Lipoic Acid for Rheumatological Diseases: A Systematic Review

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Abstract

Lipoic acid (LA) is a potent antioxidant and has been tested in a few rheumatic diseases. To review the use of LA in rheumatic diseases. PubMed/MEDLINE, EMBASE, and Scielo databases were screened for articles on LA and rheumatic diseases between 1966 and May 2023. Four articles were found, including 177 patients. The investigated diseases were fibromyalgia (FM) (n = 2) and rheumatoid arthritis (RA) (n = 2). Age varied from 36.09 ± 8.77 to 57 (25-74) years old, and the female gender ranged from 81% to 100%. LA dosage ranged from 300 mg to 1663mg/day. Concerning outcomes, three-fourths of the article did not observe any difference when LA was compared to placebo. On the contrary, in one study, a significant decrease in pain and an improvement in fibromyalgia impact questionnaire (FIQ) and Fatigue Severity Scale (FSS) scores were seen in the LA-supplemented group. Lipoic acid is a potent antioxidant, and it was a safe therapy for FM and RA, although in only one study, in FM subjects, a positive result was found.

Keywords: Lipoic acid, antioxidants, anti-inflammatory, rheumatological diseases, rheumatoid arthritis, fibromyalgia

Introduction

The alpha-lipoic acid or lipoic acid (LA) is an organosulfur component synthesized by plants, animals, and also human beings. It has various properties, the most relevant being its antioxidant potential, and is widely used for diabetic polyneuropathy. LA improves glycemia and diabetes mellitus complications, and even peripheral neuropathy while effectively lessening heavy metal toxicity.[1] In addition, LA was also studied in schizophrenia, câncer, multiple sclerosis, and obesity with promising results.[1]

The impact of the oxidative system on the development of autoimmune disorders is widely acknowledged, and the interplay between reactive oxygen species (ROS) and the immune system has been extensively studied. ROS may play a significant role in the signaling system of immune cells, such as macrophage and regulatory T cells (Treg).[2] Furthermore, during pathological disorders, immune cells produce an excessive amount of ROS, which intensifies inflammatory processes and disrupts the stability of the immune system stability. Nowadays, the role of redox-controlled activation on the mechanistic target of rapamycin (mTOR) is known to play a regulatory role in the immune system.[2] It is possible to speculate about the use of antioxidant substances for the therapy of specific autoimmune diseases.

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LA has potent antioxidant and anti-inflammatory activity; it is used as a complementary therapy in a few rheumatological conditions that include fibromyalgia (FM) and rheumatoid arthritis (RA).

In this line, this article had the objective of systematically reviewing the works that analyzed LA in rheumatologial diseases.

Methods

Literature review

We performed a search of articles published in PubMed/MEDLINE, EMBASE, and Scielo until May 2023, using the following MeSH entry terms: "lipoic acid" AND "rheumatic" OR "rheumatologic" OR "systemic lupus erythematosus" OR "lupus" OR "fibromyalgia" OR "rheumatoid arthritis" OR "spondyloarthritis" OR "Sjögren's syndrome" OR "myositis" OR "systemic sclerosis" OR "vasculitis" OR "osteoarthritis" OR "gout." No language restriction was used.

Two authors (JFC and TFS) initially conducted the literature search and independently chose the study abstracts. Then, in the second phase, the same authors read the complete articles that were chosen based on their abstracts. Once more, the authors adhered to the PRISMA guidelines.[3] Last, a standardized form was created to extract the necessary information from relevant articles, which included authors, publication year, number of patients studied, age, gender, disease duration, follow-up, LA dosage, outcomes, and adverse effects.

Inclusion criteria were: age of 18 years old or more, both genders, and any rheumatic diseases, any study design (except for those of exclusion criteria). Exclusion criteria were: review articles, in vitro studies, and animal model studies.

