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O USO ORAL DA CURCUMA É SEGURO? UMA REVISÃO INTEGRATIVA

IS THE ORAL USE OF CURCUMIN SAFE? AN INTEGRATIVE REVIEW

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RESUMO

O uso de plantas medicinais está historicamente associado à medicina popular em diferentes regiões do mundo. *Curcuma longa* L., também conhecida como cúrcuma ou açafrão-da-terra, é um rizoma amarelo amplamente utilizado como agente terapêutico com múltiplas indicações. Diversos estudos relatam o potencial anti-inflamatório dos componentes da cúrcuma e, no contexto atual, torna-se relevante avaliar seus possíveis efeitos tóxicos. Este estudo tem como objetivo investigar se existe toxicidade no uso oral da curcumina, por meio de uma revisão integrativa. As buscas são realizadas utilizando os descritores “Safety of oral use of curcumin” e “Safety in the Oral Use of Curcumin” nas bases Medical Literature Analysis and Retrieval System Online, SciELO e Literatura Latino-Americana e do Caribe em Ciências da Saúde. Um total de 100 artigos é inicialmente identificado; 93 são excluídos por duplicidade, incompletude ou falta de relevância, resultando em 7 selecionados para análise detalhada. Os resultados mostram que a curcumina oral não apresenta efeitos adversos graves, sustentando sua segurança para uso humano. Entretanto, a revisão destaca desafios relacionados à baixa biodisponibilidade e à instabilidade química. Essas limitações sugerem a necessidade de novos estudos para o desenvolvimento de formulações aprimoradas que garantam maior biodisponibilidade e estabilidade, ampliando, assim, seu potencial terapêutico.

Palavras-chave: cúrcuma; segurança do paciente; administração oral.

ABSTRACT

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The use of medicinal plants is historically associated with folk medicine in different regions of the world. *Curcuma longa*L., also known as turmeric, is a yellow rhizome widely used as a therapeutic agent with multiple indications. Numerous studies report the anti-inflammatory potential of curcumin components, and in the current context, evaluating their possible toxic effects becomes relevant. This study aims to investigate whether there is toxicity in the oral use of curcumin through an integrative review. Searches are conducted using the descriptors "Safety of oral use of curcumin" and "Safety in the Oral Use of Curcumin" in the databases Medical Literature Analysis and Retrieval System Online, SciELO, and Literatura Latino-Americana e do Caribe em Ciências da Saúde. A total of 100 articles is initially identified; 93 are excluded due to duplication, incompleteness, or lack of relevance, resulting in 7 studies selected for detailed analysis. The results show that oral curcumin does not present serious adverse effects, supporting its safety for human use. However, the review highlights challenges related to its low bioavailability and chemical instability. These limitations suggest the need for further studies to develop improved formulations that ensure greater bioavailability and stability, thereby enhancing its therapeutic potential.

Keywords: curcuma; patient safety; oral administration.

1 INTRODUCTION

The use of medicinal plants is related to folk medicine from different parts of the world. Natural products from plants, fungi, bacteria and other organisms continue to be used in pharmaceutical preparations to this day, either as pure compounds or extracts. There is a wide variety of compounds that can be extracted and characterized from plants, such as *Curcuma longa* L. (Araújo; Leon, 2001).

The space that herbal medicines are gaining over time is notable, especially with the confirmation of some research. Thus, Brazil created public policies that aim to meet this demand, making the use of herbal medicines safer. To this end, a National List of Medicinal Plants that are of Interest to the Unified Health System (RENISUS) was presented. On this list, there are several plants as therapeutic options, including *Curcuma longa* L., a substance that has led studies and research both nationally and internationally on its use (Silva; Silva; Siqueira, 2020).

There are many species of the *Curcuma genus*, such as *Curcuma longa* L., which is one of the most recognized. It is a yellow rhizome also known as saffron (Diziwenka *et al*, 2022; Ortega; Campos, 2019), has been used for centuries in gastronomy and as medication with a wide variety of indications, including treatment of injuries, liver disease and microbial control (Haukvik *et al*, 2009). A variety of biological activities have been attributed to curcumin,

including anti-inflammatory, cardioprotective, neuroprotective, and antioxidant activities (Tsuda, 2018).

Turmeric is a small, herbaceous plant, with a long life cycle, in its structure with oval-shaped rhizomes that can measure up to 10 cm in length, its interior stands out for a greenish yellow color, with flowers in yellowish or light tones, arranged on its surface in the shape of long ears, has a strong odor, however, it is considered pleasant to taste, due to its spicy characteristic (Marchi *et al*, 2016).

