

HERBAL BALM INNOVATION FROM JERIANGAU (*ACORUS CALAMUS*) EXTRACT: A REVIEW OF SUPPORTIVE MEDICAL POTENTIAL AS AROMATHERAPY AND PAIN RELIEF

Use of Herbs as Raw Materials for Supportive Therapy

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ABSTRAK

Pendahuluan: Indonesia merupakan daerah yang memiliki beragam jenis tanaman obat, namun hingga saat ini baru sekitar 1.200 spesies yang dimanfaatkan sebagai bahan baku obat tradisional atau jamu. *A. calamus* (Acoraceae) atau jeriangu merupakan tanaman obat yang mempunyai rimpang. Jeriangu dimanfaatkan sebagai bahan baku obat tradisional untuk berbagai keperluan terapi. Hal ini dikarenakan jeriangu mengandung bahan kimia glikosida, flavonoid, saponin, tanin, polifenol, dan minyak atsiri yang dapat digunakan sebagai aromaterapi.

Pembahasan: Jeriangu merupakan ramuan tahunan yang digunakan sebagai obat tradisional. Tanaman ini merupakan tanaman aromatik dengan rasa pedas. Rimpang jeriangu mempunyai sifat antispasmodik, aromatik, ekspektoran, antimal, obat penenang, efek stimulan, penyakit jiwa, diare, dan bronkitis. Minyak atsiri Jeriangu berfungsi sebagai pereda nyeri sakit gigi dan sakit kepala. Rimpang tanaman Jeriangu mengandung minyak atsiri 1,2,4-trimetoksi-5-(1-profenil)-benzena atau lebih dikenal dengan asarone. Asarone merupakan kandungan utama pada daun sedangkan acorenon merupakan kandungan utama pada rimpang. Hal ini menunjukkan adanya efek antikolinergik seperti atropin. Senyawa Jeriangu mempunyai sifat analgesik, sedatif dan neurodepresif yang dapat memberikan efek sedatif. Pada neonatus yang menderita diare, efek spasmolitik dan antisekresi dari ekstrak dapat mengurangi frekuensi buang air besar encer, penghambatan respons terhadap berbagai spasmogen, dan relaksasi saluran napas.

Simpulan: Jeriangu dengan kandungan minyak atsiri dan beberapa komponen bioaktif seperti asarone dan isocalamendiol berpotensi sebagai pereda nyeri dan aromaterapi.

Kata Kunci: aromaterapi, asarone, balsem herbal, jeriangu, pereda nyeri.

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ABSTRACT

Background: Indonesia is an area that has various types of medicinal plants, but until now only about 1,200 species are used as raw materials for traditional medicines or herbs. *A. calamus* (Acoraceae) or jeriangau is a medicinal plant that has a rhizome. Jeriangau is used as a raw material for traditional medicine for various therapeutic purposes. This is because jeriangau contains chemical glycosides, flavonoids, saponins, tannins, polyphenols, and essential oils that can be used as aromatherapy.

Discussion: Jeriangau is an annual herb used as a traditional medicine. This plant is an aromatic plant with a spicy taste. Jeriangau rhizome has anti-spasmodic, aromatic, expectorant, anti-nausea, sedative properties, stimulant effects, mental illness, diarrhea, and bronchitis. Jeriangau essential oil serves as a pain reliever for toothaches and headaches. The rhizome of the Jeriangau plant contains 1,2,4-trimethoxy-5-(1-prophenyl)-benzene essential oil or better known as asarone. Asarone is the main content in leaves while acorenon is the main content in rhizomes. It suggests the presence of atropine-like anticholinergic effects. Jeriangau compound has analgesic, sedative and neurodepressive properties which can have a sedative effect. In neonates with diarrhea, the spasmolytic and antisecretory effect of the extract can reduce the frequency of watery bowel movements, inhibitory responses to different spasmogens, and airway relaxation.

Conclusion: Jeriangau with essential oil and several bioactive components such as asarone and isocalamendiol has the potential as a pain reliever and aromatherapy.

Keywords: aromatherapy, asarone, herbal balm, jeriangau, pain reliever.

