

Analgesic Potential of Flavonoids for Cancer-Associated Pain and its Treatments: Systematic Review

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Potencial Analgésico dos Flavonoides na Dor Associada ao Câncer e ao seu Tratamento: Revisão Sistemática

Potencial Analgésico de los Flavonoides para el Dolor Asociado al Cáncer y sus Tratamientos: Revisión Sistemática

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ABSTRACT

Introduction: Pain is a prevalent and debilitating symptom in cancer patients, reducing quality of life. Its management is often challenging, with conventional pharmacological treatments associated with undesirable side effects. Natural compounds as flavonoids have garnered attention among emerging therapeutic approaches. Flavonoids are phenolic compounds abundant in the plant kingdom, recognized for their antitumor, anti-inflammatory, anti-allergic, and antiangiogenic properties. However, their analgesic potential is yet to be explored. **Objective:** Literature review of the analgesic potential of flavonoids in cancer pain and/or treatment-related. **Method:** A search was conducted at the PubMed, SciELO, Lilacs, and Cochrane Library databases with the keywords “cancer”, “flavonoids”, and “pain”. Inclusion criteria were clinical studies published between 2010 and 2024 in English, Portuguese, or Spanish, with patients over 18 years of age, that investigated the association among cancer, flavonoids, and pain. All the studies were submitted to risk of bias analysis. The study was approved by PROSPERO and based on PRISMA. **Results:** 14 clinical trials were included. The most frequently studied compound was Epigallocatechin gallate, for breast, lung, head and neck, and esophagus (n=9) cancers. All the studies investigated flavonoids in treatment-related pain, demonstrating pain reduction in cases of radiodermatitis, mucositis, esophagitis, and onycholysis. Flavonoid administration, either prophylactic or therapeutic, was well tolerated when applied topically or orally. **Conclusion:** Flavonoids exhibit promising analgesic potential in cancer-related pain, with minimal or no reported side effects. Further clinical studies are needed to elucidate their effectiveness in this context.

Keywords: Neoplasms/drug therapy; Flavonoids/pharmacology; Pain Management.

RESUMO

Introdução: A dor é um sintoma prevalente e incapacitante em pacientes com câncer, contribuindo para redução da qualidade de vida. Seu manejo é desafiador, com tratamentos farmacológicos convencionais associados a efeitos colaterais indesejáveis. Entre as abordagens terapêuticas emergentes, compostos naturais como flavonoides têm recebido atenção. Flavonoides são compostos fenólicos abundantes no reino vegetal, que possuem propriedades antitumorais, anti-inflamatórias, antialérgicas e antiangiogênicas, embora seu potencial analgésico seja pouco explorado. **Objetivo:** Revisar a literatura acerca do potencial analgésico dos flavonoides na dor oncológica e/ou relacionada ao tratamento. **Método:** Foi realizada uma pesquisa nas bases PubMed, SciELO, Lilacs e Biblioteca Cochrane utilizando as palavras-chave “câncer”, “flavonoides” e “dor”. Foram incluídos estudos clínicos publicados entre 2010 e 2024, em inglês, português ou espanhol, com pacientes acima de 18 anos. Foram considerados estudos que avaliaram a relação entre câncer, flavonoides e dor. Todos os estudos foram submetidos à análise de risco de viés. O estudo foi aprovado pelo PROSPERO e elaborado a partir do PRISMA. **Resultados:** Foram incluídos 14 estudos clínicos. O composto mais frequentemente estudado foi a epigallocatequina galato, avaliado em cânceres de mama, pulmão, cabeça e pescoço e esôfago (n=9). Todos os estudos investigaram flavonoides na dor relacionada ao tratamento, com redução algica em radiodermatite, mucosite, esofagite e onicólise. A administração de flavonoides, profilática ou terapêutica, foi bem tolerada tanto por via tópica quanto oral. **Conclusão:** Os flavonoides demonstram potencial analgésico promissor na dor associada ao câncer, com poucos ou nenhum efeito colateral. Estudos adicionais são necessários para elucidar sua eficácia.

Palavras-chave: Neoplasias/tratamento farmacológico; Flavonoides/farmacologia; Manejo da Dor.

RESUMEN

Introducción: El dolor es un síntoma debilitante en pacientes con cáncer, reduciendo la calidad de vida. Su tratamiento es complicado, ya que los fármacos convencionales suelen causar efectos secundarios. Entre los enfoques emergentes, los flavonoides, compuestos fenólicos del reino vegetal, han recibido atención por sus propiedades antitumorales, antiinflamatorias y antiangiogénicas. No obstante, su potencial analgésico aún está poco explorado. **Objetivo:** Revisar la literatura sobre el potencial analgésico de los flavonoides en el dolor oncológico y el asociado a tratamientos. **Método:** Se realizó una búsqueda en PubMed, SciELO, Lilacs y Cochrane Library utilizando las palabras clave “cáncer”, “flavonoides” y “dolor”. Se incluyeron estudios clínicos publicados entre 2010 y 2024 en inglés, portugués o español, con pacientes mayores de 18 años. Se evaluaron estudios que investigaron la relación entre cáncer, flavonoides y dolor, y se realizó un análisis del riesgo de sesgo. El estudio fue aprobado por PROSPERO y se basó en PRISMA. **Resultados:** Se incluyeron 14 estudios clínicos. El galato de epigallocatequina galato fue el compuesto más estudiado, evaluado en cánceres de mama, pulmón, cabeza y cuello, y esófago (n=9). Todos los estudios investigaron el uso de flavonoides en el dolor relacionado con el tratamiento, observando una reducción en casos de radiodermatitis, mucositis, esofagitis y onicólisis. La administración de flavonoides, profiláctica o terapéutica, fue bien tolerada tanto por vía tópica como oral. **Conclusión:** Los flavonoides muestran un prometedor potencial analgésico en el dolor asociado al cáncer, con efectos secundarios mínimos o inexistentes. Se requieren más estudios clínicos para confirmar su eficacia. **Palabras clave:** Neoplasias/quimioterapia; Flavonoides/farmacología; Manejo del Dolor.