The main advantages of using curcumin are that it is economically advantageous, easy to obtain, use and apply, in addition to being highly efficient (Araújo *et al*, 2012). It is worth mentioning that curcumin is a natural product, easily accessible commercially, which when used correctly has great yield, making it an economically accessible product for healthcare professionals. Due to this, there are many studies that evaluate its effectiveness and toxicity, in the most varied types of uses.

There is a range of articles in the literature reporting the anti-inflammatory capacity of curcumin components, with two types of situations being studied: models of chronic inflammation, demonstrating the proliferative phase of inflammation; and models of acute inflammation, characterizing curcumin's ability to inhibit the development of the inflammatory process (Araújo; Leon, 2001).

In this context, it is important to develop more and more research on this topic, due to the growth in the use of curcumin, making it important to seek more answers about its possible toxic effects when administered. Therefore, this study aims to investigate whether there is toxicity in the oral use of curcumin, through an integrative review.

2 METHODOLOGY

The study carried out was an integrative bibliographic review, whose objective is to explore and condense information about the toxicity of curcumin when used orally. To develop the research, the following steps were carried out: guiding question and objectives of the integrative review; article inclusion and exclusion criteria; establishment of the most relevant information that was used for data collection; analysis, discussion and presentation of the results found.

The following databases were used to search for articles: Medical Literature Analysis and Retrieval System Online (Medline/PubMed), SciELO and Latin American and Caribbean Literature in Health Sciences (LILACS).

Inclusion criteria: Articles published in Portuguese or English, available free of charge or for a fee, published in the last 5 years (2019-2023), related to the central question of the study, were considered.

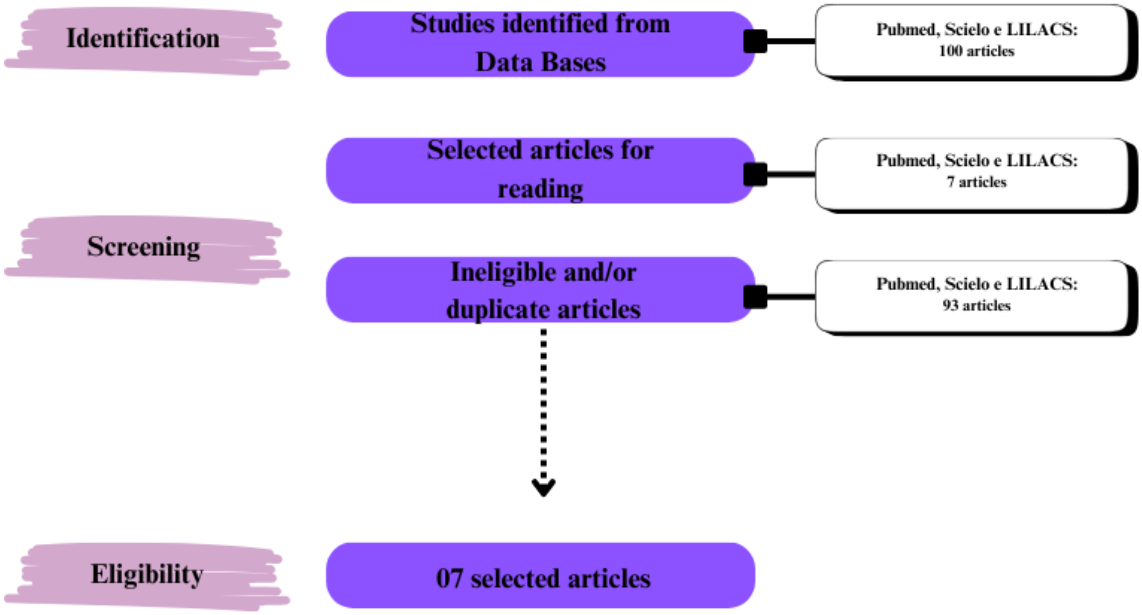
Exclusion criteria: Duplicity, incomplete text, inconclusive results or when the theme does not address the theme of the present work. Articles that did not have the words: safety or toxicity in their titles were excluded from the study.

Online searches were carried out using the following descriptors: Safety of oral use of curcumin. Microsoft Office Excel 2022 software was used for data tabulation and analysis

3 RESULTS

After searching the databases Medical Literature Analysis and Retrieval System Online (Medline/PubMed), SciELO and Latin American and Caribbean Literature in Health Sciences (LILACS), a total of 100 articles were found. After submitting them to the inclusion criteria, 93 articles were rejected for being duplicates, incomplete, or for not covering the theme of the present work. Figure 1 illustrates the search and selection process for articles.