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Results

Figure 1 shows the flowchart of the included articles. Table 1 summarizes the articles on LA supplementation in rheumatic diseases.[4-7] Four articles were found, including 177 patients. The countries where these studies were conducted were Korea (n = 2), Iran (n = 1), and Canada (n = 1). Two studies were double-blinded randomized and controlled crossover trials; one was a randomized controlled and crossover trial, and one article was a double-blind randomized and controlled trial. The included diseases were FM (n = 2) and RA (n = 2). Age varied from 36.09 ± 8.77 to 57 (25-74) years old, and the female gender ranged from 81% to 100% in the included articles. The disease duration varied from 7.26 ± 4.9 to 19.5 (4-40) years. The LA dosage ranged from 300 mg to 1663 mg/day. The follow-up of all studies ranged from 4 to 24 weeks.

About outcomes, 3 out of 4 articles did not observe any difference when LA was compared to placebo. On the contrary, in one study, a significant pain decrease and FIQ and FSS scores were seen in the LA-supplemented group and were also observed in the acupuncture group.

In addition, the side effects were absent in 1 out of the 4 studies; in 1/4, they were similar to the placebo group. In one study,[5] side effects appeared in 23.1% of the Migratens group and 14% in the acupuncture group; 4 patients stopped medication.

Discussion

This is the first systematic review on LA supplementation and rheumatic diseases. Most articles did not observe a positive clinical or biochemical response, with only one verifying improvement in pain and fatigue in patients with fibromyalgia, equaling the acupuncture control group.

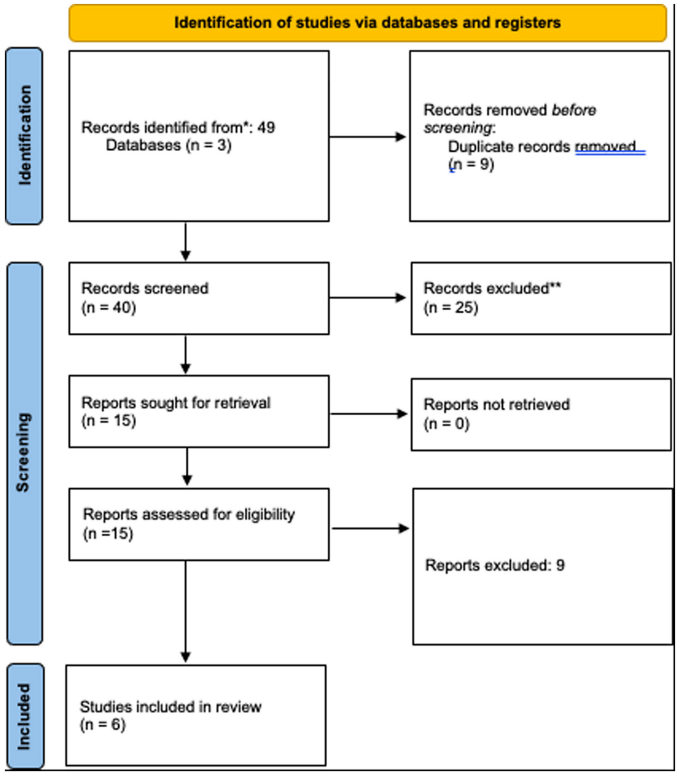

Figure 1. PRISMA flowchart of the included articles.

LA may have its antioxidant properties via direct or indirect ways. LA itself is the most potent naturally occurring antioxidant. Indeed, LA is able to scavenge a variety of reactive oxygen species, including hydroxyl radicals, hypochlorous acid, and also terminates singlet oxygen.[8] Recent studies suggest that LA may indirectly contribute to maintaining cellular antioxidant status by either increasing the uptake or enhancing the production of endogenous low molecular weight antioxidants or antioxidant enzymes. For example, studies demonstrated that lipoic acid increases intracellular vitamin C levels.[9]