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INTRODUCTION

During the cancer patient's journey, several events cause loss of performance. Among the lines of treatment, the main tool in cancer therapy is the association between surgical resection and radiotherapy and chemotherapeutic compounds, which may damage the healthy tissue. In this sense, local and systemic toxicity triggers side effects that are often limiting to the patient and with loss of quality of life^{1,2}.

Pain is a common symptom of cancer and its treatment³. A study by Breivik et al. in 2009 evaluated 5,000 adults with cancer, showing that 56% of them suffered from moderate to severe pain at least monthly⁴. Cancer patients may develop hyperalgesia, allodynia, and spontaneous pain, impacting their quality of life⁵. However, pain can be relieved in up to 90% of these patients⁶ and, in despite of management efficacy, some studies show that pain remains poorly controlled for many of them^{6,7}.

In the oncologic patient, pain can be related to the tumor invasion process to adjacent tissues, compressing peri-tumoral structures; for example, phantom pain associated with resection in surgical treatment, and peripheral neuropathy associated with chemotherapy or radiotherapy where there is tissue damage and pain, such as mucositis^{8,9}. Furthermore, the patient's experience related to pain can positively or negatively influence the clinical outcome¹⁰.

The medications proposed to relieve pain are often associated with other side effects, as fatigue, sleep apnea, decreased libido, nausea, vomiting, and constipation¹¹⁻¹⁴. Thus, it is necessary to search for new compounds with fewer side effects and similar efficacy to control pain.

Plants and their secondary metabolites have been used to treat various pathological conditions. In many regions with little access to modern medicine, plants are the primary source for home treatment of some diseases^{15,16}. The science of natural products has discovered many substances used today.

Flavonoids, one of the main biocomposites, are the focus of tumor biology researches in recent decades. These are compounds of polyphenolic origin widely distributed in the plant kingdom and found in aglycones, glycosides, or methylated derivatives, usually detected in a healthy diet containing fruits and vegetables and concentrated in teas, wines, apples, onions, and cocoa¹⁷.

One of its most important mechanisms of actions is the antioxidant property, preventing damage caused by free radicals through direct neutralization of reactive oxygen species, activation of antioxidant enzymes, chelation of metals, reduction of α -tocopheryl radicals,

inhibition of oxidases, reduction of oxidative stress caused by nitric oxide, increase in uric acid levels, and increase of the activity of low molecular weight antioxidants. The antioxidant capacity of some flavonoids, as Epigallocatechin gallate (EGCG), is higher than that of vitamins C and E^{18,19}.

The molecular structure of flavonoids is based on the *flavilium* core, composed of three phenolic rings. Variations in the central phenolic ring give rise to flavonoid classes, as flavonols, flavones, catechins, flavanones, anthocyanidins, and isoflavonoids, and lead to the formation of compounds with distinct rates of absorption and bioavailability, responsible for different pharmacological actions of flavonoids *in vivo*¹⁹⁻²¹.

Flavonoids have a broad pharmacological activity already described, presenting antioxidant, anti-inflammatory, cardioprotective, vasorelaxant, antibacterial, antiviral, hepatoprotective, anti-proliferative, chemopreventive, neuroprotective, and antiangiogenic effects^{19,22-35}. Although the literature points to the potential of flavonoids in pain management, little is known about their cancer-related analgesic potential. Thus, the objective of the present literature review is to evaluate the potential of flavonoids in the management of cancer-related pain and/or its treatment.

METHOD

Systematic review registered at PROSPERO³⁶ (International Prospective Register of Systematic Reviews), number CRD42022311072, utilizing PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)³⁷.

Relevant articles published in English, Portuguese and Spanish were searched at the databases PubMed, SciELO, Lilacs, and Cochrane Library from February 6, 2022 to September 25, 2024 applying the keywords combined with the Boolean operators AND OR for closed vocabularies: cancer AND pain OR cancer pain AND flavonoids OR flavonols according to DeCS/MESH (*Descritores em Ciências da Saúde*/Medical Subject Headings).

The authors selected the studies independently and, in case of any disagreement, a discussion was held to reach a consensus. The full text of the studies that met the inclusion criteria was separated for further evaluation. To expand the coverage of the literature, reference lists of the studies included and systematic reviews identified during the screening process were also investigated.