1. INTRODUCTION

Indonesia is known as a place where medicinal plants grow so it got the nickname live laboratory. About 30,000 kinds of medicinal plants are owned by Indonesia. With this rich flora, of course, Indonesia has the potential to develop products of herbs of equal quality with modern medicine. However, these natural resources yet optimally utilized for the public interest. Just about 1200 species of medicinal plants are

utilized and researched as traditional medicine Our ancestors have used traditional medicine from natural plants for generations to maintain stamina and treat several diseases.^[1,2]

Traditional herbal medicine is commonly known as an herbal medicine. The use of herbal medicine is not only used for humans, but herbal medicine has begun to be widely used known among poultry breeders. Middle and lower scale farmers generally use this plant as

traditional medicine for their livestock. They rarely use factory drugs because they are considered expensive. Research on the use of herbal medicine in various test animals has been carried out on broilers, ducks, quail in rabbits, and cows. The higher the cost drugs and drug prices chemicals, and lots of side effects the results of using chemical drugs, now is people's time make use of medicinal plants.^[3,4]

The usage of natural products, principally herbal medicines is one of the ancient therapies used by humanity.^[5] During recent years, people are eager to use herbal medicines due to their lower complications and fewer side effects than synthetic drugs.^[6] Regarding to the increasing demand for medicinal plants and related compounds phytopharmaceutical studies and the use of these remedies for the management of many diseases, including painful neuropathy have been growing throughout the world.^[7]

Pain, an unpleasant sensation and emotional experience that in our daily life, is an alert of tissue injury to prevent further or impending tissue damage.^[8] Acute pain is a useful biologic purpose and self-limiting in nature that arises in response to a specific injury. Chronic pain, in contrast, may be considered as a disease state. It may outlast the usual duration of recovery, if accompanied with a disease or injury.^[9] The definition of chronic neuropathic pain is "pain that comes from direct consequence of a lesion or disease which affect the somatosensory system".^[10] It may be classified as central or peripheral, depending on the site of the lesion. The most causes of chronic neuropathic pain are metabolic disease, viral, trauma,

severe ischemic insults, and autoimmune diseases.^[11,12] Neuropathic pain usually does not have effective treatment, because of heterogeneous etiology and complex underlying pathophysiology, moreover, the unwanted side effect profiles limit the use of available drugs.^[13,14] One of the alternative ways to choose is the pain reliever, especially using herbals.

Jeriangau (*Acorus calamus*) is one of the herbal plants that have been used massively as traditional medicine agents. Traditionally, Jeriangau was widely used as a medicine for skin and abdominal pain. Jeriangau rhizome was useful as a spasmolytic, carminative, and useful for sedation, digestive, sedative, increase appetite, tonic, antiinflammatory, relieve nasal congestion, and antiseptic ingredients. Jeriangau rhizome contains essential oils, saponins, and flavonoids.^[15]

Phongpaichit et al. also reported that the methanol extract of the rhizome Jeriangau active as inhibitors of growth of filamentous fungi (*Microsporum gypseum*, *Trichophyton rubrum*, and *Penicillium marneffeii*).^[16] Venskutonis and Dagilyte reported that the essential oil content of dry rhizome of Jeriangau, collected in Lithuania was $1.20 \pm 0.12\%$, while the leaves ranged from 0.56 to 1.01% depending on the vegetation period. δ asarone [(Z)-asarone] was the main constituent in the leaves (from 27.4 to 45.5%), whereas the main compound of the rhizomes was acorenone (20.86%) followed by isocalamendiol (12.75%).^[17]

The utilization of jeriangau related to essential oils and the bioactive components contained in it

can be used as a pain reliever and aromatherapy. This active ingredient can be made in the form of such as cream or balm. Based on the Indonesian pharmacopoeia of ointments, unguentum is a semi-solid preparation that is easily applied and used as an external medicine. The drug substance must be dissolved or homogeneously dispersed in a suitable ointment base.^[18] The balm material was chosen because it is very easy to use and can be applied all over the body by simply rubbing it on.^[19] Therefore, in this study the researchers made an innovation as a solution to the problems above.

