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Review Article

The Potential Use of *Rosmarinus officinalis L.* as Antinociceptive Agent: A Systematic Review

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ABSTRACT

Pain is an uncomfortable symptom following numerous diseases, which may decrease the quality of life. Many pain-relieving agents have been used throughout history, such as non-steroidal anti-inflammatory drugs (NSAIDs). Unfortunately, these medications may increase the risk of unfavourable adverse effects, such as gastrointestinal and cardiovascular problems. Lately, herbal medicine has emerged as an effective pain-relieving medication with lower side effects. Due to its diverse phytochemical compounds, *Rosmarinus officinalis* L. (RO), a widely known herb, has a high potential to be used as a pain-relieving agent. This review aims to provide comprehensive information regarding the applications of RO as pain-relieving agents in various pain-induction methods. This study used a systematic review approach by gathering 998 studies from 3 databases and then choosing 16 studies suitable to the inclusion criteria. The process of study selection was conducted following the PRISMA diagram. Pain-related studies that involve the use of intraperitoneal or per-oral as the route of RO extract administration were reviewed in this study. RO contains various phytochemicals, such as flavonoids, carnosic acid, and carnosol, which can potentially interfere with pain mechanisms. RO reduces the pain symptoms observed through several pain evaluation methods while decreasing the expression of pain-related biomarkers.

Keywords: *Rosmarinus officinalis L.*, Rosemary, Pain, Anti-Nociceptive.

Introduction

Pain could be defined as an uncomfortable sensation and emotional experience associated with actual or potential tissue damage[1]. Generally, pain can be classified into several types according to its onset and location. Based on the onset, earlier studies divided pain into acute and chronic pain. Later, the International Association for the Study of Pain (IASP) classified pain based on its locations, such as chronic widespread pain, complex regional pain syndromes, chronic primary headache or orofacial pain, chronic primary visceral pain, and chronic primary musculoskeletal pain [2]. Almost every individual in the population experienced pain in different ways. The epidemiological data provided by Mills *et al*. reported that individuals may experience pain related to various stimuli, such as inflammation, infection, and trauma or injury. This study also noted that any individual may experience pain regardless of their age, gender, ethnicity, and socio-economic background[3]. Therefore, pain is one of the major health problems in the world. Different types of medications have been used to relieve pain, but the most commonly used are from Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) groups.

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However, NSAID intake may result in unfavourable side effects, such as gastritis, indigestion, gastrointestinal bleeding, and even an increased risk of cardiovascular diseases [4]. The use of herbal medicines to overcome pain-related problems has been studied for a long time, including the use of Rosemary (*Rosmarinus officinalis L.* / RO). RO is a shrub that belongs to the Lamiaceae family and is widely used as a mixture in foods, spices, and herbal tea [5–7]. Previous studies have reported that RO exerted many biological activities, such as anti-inflammatory, antinociceptive, antithrombotic, antioxidant, antidiabetic, anticancer, antimicrobial, and others [8–15]**.** Many studies have been conducted to understand the potential use of RO in various diseases through *in vitro* or *in vivo* studies, such as asthma, atherosclerosis, cataracts, renal colic, hepatotoxicity, peptic ulcer, inflammatory diseases, ischemic heart disease, and others [16,17]. However, to the best of the author's knowledge, this review is the first comprehensive study regarding the use of RO in *in vivo* pain models. It summarises the various phytochemical constituents present in RO and their possible molecular mechanism as antinociceptive agents.

Material and Methods

Eligibility Criteria and Literature Search

This study used a comprehensive review of the phytochemical and antinociceptive properties of *Rosmarinus officinalis L.* (RO) leaves. The qualitative systematic review (SR) was conducted by analyzing indexed and peer-reviewed articles from Scopus, PubMed, and Google Scholar, published between 2000–2023. The literature search was performed with the help of Publish or Perish 8 (Publish or Perish ver. 8, Harzing, England). All studies included in this review are written in English. The keywords used for the database search were '*Rosmarinus officinalis L.*,' 'Rosemary,' 'pain,' 'analgesic,' and 'anti-nociceptive.'This review was prepared in accordance with PRISMA (Figure 1).

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The inclusion and exclusion criteria of the studies selected in this review are displayed in Table 1. 998 studies were obtained and initially screened with the help of the Covidence website (https://www.covidence.org, Melbourne, Australia). After automatically removing duplicates using Covidence, 983 published articles were left. Five reviewers independently screened titles and abstracts of the literature collected. After reaching a consensus among reviewers, 931 studies were excluded because the title and abstract did not contain preferred keywords. Of 52 studies remaining, 21 studies were not retrieved because duplicates or full-text manuscripts were unavailable. From 31 studies, 15 were excluded. Fourteen studies were excluded because they used a combination of other herbs alongside RO, and 1 study was excluded because it was only conducted using *in silico* method. Data extraction was conducted from 16 remaining studies.