Studies associating cancer, flavonoids, and pain, utilizing control groups (flavonoid-treated versus

conventional analgesic-treated or untreated), from 2010 to 2024, have been included, since there are few studies on the subject especially in the last five years addressing patients with confirmed diagnosis of pain and cancer, regardless of the tumor site or stage, aged 18 years or older (pain was associated with cancer or oncologic treatment (chemotherapy/radiotherapy/surgery). Studies investigating patients with diagnoses other than cancer, different types of symptoms, not addressing pain, off the scope, literature reviews and low level of scientific evidence were excluded.

Two authors collected the data and information (author's name, year of publication, method, sample type, and results) that met the inclusion criteria, and another author checked the information independently. The quality of the evidence and the risk of bias were assessed using the Cochrane Collaboration Risk of Bias Tool (RoB 2.0) for randomized clinical trials³⁸, and Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I), for non-randomized studies³⁹. Each study was categorized for risk of bias into low, high, and unclear. Any disagreements were discussed and resolved by another author.

RESULTS

Following the analysis, 15 studies collected at the Cochrane Database have been excluded due to other comorbidities, as hemorrhoids, postpartum pain, and osteoarthritis. Among the five pre-selected studies, four were excluded because they involved different compounds or were preclinical studies with animal models.

Similarly, 186 studies collected at PubMed database were excluded because they addressed unrelated pathologies, as cardiovascular diseases, arthritis, and other inflammatory processes, in addition to studies utilizing different compounds, flavonoids outside the analgesic context, or literature reviews/pre-clinical studies. As a result, after pre-selecting 50 studies, 37 articles have been excluded and 13 were included in the review.

Eventually, 13 articles have been identified at PubMed and one at the Cochrane Library (Figure 1), resulting in 14 studies summarized in Table 1. No results were found at SciELO and Lilacs.

All selected studies are in English, 50% of which were randomized (n=7). Of these, 71.42% were double-blinded (patient and investigator, n=5). 28.57% were single-blinded, only the patient (n=2). The studies investigated a minimum of 20 and a maximum of 180 patients.

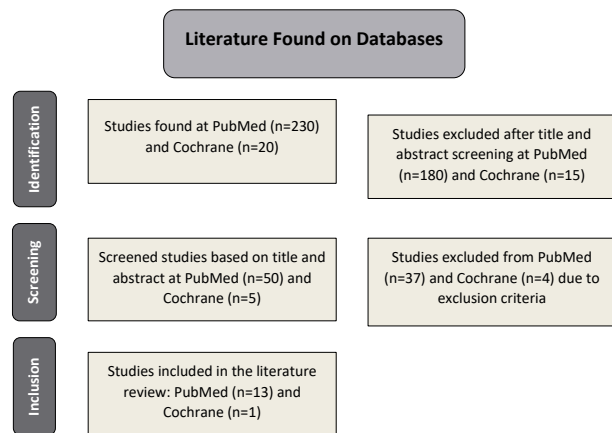


Figure 1. Flowchart of the selection of studies for the review based on the inclusion and exclusion criteria

Source: The authors, based on PRISMA³⁷.

Among the cancer topographies (Figure 2), 26.66% were lung cancer (n=4), 26.66%, breast cancer (n=4), 20%, prostate cancer (n=3), 13.33%, head and neck cancer (n=2), 6.66%, esophageal (n=1), and one (n=1), gynecological. One study evaluated two types of cancer (breast and prostate).

Epigallocatechin gallate was the most evaluated flavonoid by 62.28% of the studies (n=9), due to its efficacy in improving pain with few side effects associated with the compounds. The most common effects were burning and nausea⁴⁰. In cases of topical application, there were no reports of adverse effects (Table 1).

The studies used the Common Terminology Criteria for Adverse Events (CTCAE)⁴¹⁻⁴³, Radiation Therapy Oncology Group (RTOG)^{41,42,44}, and European Organization for Research and Treatment of Cancer (EORTC)⁴⁴ to assess toxicity. A questionnaire was used to assess the quality of life^{40,42,45,46}. In addition, pain was also assessed using the Verbal Numeric Scale^{40,42,44,47,48}. For skin toxicity, pain, burning, itching, pulling, and tenderness were assessed using the Skin Toxicity Assessment Tool in cases of patients undergoing radiotherapy⁴¹. Mucositis was assessed using a specific scale⁴⁹.

In addition to radiotherapy, the chemotherapy drugs utilized were cisplatin, etoposide, fluorouracil, docetaxel, and cabazitaxel^{49,50}.

The studies were statistically analyzed using the paired or unpaired t-test, chi-square, Mann-Whitney, and ANOVA. All statistical tests considered a significance level of less than or equal to 0.05.

The risk of bias was assessed individually for each selected study using Cochrane's assessment tool for randomized and non-randomized trials (RoB 2.0 and ROBINS-I, respectively) (Figure 3).