2. DISCUSSION

Utilization of Jerangau (*Acorus calamus*)

Indonesia is a tropical country with the highest biodiversity in the world (Murdopo, 2014), most of which are medicinal plants. There are 30,000 medicinal plants grown in Indonesia, but only 1,200 are used as raw materials for herbal medicines.^[20] The jeriangau plant (*Acorus calamus* L.) is one of the medicinal plants that can be used in herbal medicine. It has many properties, and its rhizome is rich in essential oils. Jeriangau rhizome essential oil contains the active ingredients -asarone (82%), colamenole (5%), colamen (4%), colameone (1%), methyl eugenol (1%), and eugenol (1%).^[21]

According to the Chape. Et al study, about 78 chemical components were detected from the rhizomes of *Acorus calamus* L. by headspace method. The major components are as follows: 75.8% asarone, 79% benzen, 25,8 % trans- β -Ocimene, 20,5% Isocalamendiol, 20,1 % Methyleugenol, 22,6% 3-Carene 17.40% β -asarone and 17.1% α -Pinene. In terms of the characteristics of the components contained in this

plant and studies show that *Acorus calamus* could be a potential source of novel antibacterial, antioxidant ve anticancer agent.^[22]

The rhizome of the Jeriangau plant contains 1,2,4-trimethoxy-5-(1-prophenyl)-benzene essential oil or better known as asarone. The essential oil content of dried jeriangau rhizome is $1.20 \pm 0.12\%$ while the content in the leaves is 0.56-1.01% depending on the growth phase.

Asarone is the main content in leaves (27.4-45.5%), while acorenon is the main content in rhizomes (20.86%) followed by isocalamendiol (12.75%). It is well known for its medicinal properties such as the remission of fever, besides being used as an emetic in dyspepsia and also as a sedative, nerve tonic, antimicrobial agent, and expectorant. Recent research reported that the ethanol extract of *Acorus calamus* L. has antidiabetic action.^[23,24]

Empirically green jeriangau leaves (*Acorus calamus* L.) are used by the community to treat several diseases, one of which is skin disorders such as inflammation (anti-inflammatory) by applying squeezed jeriangau leaves on the part to be treated. Green jeriangau leaves (*Acorus calamus* L.) contain flavonoid and saponin compounds which have antibacterial and anti-inflammatory activity.^[25]

Extract of *Acorus calamus* as Pain Reliever

Pain is the most common complaint found in health services. The most common types of acute and chronic pain based on etiology and clinical presentation include nociceptive, inflammatory and neuropathic syndromes. Nociceptive pain, frequently accompanied by

inflammation, occurs because of stimulation of unaltered nociceptors by external stimuli and/or release of pain-causing substances.^[25]

Inflammation is a response to tissue damage due to various harmful stimuli, both stimuli chemical, mechanical, infectious, or foreign bodies such as bacteria and viruses. Signs of the process. inflammation include rubor, calor, tumor, dolor, and functio laesa. Drugs to cope inflammation is usually anti-inflammatory non-steroidal anti-inflammatory drugs (NSAIDs) and steroids. However, the two drug classes have the potential cause side effects; anti-inflammatory steroids can cause ulcers peptic ulcer, decreased immunity, osteoporosis, atrophy of muscle and fat tissue, increase intraocular pressure, and is diabetic.^[26]

One of the nutritious plants that can used as an anti-inflammatory drug is Jeriangau (*Acorus* sp.) as pain reliever. Phytochemical screening results show the presence of flavonoid compounds in the rhizome Jeriangau (*Acorus* sp.) capable of increase blood platelets in animals test. Jeriangau Rhizome (*Acorus* sp.) contains alkaloids, essential oils, tannins, flavonoids, and saponins. Compounds it is based on research suspected efficacious as anti-inflammatory. Rhizome Jeriangau (*Acorus calamus*) has activity anti-inflammatory and antipyretic in white rats, compounds with anti-inflammatory effects are thought to from the content of essential oils or oils essential.^[25]