Data Extraction

Relevant data from the 16 included studies were gathered, including the type of study design, methods of pain induction, methods of nociceptive evaluation, and information regarding the use of RO, including the results of the studies. This study also focused on reviewing the RO effects of biomarkers associated with pain. Retrieved data are presented in descriptive manner (Table 2).

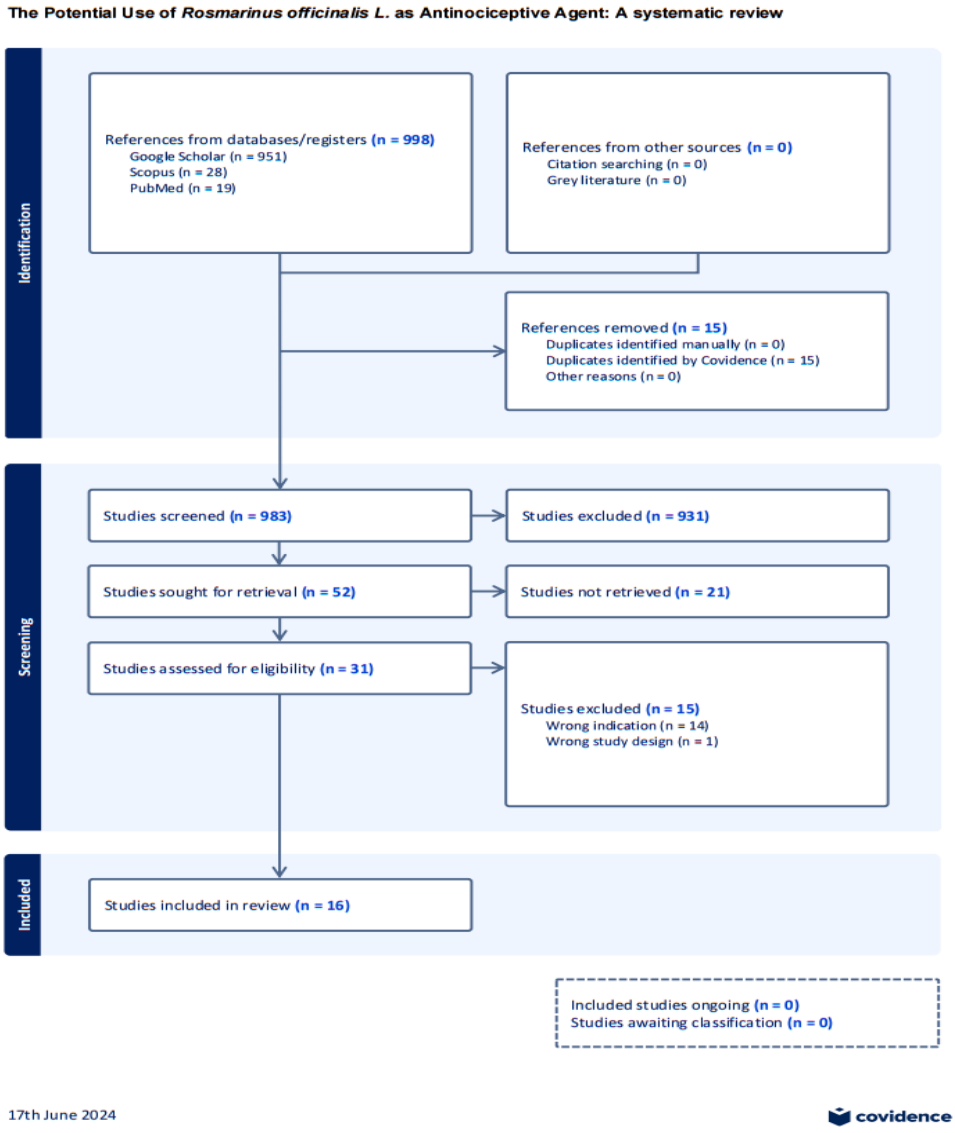

Figure 1. PRISMA Diagram. A total of 998 articles were reviewed between 2000-2023, and only 16 studies were included in this review.