Table 1. Characteristics of the studies included, 2020-2024

Title/year	Author	Compound	N*	Site	Design	Conclusion
Epigallocatechin-3-gallate mouthwash protects mucosa from radiation-induced mucositis in head and neck cancer patients: a prospective, non-randomised, phase 1 trial (2020)	Zhu W, et al. ⁴⁰	Epigallocatechin	20	Head and neck cancer	Non-randomized	EGCG administration reduces radiation-induced oral mucosal injury in patients
Phase I study of topical epigallocatechin-3-gallate (EGCG) in patients with breast cancer receiving adjuvant radiotherapy (2016)	Zhao H, et al. ⁴¹	Epigallocatechin	24	Breast cancer	Non-randomized	Patient-reported symptom scores were significantly decreased in two weeks after the end of radiotherapy in pain, burning, itching and tenderness, $p < 0.05$
Phase II Trial of Epigallocatechin-3-Gallate in Acute Radiation-Induced Esophagitis for Esophagus Cancer (2020)	Li X, et al. ⁴²	Epigallocatechin	51	Esophageal cancer	Non-randomized	EGCG might be an acute radiation-induced esophagitis-reliever without compromising the efficacy of radiation therapy
Efficacy of Epigallocatechin-3-Gallate in Preventing Dermatitis in Patients with Breast Cancer Receiving Postoperative Radiotherapy: A Double-Blind, Placebo-Controlled, Phase 2 Randomized Clinical Trial (2022)	Zhao H, et al. ⁴³	Epigallocatechin	180	Breast cancer	Double-blind randomized	Prophylactic use of EGCG solution significantly reduced the incidence and severity of radio-induced dermatitis in patients receiving adjuvant radiotherapy for breast cancer
A prospective, three-arm, randomized trial of EGCG for preventing radiation-induced esophagitis in lung cancer patients receiving radiotherapy (2019)	Zhao H, et al. ⁴⁴	Epigallocatechin	83	Non-small-cell lung cancer	Randomized controlled	The application of EGCG could effectively alleviate acute radiation esophagitis in advanced lung cancer without obvious side effects. Prophylactic application of EGCG had a slight advantage over therapeutic use in treatment of acute esophagitis
Soy isoflavones in conjunction with radiation therapy in patients with prostate cancer (2010)	Ahmad IU, et al. ⁴⁵	Soy isoflavone	27	Prostate cancer	Double-blind randomized	The results suggest that soy isoflavones taken in conjunction with radiation therapy could reduce the urinary, intestinal, and sexual adverse effects in patients with prostate cancer including less pain with bowel movements
A double-blind, randomized trial of a polyphenolic-rich nail bed balm for chemotherapy-induced onycholysis: the UK polybalm study (2018)	Thomas R, et al. ⁴⁶	Plant balm	60	Breast and prostate cancer	Double-blind, randomized	The polyphenolic-rich essential oils reduced chemotherapy-related nail damage and improved nail-related quality of life, compared to a control

Continue...



Table 1. Continuation

Title/year	Author	Compound	N*	Site	Design	Conclusion
A phase I study of concurrent chemotherapy and thoracic radiotherapy with oral epigallocatechin-3-gallate protection in patients with locally advanced stage III non-small-cell lung cancer (2014)	Zhao H, et al. ⁴⁷	Epigallocatechin	24	Non-small-cell lung cancer	Non-randomized	The oral administration of EGCG is feasible, safe and effective, with dramatic regression of esophagitis to grade 0/1 and reduced pain score
A prospective phase II trial of EGCG in treatment of acute radiation-induced esophagitis for stage III lung cancer (2015)	Zhao H, et al. ⁴⁸	Epigallocatechin	37	Lung cancer	Non-randomized	The oral administration of EGCG is an effective and safe method to deal with acute radiation-induced esophagitis
Antioxidant capacity of calendula officinalis flowers extract and prevention of radiation induced oropharyngeal mucositis in patients with head and neck cancers: a randomized controlled clinical study (2013)	Babaei N, et al. ⁴⁹	Calendula extract (quercetin)	40	Head and neck cancer	Double-blind randomized	Calendula extract was effective in decreasing the intensity of radiotherapy-induced mucositis, and the antioxidant capacity of quercetin may be partially responsible for the effect
Phase I/II Trial of the Combination of 177Lutetium Prostate specific Membrane Antigen 617 and Idroneoxil (NOX66) in Men with End-stage Metastatic Castration-resistant Prostate Cancer (LuPIN) (2021)	Crumbaker M, et al. ⁵⁰	Idroneoxil (genistein)	32	Prostate cancer	Non-randomized	Idroneoxil with LuPSMA-617 is a safe and feasible therapeutic strategy, with pain improvement in men treated with third-line therapy for prostate cancer
Epigallocatechin-3-gallate ameliorates radiation-induced acute skin damage in breast cancer patients undergoing adjuvant radiotherapy (2016)	Zhu W, et al. ⁵¹	Epigallocatechin	49	Breast cancer	Non-randomized	EGCG reduced the pain in 85.7% of patients, burning-feeling in 89.8%, itching in 87.8%, pulling in 71.4%, and tenderness in 79.6%
A Randomized Placebo- Controlled Double Blind Clinical Trial of Quercetin in the Prevention and Treatment of Chemotherapy-Induced Oral Mucositis (2017)	Kooshyar MM, et al. ⁵²	Quercetin	23	Hematologic cancer	Double-blind, randomized	The incidence of mucositis was lower in the quercetin group. Mucositis was more severe in the intervention group, which may be due to lower oral health status.
Sinecatechins ointment as a potential novel treatment for usual type vulvar intraepithelial neoplasia: a single-centre double-blind randomised control study (2020)	Yap J, et al. ⁵³	Sinecatechins	26	Vulvar intraepithelial neoplasia	Double-blind randomized	The application of sinecatechins is safe and shows promise in inducing clinical resolution of vulvar intraepithelial neoplasia lesions and improving symptoms such as pain
Evaluation of Epigallocatechin-3-Gallate as a Radioprotective Agent During Radiotherapy of Lung Cancer Patients: A 5-Year Survival Analysis of a Phase 2 Study (2021)	Zhu W, et al. ⁵⁴	Epigallocatechin	38	Small cell lung cancer	Randomized controlled	EGCG can relieve some esophagitis-related scores, such as pain, in SCLC patients exposed to ionizing radiation without reducing survival