Figure 1: Flowchart of the steps for obtaining the study sample



Source: Own authorship (2024)

After selecting the articles, table 1 was prepared to summarize the type of study and the main results found by the authors.

Table 1: Database, type of study and main results on curcumin toxicity, from 2019 to 2023.

Number	Database	Author(s) and year of publication	Kind of study	Main results
1	Pubmed	Bhat *et al*, 2023	Double-blind clinical trial	No serious adverse effects were observed
2	Pubmed	Majeed *et al*, 2023	Experimental study on animals	No adverse effect level was observed
3	Pubmed	Dziwenka *et al*, 2022	Experimental study in animals and in vitro	A single oral dose of 5000 mg CuminUP60® was well tolerated by male and female Sprague-Dawley rats. No adverse effects were observed for CuminUP60® in male and female Sprague-Dawley rats. Lack of mutagenicity for CuminUP60® in in vitro assays
4	Pubmed	Jeon *et al*, 2022	Prospective, observational, single-group analysis	Acceptable toxicity
5	Pubmed	Jantawong *et al*, 2021	Experimental study on animals	The risk of toxicity in the use of high doses of curcumin nanocomplexes was classified as very low, and potentially caused by components of the nanocomplex
6	Pubmed	Howells *et al*, 2019	Randomized and controlled clinical trial	The addition of daily oral curcumin to FOLFOX chemotherapy was safe and tolerable
7	Pubmed	Phipps *et al*, 2020	Experimental study on animals	No adverse effects were observed

Source: Own authorship (2025).

4 DISCUSSION

In all the studies analyzed, no serious toxic effects related to the oral use of curcumin were reported (Bhat *et al*, 2023; Majeed *et al*, 2023; Dziwenka *et al*, 2022; Jeon *et al*, 2022; Jantawong *et al*, 2021; Phipps *et al*, 2020; Howells *et al*, 2019).

Howells *et al* (2019) used in their study the combination of curcumin with a chemotherapy drug in patients undergoing chemotherapy treatment, and this combination proved to be well tolerated. It is worth mentioning that the use of curcumin in this study was

done orally and, for this reason, it was included in the works for this literature review (Howells *et al*, 2019).

Briefly, patients with a histological diagnosis of metastatic disease awaiting first-line chemotherapy were recruited from the Department of Oncology at University Hospitals Leicester and randomly assigned to receive standard chemotherapy (FOLFOX ± bevacizumab) or FOLFOX ± bevacizumab plus 2g oral curcumin complex (Howells *et al*, 2019). The combination was shown to be safe and tolerable, in addition to providing benefits to the patient, which strengthens studies that identify low or no toxicity associated with the oral use of curcumin (Howells *et al*, 2019).

Still in this context, it is observed that more alternatives and supporting therapies are being sought with the aim of favoring and/or improving the quality of life of patients with malignant neoplasms, with curcumin gaining prominence as the results of new Studies involving this molecule show promise. In a prospective, observational study, patients diagnosed with colon or rectal cancer and metastases not amenable to surgical resection were treated with bevacizumab/FOLFIRI in oral supplementation with a lipid carrier containing curcumin (Jeon *et al*, 2022).

The results of this study analyzed the rates of overall survival, progression-free survival, tumor response and adverse events, demonstrating that the therapy used in association with the oral use of curcumin presented long-term survival rates with acceptable toxicity results (Jeon *et al*, 2022). These findings can be justified based on the low inherent toxicity of curcumin and its already known pharmacological effects, including its anti-inflammatory, antioxidant and, mainly, antineoplastic activity, which makes it a potential complementary agent in cancer chemotherapy (Mansouri *et al*, 2020).

Bhat *et al* (2023) evaluated the efficacy and safety of curcumin for maintaining remission in patients with rheumatoid arthritis. The study found that curcumin had no impact on seizure-free survival or seizure time during tapering from conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), despite its good bioavailability. The study also highlighted the limitations of established therapeutic ranges for curcumin levels, suggesting that higher doses may be needed to achieve clinically meaningful results. Additionally, the study showed side effects such as infections, benign tumors, and elevated transaminases in the curcumin group, as well as new diagnoses of psoriasis in the placebo group.