Kumar, et al, said that 80% ethanol extract of Jeriangau leaves (*Acorus calamus*) has anti-inflammatory activity in albino mice; It is suspected that the compound

efficacious are flavonoids and terpenoids.^[20]

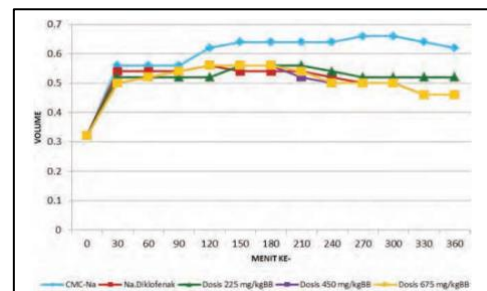


Figure 1. Graph of the average change in the volume of the test animal images.^[27]

Compounds suspected of having activity anti-inflammatory in rhizome ethanol extract Jeriangau is a flavonoid. Mechanism the action of flavonoids is to inhibit the release of arachidonic acid and lysosomal secretion and Inhibits the proliferative and exudative phases of the inflammatory process. Flavonoid compounds also inhibits the cyclooxygenase (COX) enzyme and lipoxygenase. The enzyme cyclooxygenase is an enzyme that catalyzes formation of prostaglandins and their products arachidonic acid metabolism, whereas lipoxygenase enzymes that form leukotrienes that play a role in the process inflammation and allergy in asthma. Thus, if the two enzymes is inhibited, the trigger for inflammation is not will form and the inflammatory process can reduced.^{[27-29][28,29]}

Compounds of other groups in ethanol extract the rhizome of the alleged Jeriangau has an anti-inflammatory effect, namely essential oils (terpenoids) and saponins; group compound terpenoids can inhibit the production of TNF- α (tumor necrosis factor) which is a proinflammatory cytokines, in addition to terpenes can inhibit the enzyme cyclooxygenase (COX) which is a

trigger for inflammation. While the compounds of the saponin group inhibit inflammation by inhibits the formation of exudate and increase in vascular permeability blood.^[27,30]

Beneficial Effects of Herbal Balm Jeriangau on the Respiratory Tract

Acorus calamus Linn. (Araceae) is a semi-aquatic herb with aromatic rhizomes that grow creeping and branching has been known for at least 2000 years. Aromatic rhizomes are often referred to as calamus or sweet-scented. It has been used for centuries as an herbal remedy for disorders of the respiratory tract, such as: asthma, cough, throat irritation, bronchitis and as an expectorant.^[30]

The use of *Acorus calamus* has been known as a remedy for respiratory disorders, but there are not many studies that discuss the therapeutic potential of gizzard in overcoming this respiratory disorder. A study by Shah et al 2010 in an in vivo experiment conducted a test of the effect of gizzard on the trachea of pigs. Experimental animals were induced with high K⁺ and CCh procontraction, and the effect of crude extract of *Acorus calamus* had an effect that could inhibit the constriction, which depended on the given concentration.^[31]

The use of *Acorus calamus* is traditionally used for hyperactive airway disorders, assays *A. calamus* plant extracts were tested on tracheal preparations causing precontractual relaxation induced by high K⁺ and CCh. The pre-contraction inhibitory potential of *A. calamus* was found to be higher with respect to K⁺, this is similar to the effect of verapamil. Airway contraction induced by high K⁺ (>30 mM) depends on Ca⁺⁺ entry into cells via voltage-dependent

calcium channels (VDCs) and a certain compound that can inhibit high K⁺-induced contraction is a compound that is considered a CCB (Calcium Channel Blockers).^[32] Thus, K⁺-induced inhibition of precontraction by *A. calamus*, at low concentrations, reflects limited Ca⁺ entry via VDC, although additional mechanisms cannot be ruled out.^[30]