(*) Sample.

Each study was analyzed individually for methodological quality, according to questionnaires established by the Cochrane tools for systematic reviews. Seven randomized studies were assessed by Risk of Bias 2.0 for randomized studies. The main issue was bias due to missing results, because of loss to follow-up mainly associated with side effects in patients in the placebo group. The other seven studies were assessed using the ROBINS-I tool for non-randomized studies, with bias in the measurement of outcome and no-blinding of the participants.

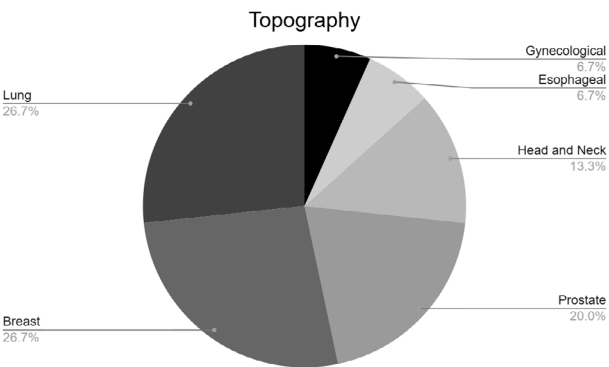


Figure 2. Percentage of cancer topographies analyzed by the studies included

DISCUSSION

Flavonoids, polyphenolic compounds of natural origin, are easily found in fruits and vegetables, and besides innumerable health benefits, their toxicity is low, emerging as new alternative therapies for some diseases as cancer. These molecules are known for their antioxidant effects and, therefore, for their direct action on oxidative stress. However, there is a wide range of benefits of flavonoids, as anti-inflammatory, antioxidant, antiallergic, antiproliferative, neuroprotective, antitumor, and antiangiogenic actions^{17,55,56}.

Pain is the most reported and feared symptom for cancer patients. About 90% of patients experience pain at different stages of the disease progression. It is reported by 33% of survivors, 59% of those on treatment, 64% with active disease, and up to 80% in advanced stages and/or terminally ill, being the main cause for seeking medical care^{4,57}.

The type of pain varies according to its origin. About 93% of patients complain of pain related to cancer itself, arising from bone lesions (spinal cord compression, skull metastases, fractures, and long bone lesions), nerve infiltration in epidural and meningeal sinuses, visceral infiltration in pleura, liver, peritoneum, and pancreas, and vascular infiltration, triggering stroke, thromboembolism, and vena cava obstruction. In addition, 21% of pain complaints are associated with

