.

Table 2. Summary of the antinociceptive and antiallodynic properties of the essential oil of bergamot (BEO).

Study ID	Experimental Pain Model	Route of Administration	Analgesic Properties	Outcome
Sakurada et al. (2009) [26]	Capsaicin test	Intraplantar (i.pl.)	Reduction in the time of licking/biting	BEO (5, 10 and 20 mg) reduces the seconds of licking/biting induced in the 5 min following capsaicin i.pl. injection
Sakurada et al. (2011) [37]	Capsaicin test	I.pl.	Reduction in the time of licking/biting	BEO (20 µg) exerts significant antinociceptive effect in the hindpaw ipsilateral to capsaicin injection, counteracted by naloxone hydrochloride and methiodide
Katsuyama et al. (2015) [38]	Formalin test	I.pl.	Reduction in the time of licking/biting	BEO (10 µg) significantly inhibits licking/biting response in the ipsilateral side, and this is reverted by naloxone hydrochloride and methiodide
Scuteri et al. (2018) [39]	Formalin test	Inhalatory	Reduction in the time of licking/biting	A filter paper disc soaked with different volumes of BEO are applied to the edge of the cage to allow inhalation of BEO, proving its antinociceptive activity in the formalin test that is dependent on the volume and the time of exposure
Scuteri et al. (2022a) [35]	Formalin test	Inhalatory	Reduction in the time of licking/biting	BEO and its decolored fraction enriched in D-limonene in its highest volume are effective
Scuteri et al. (2022b) [36]	Formalin test	Transdermal	Reduction in the time of licking/biting	Both decolored and deterpenated fractions of BEO reveal equal activity to the phytocomplex in the early phase, but the reduction in the time of licking/biting during the late phase is more markedly induced by the decolored fraction
Bagetta et al. (2010) [40]	Spinal nerve ligation (SNL)	Subcutaneous (s.c.)	Mechanical allodynia assessed through the Von Frey's test	BEO (1 mL/kg) daily administration for 7 days following SNL attenuates mechanical allodynia
Kuwahata et al. (2013) [27]	Partial sciatic nerve ligation (PSNL)	S.c.	Mechanical allodynia assessed through the Von Frey's test	BEO (5.0, 10.0 and 20.0 µg) reduces mechanical allodynia dose-dependently on the 7th post-operative day of peak of threshold reduction
Hamamura et al. (2020) [28]	PSNL	Continuous s.c., with the aid of an osmotic pump	Planar activity	BEO decreases the PSNL-induced increase in planar activity during the light period post-operative day 7

4. Unmet Need: Agitation in Severe Dementia

The global burden of dementia is constantly growing; about 55 million people are affected all over the world and some 75–90% are not diagnosed and this problem has even worsened during the Coronavirus disease (COVID)-19 pandemic in which these patients take the greatest risk [41]. Along with dementia and its most common cause, i.e., Alzheimer's disease (AD), aging is tightly associated to pain altered processing [29] and to chronic pain development caused by age-related comorbidities inducing: chronic inflammatory pain including rheumatic conditions [42–44]; low back pain [45] because of lesion or disease of the somatosensory system [46], stroke [47] or neuropathies [48]. Pain is experienced by up to 80% nursing home patients suffering from dementia and it is under diagnosed and under treated in community [49–51] because of the lack of self-

report skills [52]. The problem of unrelieved chronic pain is importantly associated to the management of the neuropsychiatric symptoms of dementia (NPS), developed by some 97% patients and remarkably reducing their health-related quality of life (HRQL) [53]. Alteration of the signaling of the nuclear transactivation response (TAR) DNA binding protein-43 (TDP-43), a 43 kDa protein binding to 3′-untranslated region (UTR) of RNA involved in RNA processing, is often a comorbidity of AD inducing similar cognitive impairment [54] correlated with agitation in AD [55]. Agitation is one of the most challenging NPS and it is correlated to pain [56], as aggression and anxiety [52]; in fact, accurate pain treatment offers effective management of agitation [57] as supported by the evidence that pain severity is associated with NPS and with the use of antipsychotics [58]. A safe and effective therapy of NPS is not available since the latter symptoms are treated with atypical antipsychotics, almost doubling mortality risk [59]. Analgesia is the most efficacious treatment for the management of NPS [60] and it reduces the need for antipsychotics [61,62]. Therefore, novel effective analgesic treatments are necessary for the management of NPS.

5. Tool for Solution: NanoBEO

The typical problems of aromatherapy clinical trials can be solved by the engineering of BEO. In fact, aromatherapy with *Melissa officinalis* and *Lavandula officinalis* prove some efficacy for the control of agitation in dementia [61], not linked to analgesic action since the latter essential oils have not proven strong antinociceptive effects. However, the crtitical appraisal downgrades the quality of the evidence for methodological flaws of clinical trials in aromatherapy as the lack of double-blind due to the strength of aroma that does not allow indistinguishability of intervention and placebo. BEO deprived of furocoumarins is loaded in a nanotechnology delivery system based on SLN named NanoBEO [15]. The essential oil is encapsulated in SLN entrapping the aroma, enriched with the anti-oxidant α-tocopherylstearate (α-TFS-SLN); these have diameter equal to 450 nm and a polydispersity index of 0.30 and they are synthesized using a microemulsion technique at moderate temperature [63,64] and incorporated into a cream for transdermal administration. The production of the nanotechnology-based delivery system NanoBEO overcomes the following problems of clinical trials in aromatherapy: (1) lack of titration of the active principles: the phytocomplex components are titrated in the nanotechnological delivery system; (2) active components content degradation: NanoBEO prevents the active components from degradation; (3) lack of reproducibility of effects: the constant content and dosage of the phytocomplex allows to obtain reproducible effects; 4) lack of double-blind clinical trials because of aroma: NanoBEO affords the possibility to perform high-quality, double-blind clinical trials impeding recognition of intervention and placebo. Furthermore, NanoBEO retains all the antinociceptive and anti-allodynic properties of BEO together with efficacy on the typical NPS scratching behavior. Moreover, another issue with severe dementia clinical trials is the difficulty to unravel pain in patients unable to communicate. To solve this problem, our group recently validated in the Italian nursing home setting the Italian version of the Mobilization–Observation–Behaviour–Intensity–Dementia (I-MOBID2) [65]: it is the sole pain scale for severe dementia to take into account the frequent co-occurrence of musculoskeletal and visceral pain [66], thanks to its two parts [67] and to unravel even concealed pain through five guided movements. Therefore, NanoBEO was patented (EP 4003294) and it is now investigated in the first registered (NCT04321889) actually recruiting randomized, double-blind, placebo-controlled clinical trial to assess the efficacy and safety of a nanotechnology-based delivery system of an essential oil with rigorously preclinically proven antinociceptive and antiallodynic proprerties on agitation and pain in over 65 patients with severe AD. The present clinical trial follows the Consolidated Standards of Reporting Trials (CONSORT) [68] statements. Clinical trials assessing novel treatments for all the types of pain [69] and pharmacokinetic interactions [70] need to include the elderly suffering from comorbidities and physiopathological alterations affecting the responses to drugs and often neglected [71,72]. Therefore, this scoping review highlights for the first time that BEO is the sole essential oil that has undergone a pharmacotechnological

process of engineering to be loaded in SNL for investigation of its efficacy and safety in the management of agitation and pain in patients suffering from severe AD. This discovery indicates the need to follow the way paved by BEO for rigorous preclinical research to prompt the identification of other candidate essential oils to be subjected to engineering processes for clinical translation, mainly in diseases that represent a still unmet need.

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