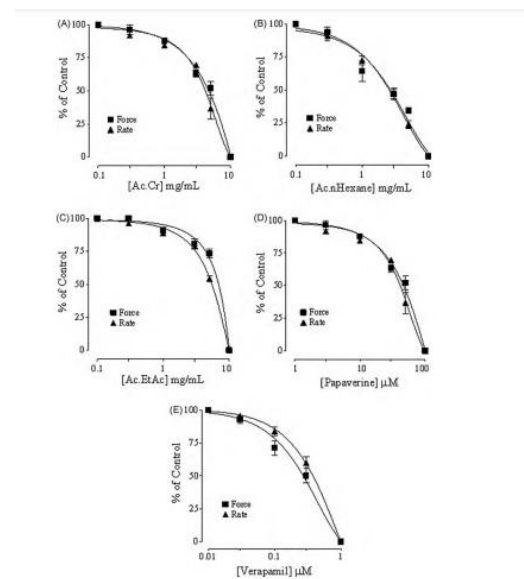


Figure 2. Inhibitory effect of (A) the ethylacetate (Ac.EtAc) fraction of the crude extract of *Acorus calamus*, (B) atropine and (C) rolipram on the high K⁺ and carbachol (CCh)-induced contractions in isolated guinea-pig tracheal preparations. Symbols represents \pm SE, n = 4–7.^[31]

Some of the compounds contained in *A. calamus* are testing, one of the n-hexane compound in *A. calamus* (Ac.n-hexane) is equipotential for high K⁺ and CCh-induced contraction, similar to the action of papaverin as a dual inhibitor of PDE (phosphodiesterase)^[33] and calcium channels suggesting possible PDE-like inhibitory effects in addition to CCBs. The PDE inhibitory effect of Ac.n-hexane was further studied when the pretreatment shifted the isoprenaline-induced inhibition of

CRC to the left, similar to the effect caused by the crude extract papaverine, i.e. verapamil without potentiating the effect, because PDE inhibitors are known to potentiate the effects of isoprenaline.^[31,34]

Meanwhile, other compounds from *A. calamus* have different effects, namely ethylacetate (Ac.EtAc) fractions. Ethylacetate has a contraction inhibitory effect induced by CCh at a markedly lower concentration with an insignificant effect at high precontraction K⁺, this action is similar to that of atropine. This suggests the presence of atropine-like anticholinergic effects, in addition to other mechanisms on *A. calamus*. This anticholinergic effect was further indirectly confirmed when pre-treatment of tracheal tissue with Ac.EtAc, at lower concentrations, caused a parallel shift to the right without altering the maximum response, similar to that induced by atropine, muscarinic receptor antagonist and non-drug shift. parallel with suppression of maximum response at higher concentrations, suggesting the presence of an additional nonspecific relaxant component.^[31]

Experimental results in the trachea, PDE4, which is a cAMP-specific PDE, is the dominant isoenzyme in most inflammatory cells, involved in airway disease, which contributes to approximately 50% of the total PDE activity, an amount similar to reported for the human airway. There is evidence to suggest that anticholinergic agents, particularly atropine, are known to synergize the effects of rolipram, a selective PDE4 inhibitor to exert a relaxing effect on airway smooth muscle.^[35]

The hypothesis of the study of Shah, et al 2010 was found that the strong nature of Ac.EtAc against CCh-induced contraction was due to additional inhibition of PDE4 inhibitory constituents such as rolipram. When rolipram was tested against CCh-induced contraction, it caused a partial inhibitory effect with a maximum response reaching about 50%, while it was found to be without any effect on the high K⁺-induced contraction effect. The complete inhibition of CCh-induced contraction may be due to the synergistic effect of the anticholinergic atropine and the rolipram-like PDE4 inhibitory effect of Ac.EtAc, whereas the partial inhibitory effect of rolipram is solely due to inhibition of PDE4, thus suggesting the presence of a specific rolipram-like PDE4 inhibitor. The PDE inhibitory effect of Ac.EtAc was further confirmed when pre-treatment of tracheal tissue with Ac.EtAc led to the potentiation of an isoprenaline-induced inhibitory response, similar to that caused by rolipram. These data suggest that Ac.EtAc has PDE4 inhibitory activity like rolipram, which is also evident from the non-parallel shift with suppression of maximum response, a non-specific characteristic of PDE inhibitor inhibitory responses to different spasmogens.^[31]