Despite the aforementioned and already well-established advantages regarding the use of natural compounds from turmeric, there is great concern among researchers and the

pharmaceutical industry, in general, in relation to the pharmacokinetic parameters of the formulations, considering that these factors can interfere negatively on the biological activity of the product in question. Studies emphasize that curcumin is poorly soluble in water, has low gastrointestinal absorption, rapid metabolism and excretion, characteristics that reduce its bioavailability and, consequently, make it difficult to use orally (Prasad; Tyagi; Aggarwal, 2014).

To overcome this situation, complexes that combine curcumin with other molecules are constantly being tested, so that its pharmacokinetic properties and efficacy can be improved, as well as its safety characteristics and low toxicity are preserved. Given this, Jeon *et al* (2022) attribute and justify part of the good results found in curcumin supplementation as an adjuvant in the treatment of colorectal cancer due to the use of a nanostructured system capable of improving its physicochemical properties. For these authors, based on previous studies, nanostructured lipid carriers containing curcumin with ginsenoside modification greatly improve the solubility of curcumin and increase its chemical stability and cytotoxicity in cancer cells (Vijayakumar *et al*, 2019; Vijayakumar *et al*, 2017).

Similarly, Dziwenka *et al* (2022) evaluated, through in vitro and in vivo studies, the safety of a complex consisting of *Curcuma longa* L. extract and poloxamer 407 (CuminUP60®). The results demonstrated the absence of mutagenicity in in vitro tests, as well as good tolerability and the absence of significant adverse effects with a single dose or repeated doses in male and female Sprague-Dawley rats, as long as the determined concentration is respected (Dziwenka *et al*, 2022).

Phipps *et al* (2020) analyzed the safety of a turmeric extract formulation that contained curcumin (30%), rhizomes (30%-40%), acacia gum (55%-65%), sunflower oil (3%-7%), and turmeric extract. quillaia (1%-3%). Safety assessment included in vitro genotoxicity tests and 28- to 90-day repeat dose oral toxicity studies in rats. The results showed no evidence of genotoxicity and no adverse effects at the highest dose tested, establishing a no adverse effect level of 3,000 mg/kg body weight/day. The formulation has demonstrated potential to be a highly bioavailable source of curcumin in food products. However, the study highlighted the challenges of curcumin bioavailability in humans and efforts to overcome this challenge.

As already mentioned, its low solubility and considerable chemical instability make it necessary to use high dosages of oral curcumin to obtain the frequently desired therapeutic effects (Mahran *et al*, 2017). Therefore, higher doses cause great concern regarding safety and

efficacy in long-term use and, therefore, numerous studies aim to evaluate such parameters in new formulations for different clinical uses.

Jantawong *et al* (2021) analyzed different dosages of a modified solid dispersion of curcumin-loaded nanocomplexes (CNCs) in gums for oral administration and tested its acute and chronic toxicity in experimental hamster and mouse models. In short, the lowest and intermediate doses did not cause any adverse effects for both species of animals, while higher doses were associated with an increase in the size of some organs, as well as biochemical changes in molecular markers, which disappeared 28 days after cessation. the administrations of the CNCs (Jantawong *et al*, 2021). Such observations allow us to infer that even the toxicity observed at high doses can be considered low, confirming the safety of using the product.

More current evidence has suggested that some curcumin metabolites may have high efficacy, which is often higher than that of isolated curcumin itself. Turmeric extracts are conventionally made up of curcumin, demethoxycurcumin and bisdemethoxycurcumin, and the mixture of all or some of these compounds appears to improve the pharmacological efficacy of the product (Majeed *et al*, 2023; Revathy *et al*, 2011). Thus, one of the studies included in this review aimed to evaluate the toxicity of an activated curcumin complex (AC3®), formulated from C. longa extract enriched with disdemethoxycurcumin. The results of the acute, sub-acute, sub-chronic, reproductive and genotoxicity assessments carried out demonstrated safety and absence of significant adverse effects with the use of the activated curcumin complex when administered orally in rodents (Majeed *et al*, 2023).

5 CONCLUSIONS

Through observation and analysis of the results related to toxicity found by the authors included in this review, we can conclude that curcumin is safe when used orally, not exhibiting serious adverse effects on patients who used it, however, there is an obstacle with regard to its bioavailability and chemical stability, which requires new formulations for them to become satisfactory. Therefore, the use of nanocarriers or the application of curcumin metabolites is interesting to increase its good properties, that is, even though its efficacy and safety are already proven, new studies are necessary so that new formulations with greater bioavailability and chemical stability are tested and proven as therapeutic strategies.

Author contributions

Conception or design of the work, data acquisition, analysis or interpretation, writing or reviewing the manuscript.

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Interest conflicts

The authors declare that there is no conflict of interest related to this study.

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