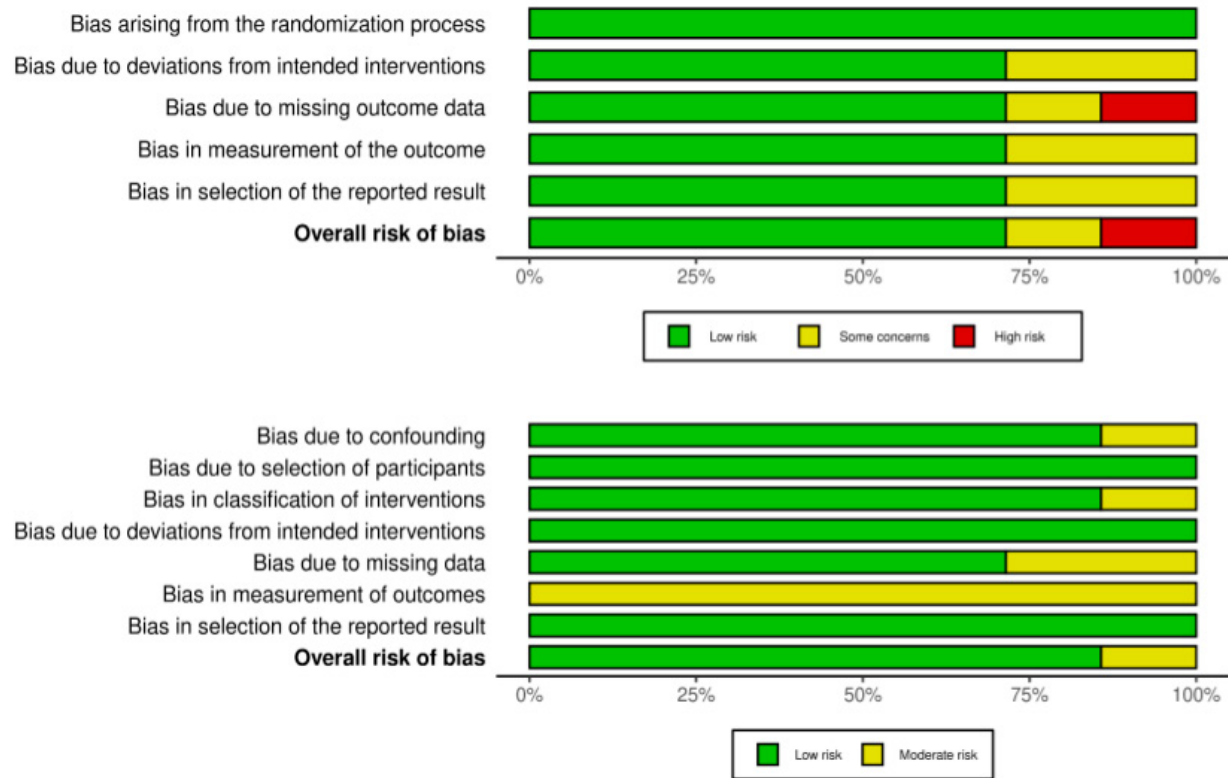


Figure 3. Risk of bias analysis performed by the Cochrane Collaboration Risk of Bias Tool (RoB 2.0 and ROBINS-I, respectively)



treatment. The complaints depend on the modality of choice: surgery (post-thoracotomy, post-amputation), post-radiotherapy, post-chemotherapy (especially when submitted to platinum compounds, paclitaxel, vincristine, and bortezomib). There is also the pain complaint associated with mucositis, enteritis, myalgia, and arthralgia, as well as peripheral neuropathy⁵⁸.

Pain management is based on the analgesic ladder postulated by the World Health Organization (WHO)⁵⁹. In addition, the National Comprehensive Cancer Network has developed a guideline to systematize the care of patients with pain. The medications of choice vary between non-steroidal anti-inflammatory drugs (dipyrone), weak opioids (codeine), and strong opioids (morphine), further to the potential implementation of adjunctive medications as corticoids, antidepressants, anticonvulsants, and neuroleptics to help manage the symptoms¹.

Although the guidelines help to treat pain associated with cancer or its treatment, many patients remain with uncontrolled pain. In addition, the prescribed medications are associated with other side effects, as fatigue, sleep apnea, decreased libido, nausea, vomiting, and constipation¹¹⁻¹³. Thus, new studies that seek to support the treatment of cancer patients with the development of new drugs, reduction of pain complaints, and improvement of quality of life are essential.

Recent studies highlight flavonoids as antinociceptive agents in animal models for chronic pain, including pain associated with inflammation, neuropathic pain, and cancer pain^{60,61}. Quercetin, for example, in a dose-dependent administration, significantly reduces thermal hyperalgesia and mechanical paclitaxel-induced allodynia⁶² or cold exposure⁶³. Furthermore, an animal model of neuropathic pain induced by constriction injury showed that quercetin's analgesic effect was superior to gabapentin and morphine⁶⁴.

Additionally, there are published studies demonstrating the action of flavonoids in delaying cognitive decline, reducing neuronal cell death, and improving memory related to neuroprotective effects, antioxidant properties, and anti-inflammatory action^{28,65}. In addition, there are also reports of anxiolytic potential^{66,67} due to affinity and selectivity at benzodiazepine receptor sites and actions at GABA (gamma-aminobutyric acid) receptors⁶⁷. The mechanism of action of flavonoids involves the suppression of inflammation (via Tumor Necrosis Factor- α , Interleukin-12, Interferon- γ , Interferon- α , Interleukin-8, cyclooxygenase-2, and prostaglandin) and oxidative stress^{52,68}, as well as the modulation of GABAergic^{69,70} and opioid pathways^{71,72}.

The analysis of the tumor site of the patients investigated by the studies reveals alignment with global

cancer incidence data. The studies focused on lung cancer, currently the most prevalent and lethal cancer worldwide, as well as breast and prostate cancers, are highly prevalent among women and men, respectively⁷³.

Although other highly incident cancers as colorectal and gastric were not directly addressed, recent preclinical studies have investigated paclitaxel and oxaliplatin which are drugs commonly utilized in therapeutic protocols for these tumors. These agents are associated with painful complications, including peripheral neuropathy. The findings suggest that prophylactic or therapeutic administration of these drugs is associated with reduced chronic neuropathy, alleviation of allodynia, and behavioral alterations related to pain⁷⁴⁻⁷⁷.

Additionally, preclinical analyses also evaluated the efficacy of flavonoids in managing pain associated with bone invasion or metastasis, a condition commonly observed in breast, prostate, and lung cancers. The results are promising, with improvement in pain, pain-related behavior, reduction of inflammation, and inhibition of tumor necrosis factor (TNF α), a cytokine with proliferative activity, tumorigenesis, and cell differentiation^{69,71,78-80}. Considering that about 93% of the patients have pain associated with cancer itself⁵⁸, clinical studies evaluating the effect of these molecules, based on *in vitro* and *in vivo* results, should be conducted to promote alternatives for cancer pain management.