Airway relaxation is associated with a net increase in cAMP concentrations as a consequence of inhibition of PDE and Ca⁺⁺ movement. Recent studies have helped to understand the important role of PDE4 in addition to non-specific PDE in airway function and its inhibitors are one of the new candidates for asthma treatment. Similarly, cholinergic innervation is

the predominant neural bronchoconstrictor in humans and rodents associated with asthma. Anticholinergic agents are now considered important bronchodilators for the treatment of asthma. Thus, the presence of non-specific PDE4 inhibitors such as papaverine, such as rolipram and anticholinergic constituents in *Acorus calamus* provides a possible pharmacological basis for its traditional use in airway disorders. PDE inhibitors themselves are considered to be highly effective bronchodilators but have limited therapeutic use in patients with cardiac disorders such as stimulatory events (tachycardia), as a side effect.^[36]

Herbal Balm as Pain Reliever and Aromatherapy

Aromatherapy is a holistic healing treatment that uses natural plant extracts to promote health and well-being. It is sometimes called essential oil therapy. Aromatherapy uses aromatic essential oils medicinally to promote a healthy body, mind, and spirit. It improves physical and emotional health. Nowadays, the use of alternative and complementary therapies with mainstream medicine has gained the momentum. Aromatherapy is one of the complementary therapies which use essential oils as the major therapeutic agents to treat several diseases.^[21]

The essential or volatile oils are extracted from the *A. calamus*. Inhalation, local application and baths are the major methods used in aromatherapy that utilize these oils to penetrate the human skin surface with marked aura. Once the oils are in the system, they remodulate themselves and work in a friendly manner at the

site of malfunction or at the affected area. This type of therapy utilizes various permutation and combinations to get relief from numerous ailments like depression, indigestion, headache, insomnia, muscular pain, respiratory problems, skin ailments, swollen joints, urine associated complications etc.^[24]

The use of extracts *A. calamus* in the form of an inhaler is preferred, because considering some of the side effects caused if some components enter the bloodstream in large quantities. The biochemical component of *A. calamus* is asarone. This compound has analgesic, sedative and neurodepressive properties which can have a sedative effect. In neonates with diarrhea, the spasmolytic and antisecretory effect of the extract can reduce the frequency of watery bowel movements.^[36]

Moreover, *A. calamus* contains steroid compounds that can worsen the underlying disease or predispose to infection. *A. calamus*'s neurodepressive properties tend to result in reduced activity and seizures in neonates that mimic meningitis.^[37,38] Therefore, public health education on the harmful effects of *A. calamus* should be given, and the pediatrician should be made aware of this dangerous practice.

3. CONCLUSION

Jeriangau (*Acorus calamus*) can be used as the main ingredient in making herbal balm. The main content is essential oil and several bioactive components such as asarone and isocalamendiol which can provide a warm effect so that it has the potential to be used as aromatherapy and pain reliever in acute and chronic pain. The

formulation of the balm preparation is made using the main ingredient of jeriangau extract with other additives to increase efficacy and efficiency.