Result and Discussion

Types of pain primarily studied in the included literature are neuropathic and inflammatory pain. Neuropathic pain can be described as pain caused by existing lesions or dysfunction in the nervous system[18]. On the other hand, inflammatory pain is the type of pain triggered by the onset of inflammation, mediated by the release of pro-inflammatory mediators, which are also involved in generating pain[19]. In animal models, neuropathic pain is commonly induced by ligation of the sciatic nerves, causing chronic constriction injury (CCI). In contrast, inflammatory pain may be induced by administration of various pro-inflammatory agents, such as carrageenan, formalin, or bacterial lipopolysaccharide (LPS). 1% Carrageenan suspension is commonly used in animal pain models by subplantar injection [20]. After pain induction, researchers are also required to assess the pain response. These assessments can be conducted using several methods, such as the paw pressure test (The Randall-Selitto test), Von Frey test, plantar test, writhing test, hot-plate test, and tail immersion test. Those tests were also used to evaluate and compare pain responses in the control and RO extract-treated groups. The paw pressure test is one of the methods used to assess and evaluate the response thresholds to mechanical pressure stimulations. The stimuli can be applied to the rodent's tail or hind paw, and the pressure will increase consistently. The Von Frey test is the gold standard used to determine the mechanical non-noxious threshold in

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Table 1. Inclusion and exclusion criteria in study selection

Inclusion criteria	Exclusion criteria
Original articles conducting accurate experimental studies	Literature or systematic review articles
In vivo or animal studies using pain induction models (inflammatory, neuropathic, acute and chronic pain, etc.)	Studies not written in English
Studies that used RO in any form of preparation: extract, emulsion, gel, essential oil, etc.	Studies that used a combination of RO with other types of herbs or compounds
Studies that used phytochemical compounds isolated from RO, such as rosmarinic acid	Only *In-silico* studies (without enhancement using *in-vivo* method)
	Studies that used phytochemical compounds not isolated from RO

rodents by evaluating a reduction in the initial withdrawal threshold, one of which is for the neuropathic pain test [21,22]. On the other hand, the plantar test is used to assess thermal sensitivities with the plantar test apparatus. Another method is the writhing test, a chemical method used to induce pain of peripheral origin by injecting irritant principles like phenyl quinone and acetic acid in mice, which has been used as a screening tool for assessing analgesic agents[23]. The writhing test consists of the intra-peritoneal (i.p) administration of 0.6% acetic acid that irritates serous membranes. This test generates typical behaviour characterised by abdominal contractions (writhing) combined with the outstretching of the hind limbs. The hot-plate test evaluates the antinociceptive effect of RO by measuring the response latencies in rodents through discomfort demonstrated by jumping, withdrawal of paws, or licking of paws. Most of the studies included in this review showed that RO administration decreases pain response and pain biomarkers dose-dependently. However, the route of administration is unlikely to interfere with the effectiveness of RO. Both Mannelli *et al.* and Ghasemzadeh *et al.* used chronic constriction injury (CCI) for pain induction but chose different routes of administration: oral and intraperitoneal, respectively, and both studies showed a reduction in pain parameters, including physiological and molecular markers.[21,24] Mannelli *et al.* performed paw pressure tests on several groups of RO extraction.

There was a reduction in the pain sensitivity after administration of RO ethanol-extract (100–300 mg kg^{-1}), while RO acetone-extract (100 and 300 mg kg^{-1}) could increase the pain threshold. Administration of *n*-hexane-ultrasound assisted-extraction (URE*prel)* 100 mg kg^{-1} and URE 70.0 mg kg^{-1}), as well as carnosic acid (13.5 mg kg^{-1}) also significantly showed a reduction of mechanical hypersensitivity by paw pressure test. Several extracted compounds of RO showed the capability to reduce pain. In chronic constriction injury (CCI) of the sciatic nerve, 300 mg kg^{-1} of RO ethanol and acetone extracts increased the withdrawal threshold of ipsilateral paws 14 days after injury. This study also showed that carnosic acid isolated from RO was the only effective treatment to prevent thermal hyperalgesia on day 7[21]. Martinez *et al*. showed that mice treated with hexane, ethyl acetate, and ethanol crude extract of RO could delay the first writhe significantly [25]. Additionaly, the injection of RO extract into rats also significantly reduced writhing in acetic-acid-induced abdominal contraction tests compared to control groups, suggesting a reduction of pain. Abdelhalim *et al.* showed that salvigenin, rosmanol, and cirsimaritin isolated from RO with doses of 10-100 mg/kg caused a significant increase in the latency response from 30 to 120 minutes after treatment [26]. Other antinociceptive phytochemicals are triterpenes, micromeric acid, and ursolic acid. A study by Martinez *et al.* showed that nociceptive response was significantly reduced for all the animals receiving crude hexane (100 mg/kg), ethyl acetate (100 mg/kg), and ethanol (100 mg/kg) extract of RO. The study showed that ethyl acetate fraction from RO aerial parts confirmed a significant antinociceptive effect because of the presence of micromeric, oleanolic, and ursolic acids [25].