Injury to the nail bed in patients undergoing chemotherapy is common, causing disfigurement and pain. In 2018, a study evaluated the effectiveness of a balm containing herbal oils rich in bioactive polyphenolics in protecting nails through its reported anti-inflammatory, analgesic, antioxidant, and antimicrobial properties. The authors randomized 60 prostate and breast cancer patients to evaluate the topical application of the balm two to three times daily compared to oil control. The pain was assessed from the questionnaire application. Reported symptoms were significantly lower between the start and end of chemotherapy in the balm-treated group compared to the control group. In addition, the plant balm significantly reduced chemotherapy-related damage to the nail bed, improving quality of life⁴⁶.

In 2010, Ahmad et al. conducted a pilot study with 27 patients diagnosed with prostate cancer undergoing radiation therapy, divided into a therapy group (isoflavone daily) or a placebo group, evaluating the effects of soy isoflavone administration for six months since the first treatment session. The authors observed reduced urinary incontinence, urgency, and better erectile function in the therapy group compared to the placebo at month three. The results in the sixth month were better, with less urinary leakage, fewer bowel changes as cramps, diarrhea, and less pain on defecation. Greater overall erection capacity was



also observed, confirming the role in reducing discomfort, improving quality of life, and suggesting the prophylactic administration of soy isoflavone concomitant with radiotherapy in prostate cancer⁴⁵.

In 2020, Crumbaker et al. evaluated the activity of idronoxil, a synthetic flavonoid derived from genistein with radiosensitizing properties, in association with a Lutetium-177 carrier molecule, a radiopharmaceutical, in 32 patients with metastatic castration-resistant prostate cancer. The flavonoid was administered rectally. The authors observed good tolerance to the drug combination, no serious adverse effects, high response rates to treatment, and improvement of pain in more than half of the patients with significant pain complaints at the beginning of the study⁵⁰.

Zhao et al.⁴⁷, in a phase I study, evaluated the administration of epigallocatechin gallate (EGCG), a polyphenol abundant in tea extracts, with antioxidant function, in 24 patients with stage III non-small cell lung carcinoma undergoing chemoradiotherapy with a diagnosis of dysphagia. Doses were administered immediately after identification of grade 2 dysphagia until two weeks after completion of radiotherapy. The authors observed a reduction of esophagitis and pain complaints in most of the patients⁴⁷. The same group prospectively evaluated the administration of the same drug orally, in a phase II study, during radiotherapy and two weeks after completion, in 37 patients under the same conditions as in phase I and observed a significant reduction of pain and radiotherapy-induced acute esophagitis with $p < 0.001$. The solution was well tolerated by patients who reported only nausea related to the taste of the medication⁴⁸.

Also, epigallocatechin gallate was evaluated in a randomized phase II study in 83 patients with non-small cell lung carcinoma, randomly assigned to three groups: prophylactic (EGCG at the start of radiotherapy), therapeutic, after the occurrence of esophagitis (EGCG after identification of grade 1 esophagitis up to two weeks after the end of radiotherapy) or conventional therapeutic (lidocaine, dexamethasone, and gentamicin after identification of grade 1 esophagitis up to two weeks after the end of radiotherapy). The degrees of esophagitis, pain and dysphagia were evaluated. The authors observed that treatment with EGCG three times daily showed better effects when compared to traditional treatment with lidocaine, dexamethasone, and gentamicin. In addition, prophylactic administration of the drug (at the beginning of radiotherapy) had a slight advantage over therapeutic administration in the treatment of radiotherapy-induced acute esophagitis⁴⁴. Recently, in 2021, a study with a five-year survival analysis evaluated 38 patients with small-cell lung carcinoma and found that esophagitis and pain rates in patients receiving EGCG were lower than conventional treatment ($p < 0.001$), without reducing survival⁵⁴.

Epigallocatechin gallate has also been the subject of studies on breast tumors. It was applied topically to 24 mastectomized patients after receiving adjuvant radiotherapy. The study noted that eight patients developed grade 2 dermatitis during or after radiotherapy, with regression to grade 1 after EGCG treatments. EGCG-associated acute erythema was observed in one patient. Reported symptoms (pain, burning, itching, and tenderness) decreased significantly ($p < 0.05$) two weeks after the end of radiotherapy⁴¹. A second, more robust study by the same team evaluated 49 patients with similar conditions and found that topical application of EGCG reduced pain in 85.7%, burning sensation in 89.8%, pruritus in 87.8%, pulling in 71.4%, and skin sensitivity in 79.6% of the patients⁵¹. A randomized, double-blind, clinical trial evaluated 165 breast cancer patients undergoing postoperative radiation therapy who received EGCG or placebo from the first day of radiation until two weeks after completion. The authors observed that the appearance of grade 2 or worse radiodermatitis was significantly lower in the EGCG group compared to placebo and that there was a significant reduction in symptom indices in the EGCG group, confirming its positive performance as a prophylactic agent⁴³.