REFERENCES

- Bambani A. Only 10% of Indonesia's Biodiversity Revealed: BRIN. TheIndonesia.id. 2022.
- Tobing IS, Sukara E. Industri Berbasis Keanekaragaman Hayati, Masa Depan Indonesia. *Vis Vitalis*. 2008;01(2):1–12.
- Latifah S, Hartini KS, Sadeli A, Yuandani. Identification of medicinal plants used by the community for indigenous poultry health management. *IOP Conf Ser Mater Sci Eng*. 2021;1122(1).
- Bayoa DLM, C.L.K.Sarayar, M.Najoan, W.Utiah. The addition effectiveness of curcuma xanthorrhiza roxb and curcuma zedoaria rox flours in commercial ration on performances og broilers. *J zoetek*. 2014;34(Mei).
- Li JWH, Vederas JC. Drug discovery and natural products: End of an era or an endless frontier? *Vol. 325, Science*. 2009.
- Boyd A, Bleakley C, Gill C, Mcdonough S, Hurley DA, Bell P, Mcveigh JG, Hannon-Fletcher M. Herbal medicinal products or preparations for neuropathic pain and fibromyalgia. *Vol. 2016, Cochrane Database of Systematic Reviews*. 2016.
- Garg G, Adams JD. Treatment of neuropathic pain with plant medicines. *Chin J Integr Med*. 2012;18(8).
- Wang LX, Wang ZJ. Animal and cellular models of chronic pain. *Adv Drug Deliv Rev*. 2003;55(8).
- Razavi BM, Hosseinzadeh H. A review of the role of orexin system in pain modulation. *Vol. 90, Biomedicine and Pharmacotherapy*. 2017.
- Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: Redefinition and a grading system for clinical and research purposes. *Vol. 70, Neurology*. 2008.
- Mulla SM, Buckley DN, Moulin DE, Couban R, Izhar Z, Agarwal A, Panju A, Wang L, Kallyth SM, Turan A, Montori VM, Sessler DI, Thabane L, Guyatt GH, Busse JW. Management of chronic neuropathic pain: A protocol for a multiple treatment comparison meta-analysis of randomised controlled trials. *BMJ Open*. 2014;4(11).
- Forouzanfar F, Amin B, Ghorbani A, Ghazavi H, Ghasemi F, Sadri K, Mehri S, Sadeghnia HR, Hosseinzadeh H. New approach for the treatment of neuropathic pain: Fibroblast growth factor 1 gene-transfected adipose-derived mesenchymal stem cells. *Eur J Pain (United Kingdom)*. 2018;22(2).
- Quintans JSS, Antonioli ÂR, Almeida JRGS, Santana-Filho VJ, Quintans-Júnior LJ. Natural products evaluated in neuropathic pain models - a systematic review. *Basic Clin Pharmacol Toxicol*.

- 2014;114(6).
14. Vranken JH. Current Approaches to the Management of Peripheral Neuropathic Pain. In: *Journal of Pain and Palliative Care Pharmacotherapy*. 2015.
 15. Muchtaromah B, Ahmad M, S EK, A YM, A VL. Phytochemicals, Antioxidant and Antifungal Properties of *Acorus calamus*, *Curcuma mangga*, and *Allium sativum*. *KnE Life Sci*. 2017;3(6).
 16. Phongpaichit S, Pujenjob N, Rukachaisirikul V, Ongsakul M. Antimicrobial activities of the crude methanol extract of *Acorus calamus* Linn. *Songklanakarin J Sci Technol*. 2005;27.
 17. Venskutonis PR, Dagilyte A. Composition of essential oil of sweet flag (*acorus calamus* L.) leaves at different growing phases. *J Essent Oil Res*. 2003;15(5).
 18. Kemenkes RI. *Farmakope Indonesia edisi VI*. Departemen Kesehatan Republik Indonesia. 2020.
 19. Jumardin W, Amin S, Syahdan NM. Formulation of Balm from Basil Leaf Extract (*Ocimum sanctum* Linn) and Its Use as Traditional Medicine. *J Ilm As-Syifaa*. 2015;7(1).
 20. Altaf M, Manoharadas S, Zeyad MT. Green synthesis of cerium oxide nanoparticles using *Acorus calamus* extract and their antibiofilm activity against bacterial pathogens. *Microsc Res Tech*. 2021;84(8):1638–48.
 21. Ledianasari, Tristiyanti D, Tanjung EM, Barani L. Microencapsulation of Jeringau Rhizome essential oils (*Acorus calamus* L.) using β -cyclodextrin. *Pharm Educ*. 2021;21(2):189–94.
 22. Chappie TA, Humphrey JM, Allen MP, Estep KG, Fox CB, Lebel LA, Liras S, Marr ES, Menniti FS, Pandit J, Schmidt CJ, Tu M, Williams RD, Yang F V. Discovery of a series of 6,7-dimethoxy-4-pyrrolidylquinazoline PDE10A inhibitors. *J Med Chem*. 2007;50(2):182–5.
 23. Dong W, Yang D, Lu R. Chemical constituents from the rhizome of *acorus calamus* L. *Planta Med*. 2010;76(5):454–7.
 24. Ali B, Al-Wabel NA, Shams S, Ahamad A, Khan SA, Anwar F. Essential oils used in aromatherapy: A systemic review. *Asian Pac J Trop Biomed*. 2015;5(8):601–11.
 25. Varrassi G, Alon E, Bagnasco M, Lanata L, Mayoral-Rojals V, Paladini A, Pergolizzi J V., Perrot S, Scarpignato C, Tölle T. Towards an Effective and Safe Treatment of Inflammatory Pain: A Delphi-Guided Expert Consensus. *Adv Ther*. 2019;36(10):2618–37.
 26. Vonkeman HE, van de Laar MAFJ. Nonsteroidal Anti-Inflammatory Drugs: Adverse Effects and Their Prevention. *Semin Arthritis Rheum*. 2010;39(4):294–312.
 27. Safrina N, Susanti R, Sari R. Uji efek antiinflamasi ekstrak etanol rimpang jeringau merah (*Acorus* Sp.) terhadap radang kaki tikus jantan galur wistar yang diinduksi karagenan. *J*