Tail immersion and hot plate tests by Abdelhalim *et al*. showed that salvigenin, rosmanol, and cirsimaritin fractionated from RO exerted significant antinociceptive effects at the dose level of 10-100 mg/kg [26]. Analgesic effects of salvigenin, rosmanol, and cirsimaritin might occur via one or more of several proposed non-opioid mechanisms such as blockade of voltage-gated Na+ channels, activation of the noradrenergic inhibitory system, enhancement of GABAergic and/or serotonergic systems. Another phytochemical constituent is carnosic acid (CA), which has shown neuroprotective effects in both *in vitro* and *in vivo* studies. CA is also known to inhibit the AChE activity. Treatment with RO attenuates peripheral nerve inflammation, reducing oedema and infiltrate, suggesting synergy between this extract's anti-inflammatory and anti-nociceptive effects[27,28]. Other than that, phytochemical constituents of RO may have the ability to lower the expression of pain-related biomarkers, such as TNF-*α*, COX-2, PGE-2, IL-1*β*, and MMP-2. COX-2 is a crucial enzyme in arachidonic acid metabolism and is vital in inducing PGE-2 release [29]. Higher expression of PGE-2 may induce the expression of IL-1*β*, which is an important pro-inflammatory cytokine associated with inflammatory pain. Furthermore, in neurons, IL-1*β* is also known to cause an increase in nerve growth factor (NGF), a neurotrophic factor that plays a role in both acute and chronic pain, both at the transcriptional and post-transcriptional levels [30]. Carnosic acid (CA) and carnosol (CO) contained in RO can decrease the expression of these biomarkers, possibly via inhibition of the Nuclear Factor light-chain kappa-B (NFkB) pathway. The NFkB pathway plays a vital role in the release of pro-inflammatory cytokines. Therefore, by inhibiting this pathway, several pro-inflammatory cytokines that predispose to inflammatory pain sensation, such as TNF-*α*, IL-6, and IL-1*β*, may also be inhibited[31,32]. By inhibiting these biomarkers, the inflammation process may be reduced or delayed, lowering the pain.

This systematic review provides comprehensive information regarding the potential use of RO as an antinociceptive agents. However, this study has several limitations. First, five studies included in this review did not identify the specific phytochemical constituents of RO; therefore, it was impossible to discuss the possible molecular mechanism. Secondly, limited studies evaluate each RO phytochemical constituent's exact role and mechanism in inhibiting pain.

Conclusion

This review summarises essential findings from 16 relevant articles regarding the antinociceptive properties of RO in various pain-evaluation methods *in vivo*. RO can potentially reduce clinical symptoms of pain and the expression of pain-related biomarkers due to its phytochemical constituents. However, the exact mechanism of RO in reducing the expression of pain-related biomarkers still needs to be elucidated. Further studies are still required to address this problem.

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Table 2. Summary of Important Findings from Included Studies

No	Ref.	Types of Pain (Animal type)	Methods of Pain Induction	Preparations of Compound	Phytochemical compounds	Administration (Dose)	Result of study
1.	[21]	Neuropathic pain (Sprague Dawley rat)	CCI via sciatic nerve ligation	RO leaves ethanolic extract	Carnosic acid; carnosol; cirsimaritin; rosmarinic acid; flavonoid	p.o (100 and 300 mg/kg)	GFAP positive cells ↓, paw pressure test↓, von-Frey test ↓, plantar test ↓
2.	[33]	Neuropathic pain (Wistar Rats)	CCI via sciatic nerve ligation	RO aerial part ethanolic extract	Rosmarinic acid	i.p (400 mg/kg)	All biomarkers ↓ (COX2, IL-1b, NO, PGE-2, MMP2 ↓)
3.	[15]	Neuropathic and inflammatory pain (Swiss albino and Wistar rats)	Injection of acetic acid, formalin, and carrageenan	RO stem and leaves extract; Isolated RA and AE derivative of RA	Rosmarinic acid and acetyl ester derivative of RA	p.o (Extract 100, 200, 400 mg/kg; active compounds 10, 20, 40 mg/kg)	Paw oedema volume ↓, writhing score ↓, pain inhibition score ↑after giving AE derivative of RO extract
4.	[34]	Visceral pain (albino NMRI mice)	Injection of acetic acid	RO aerial extract	n.s	i.p (50, 100, 200 mg/kg)	Abdominal constrictions ↓. RO showed effects in a dose-dependent manner.
5.	[35]	Inflammatory pain (Wistar Rats)	Injection of acetic acid; carrageenan	RO ethanolic extract	Limonene; cineole; and camphor	p.o (Extract (100 mg/kg); nanoemulsion (166, 498 and 830 µg/kg),	Number of writhes ↓: RO Nanoemulsion is 600 times more effective compared to conventional RO extract
6.	[36]	Acute toxicity (Swiss Webster Mice)	Acute toxicity induction	Petroleum ether extract of RO whole plant	Salvigenin; rosmanol; cirsimaritin	i.p (50, 150, and 200 mg/kg)	PE extract of RO shows antinociceptive, anti-depressive, and anxiolytic effects.
7.	[37]	Inflammatory and neuropathic pain (Swiss albino and Wistar rats)	Carrageenan injection; Granulomatous tissue induction; Gastric ulcer induction; Croton Oil Ear Edema induction	RO Essential oils	1,8-cineole; α-pinen; camphor; 2-ethyl-4,5-dimethylphenol; camphene; pinene; geranyl acetate; and unidentified terpenes.	p.o (300 mg/kg)	Number of muscular contractions ↓
8.	[11]	Arthritic pain (Swiss Webster Mice)	Injection of acetic acid and Formalin	RO aerial extract	n.s	p.o (10, 30, 100 and 300 mg/kg)	300 mg/kg caused paw oedema volume ↓; number of writhes ↓