Recently, the effects of epigallocatechin gallate were evaluated in 20 head and neck cancer patients diagnosed with radiotherapy-induced mucositis. The compound was used in solution as a mouthwash three times daily. The authors evaluated mucosal toxicity, patient satisfaction, and mucositis-related pain on a weekly basis and found a significant reduction in mucositis-related pain ($p < 0.05$) and oral mucosal lesions, making it feasible to administer as a mouthwash⁴⁰.

A randomized study with 40 patients with head and neck cancer was conducted to evaluate the potential of calendula extract to prevent and treat radiotherapy or chemoradiotherapy associated mucositis. The patients received *Calendula officinalis*, an extract rich in quercetin, every 12 hours by mouthwash. Statistical analysis was performed on 38 patients. The authors were able to conclude that Calendula extract was significantly effective in treating chemoradiation-induced mucositis compared to placebo from the second week onwards with good tolerance by the patients, however, it cannot completely prevent its occurrence⁴⁹.

In 2020, Li et al.⁴² evaluated EGCG in esophageal cancer patients undergoing chemoradiotherapy or definitive radiotherapy with a diagnosis of radiation-induced esophagitis. The compound was administered orally, after diagnosis of esophagitis until two weeks after completion of radiation therapy. In addition, esophagitis-related dysphagia and pain were monitored weekly. The results

showed a significant reduction in symptoms associated with radiotherapy-induced esophagitis, indicating EGCG as a protective agent in esophageal cancer.

In a randomized, double-blind phase II clinical trial, Yap et al.⁵³ evaluated the effects of sin catechins in 26 patients with vulvar intraepithelial neoplasia. Treatment was performed with topical application three times daily for 16 weeks, with follow-up for 52 weeks. In addition to the histological response, the authors also evaluated the degree of toxicity, quality of life, and pain score. As a result, sin catechins showed better clinical response compared to placebo, with significant improvement in lesion resolution ($p < 0.002$). Furthermore, pain symptoms reduced after 16 weeks of treatment, compared to the beginning of the study, showing improvement in the quality of life of the patients.

The toxicity assessment was based on the CTCAE, a widely used global tool for grading adverse events^{81,82}. Also, radiotherapy-induced cutaneous toxicity was analyzed using the RTOG criteria, a well-established and clinically recognized instrument⁸³. The studies observed minimal to no adverse effects associated with the oral or topical administration of flavonoids, with reports limited to mild burning sensations and nausea, which were well tolerated throughout the treatment.

Pain assessment was performed using the Verbal Numeric Scale, a validated method selected by the studies investigated, that demonstrates high sensitivity and efficiency, applied to patients over 18 years of age and outside the context of sedation⁸⁴. The complaint of pain was significantly lower in the groups treated with flavonoids during regular follow-up, highlighting the analgesic potential of the compounds used.

These measurement tools, globally recognized and widely utilized, are instrumental in guiding healthcare professionals in their clinical decision-making. Establishing a common communication approach is essential for determining the most beneficial interventions for the patient, particularly in managing pain, which is one of the primary complaints of cancer patients.

The assessment of the risk of bias is essential to determine the quality of the evidence and to demonstrate which aspects are methodologically weak based on analysis of the categories of the studies. The creation of a positive control group, with standard medication for pain control compared to the proposed treatment, would promote adherence and reduce the main bias identified.

The bias in the measurement of the outcome was identified in non-randomized studies. Therefore, the evaluation of the final results should be done by an individual who holds no relation with the study design or with its participants, providing safer blinding and reducing this type of bias. In this case, a double-blind

design for randomized clinical trials would reduce the risk of bias, making the study more robust and validating the hypothesis suggested.

Thus, flavonoids seem to be promising molecules in pain management, as chemotherapy-associated neuropathy and tumor invasion-related pain. By reducing or eliminating the side effects of cancer therapies through the use of natural compounds, patient experience, quality of life, and treatment compliance are improved. However, more clinical trials and pre-clinical studies evaluating the potential of flavonoids in the pain associated with cancer itself, which is the most frequent, should be encouraged, with detailed pharmacological and other molecule analyses to expand their use and bring benefits to the patients.

CONCLUSION

Evidence of low risk of bias points to flavonoids as a good alternative in pain adjuvancy, especially in treatment-associated pain as radiodermatitis and mucositis in different topographies.

Flavonoids are naturally occurring compounds found in plants. In addition to their well-established anti-inflammatory potential, their application in the management of pain associated with oncological treatments has demonstrated mild adverse effects.

Numerous beneficial effects of flavonoid use in the context of oncology are being increasingly recognized and revisited. However, further research is required for thorough investigation of the analgesic potential of flavonoids, particularly in the context of cancer pain resulting from tumor invasion or metastasis. Moreover, it is necessary to expand the number of double-blind randomized controlled trials to minimize the risk of bias.

CONTRIBUTIONS

Maycon Giovani Santana and Matheus Cavalcante De Deus contributed substantially to the study design, Maycon Giovani Santana and Rachel Verdan Dib contributed to acquisition, analysis and interpretation of the data, Ana Lúcia Teodoro and Denise Gonçalves Priolli contributed to the wording and/or critical review. All the authors approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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