- CDK-265. 2018;45(6)(6):409–13.
28. Al-Khayri JM, Sahana GR, Nagella P, Joseph B V., Alessa FM, Al-Mssallem MQ. Flavonoids as Potential Anti-Inflammatory Molecules: A Review. *Molecules*. 2022;27(9).
 29. Ribeiro D, Freitas M, Tomé SM, Silva AMS, Laufer S, Lima JLFC, Fernandes E. Flavonoids Inhibit COX-1 and COX-2 Enzymes and Cytokine/Chemokine Production in Human Whole Blood. *Inflammation*. 2015;38(2):858–70.
 30. Lopatina KA, Safonova EA, Nevskaya K V., Stakheeva MN, Gur'ev AM, Zueva EP, Razina TG, Amosova EN, Krylov SG, Belousov M V. Effect of *Acorus calamus* L. Polysaccharide on CD274 and CD326 Expression by Lewis Lung Carcinoma Cells in Mice. *Bull Exp Biol Med*. 2017;164(1):102–5.
 31. Shah AJ, Gilani AH. Bronchodilatory effect of *Acorus calamus* (Linn.) is mediated through multiple pathways. *J Ethnopharmacol*. 2010;131(2):471–7.
 32. Godfraind T. Discovery and development of calcium channel blockers. *Front Pharmacol*. 2017;8(MAY):1–25.
 33. Hsu YT, Liao G, Bi X, Oka T, Tamura S, Baudry M. The PDE10A inhibitor, papaverine, differentially activates ERK in male and female rat striatal slices. *Neuropharmacology*. 2011;61(8):1275–81.
 34. Hsu CL, Yen GC. Induction of cell apoptosis in 3T3-L1 preadipocytes by flavonoids is associated with their antioxidant activity. *Mol Nutr Food Res*. 2006;50(11).
 35. Dos Santos PDF, Francisco CRL, Coqueiro A, Leimann FV, Pinela J, Calhelha RC, Porto Ineu R, Ferreira ICFR, Bona E, Gonçalves OH. The nanoencapsulation of curcuminoids extracted from: *Curcuma longa* L. and an evaluation of their cytotoxic, enzymatic, antioxidant and anti-inflammatory activities. *Food Funct*. 2019;10(2).
 36. Tanigasalam V, Vishnu Bhat B, Adhisivam B, Plakkal N, Harichandra Kumar KT. Vasambu (*Acorus calamus*) Administration: A Harmful Infant Rearing Practice in South India. *Indian J Pediatr*. 2017;84(10):802–3.
 37. Ukkirapandian K, E K, Udaykumar KP, Kandhi S, R M. The Neuroprotective Role of *Acorus calamus* in Developmental and Histopathological Changes in Autism-Induced Wistar Rats. *Cureus*. 2022;
 38. Sharma V, Singh I, Chaudhary P. *Acorus calamus* (The Healing Plant): A review on its medicinal potential, micropropagation and conservation. Vol. 28, *Natural Product Research*. 2014.