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9.	[38]	Nociceptive pain (Swiss Webster Mice)	Hot Plate pain induction	RO aerial part ethanolic extract	1,8-cineole; α-Pinene; borneol; camphor; Linalool; verbenone; Geraniol; camphene	s.p (100, 200 and 400 mg/kg)	The mean response latency ↑, which reached a maximum of 30.28 s for a dose of 400 mg/kg, showed an effect in a dose-dependent manner.
10.	[39]	Arthritic pain (Wistar Rats)	Limb injury via uric acid injection	RO essential oil	α-pinene; camphene; β-pinene; myrcene; α-phellandrene; eucalyptol; 2-bornanone; camphor; isoborneol; borneol;	i.p and s.c (10, 30, 100, 300, or 600 mg/kg)	This study suggests an involvement of the serotonergic system via 5-HT1A receptors and endogenous opioids in the antinociceptive effect of RO
11.	[40]	Visceral pain (Swiss Webster mice)	Injection of 0.6% acetic acid	HE, EA, or ECE from RO aerial parts	Micromeric acid, oleanolic acid, and ursolic acids.	i.p of HE, EA, or ECE (each100 mg/kg bw)	Number of writhes ↓ (dose 100 mg/kg) resembled the efficacy of ketorolac given in a 10 mg/kg dose
12.	[41]	Gout arthritis (Swiss Webster mice and Wistar rats)	Injection of acetic acid and formalin	RO aerial part ethanolic extract	n.s	p.o (300 mg/kg)	Number of writhes ↓
13.	[42]	Inflammatory Pain (NMRI mice)	Formalin Injection	RO aerial part ethanolic extract	n.s	i.p (10, 20, 30, 40, 50 mg/kg)	COX1 ↓, COX2 ↓
14.	[24]	Neuropathic pain (Wistar Rats)	CCI via sciatic nerve ligation	RO aerial part ethanolic extract	Rosmarinic acid	i.p (40, 400 mg/kg)	COX2↓, PGE2↓, IL-1B↓, MMP2↓, NO↓
15.	[43]	Painful diabetic neuropathy (Wistar Rats)	Diabetes induction by STZ	RO Leaves ethanolic extract	n.s	p.o (100, 150, 200 mg/kg)	Nerve cell damage ↓; apoptosis markers ↓ (caspase 3↓; Bax:Bcl-2 ratio ↓)
16.	[44]	Neuropathic pain (Wistar Rats)	CCI via sciatic nerve ligation; LPS induction	RA isolated from RO	Rosmarinic acid	i.p (10, 20, 40 mg/kg)	GFAP↓; Iba-1↓; Bax Bcl2 ratio ↓; TNF-α ↓ iNOS↓; TLR-4↓

Ref.= References; AE = acetyl ester; CCI = Chronic Constriction Injury; PE = petroleum ether; RA = Rosmarinic Acid, RO = *Rosmarinus officinalis L.;* p.o = per oral; i.p = intra peritoneal; s.p = sub plantar; n.s = not specified; HE = Hexane; EA = ethyl acetate; ECE = ethanol crude extracts; STZ= Streptozotocin

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Conflict of Interests

The authors have no conflict of interest to declare.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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