There is large evidence in the literature suggesting an oxidative stress process present in RA and OA.[10] RA subjects have higher plasma malondialdehyde levels (oxidant compound) and a reduced antioxidant capacity in comparison to healthy individuals. These oxidative substances are generated by activated immune cells (macrophages, monocytes, and granulocytes), and also by hypoxic-reperfusion reactions that might surge with joint movements.[11] Oxidant substances initiate an activation of NFkB, which leads to gene expression of proinflammatory cytokines.[12]

The current systematic review demonstrates that most studies included in the analysis reported a reduction in oxidative substances like malondialdehyde (MDA) through supplementation with LA supplement. However, this difference was not different from placebo or control group, which included quercetin plus vitamin C supplementation in one study[3] and acupuncture in the other article.[5]

The strengths of the present study are: (1) only patients fulfilling international criteria for rheumatic diseases were included; (2) the inclusion of all kinds of study designs for using LA in rheumatic diseases, excluding review articles and animal studies and *in vitro* studies; (3) the gray literature was excluded. Therefore, the authors believe that all relevant published articles of LA supplementation in rheumatic patients were collected.

The study had certain limitations that were noted. For instance, there was no direct comparison between traditional and modern drug treatments for rheumatological conditions. Furthermore, the limited number of participants and the brief follow-up period are significant constraints. Additionally, some of the most important aspects of the articles were not addressed in detail. Finally, only two rheumatic diseases were studied (RA and FM). Future research should involve a larger number of patients over a longer period of time, with more rigorous academic protocols, to better understand the therapeutic mechanism of action and the role of LA in rheumatic disorders.

Conclusion

This systematic review revealed that only a few studies evaluated the lipoic acid in rheumatological diseases, and only two diseases were until now evaluated: fibromyalgia and rheumatoid arthritis. Moreover, most studies revealed no positive effects in comparison to placebo, except for one that observed improved pain and fatigue in FM, although equal to the acupuncture control group. Based on the above, it is concluded that LA needs to be more explored in the rheumatic field.

Table 1. Summary of the Studies on Lipoic Acid Supplementation in Rheumatic Diseases

Author, Year, Reference	Study Design	Country	N, Age (years old), gender	Disease	Disease Duration	LA Dose/day	Follow-up (weeks)	Outcome	Side Effects
Bae et al, 2009[3]	Randomized, placebo-controlled, double-blind, three treatment crossover design trial	Korea	20 52.1 ± 10.3 95% females	RA	10.2 ± 5.9 years	300 mg vs. quercetin_+ vita min C (166 mg +133 m g/capsule)	4	No significant differences were found between treatments in the serum concentrations of proinflammatory cytokines and CRP. No differences in the scores of disease severity.	ND
Mirtaheri et al, 2015[4]	Randomized, double-blind, placebo-controlled clinical trial	Iran	70 36.09 ± 8.77 100% females	RA	7.26 ± 4.9 years	1200 mg vs. placebo	8	No significant differences in serum levels of hs-CRP, TNF-a, IL-6, and MMP-3	None
Schweiger et al, 2020[5]	Randomized, placebo-controlled, double-blind, three treatment crossover design trial	Korea	60 48.2 ± 7.4 100% females	FM	ND	Migratens® vs. acupuncture	24	Both Migratens® and acupuncture reduced pain, improved quality of life and fatigue.	23.1% of Migratens and 14% in the acupuncture group had gastronintestinal effects, and 4 discontinued Migratens.
Gilron et al, 2021[6]	Single-center, proof-of-concept, randomized, placebo-controlled, crossover trial	Canada	27 57 (25-74) 81% females	FM	19.5 (4-40) years	The median maximal tolerated dose was 1663mg	5	No differences compared to placebo regarding pain intensity, frequency/severity of treatment, FIQ, MOS, PGI, BDI, SF-36, and acetaminophen consumption	Equal to placebo

FIQ: Fibromyalgia Impact Questionnaire, FM: fibromyalgia, RA: rheumatoid arthritis; MOS: Medical Outcomes Study; SS: Sleep Scale; PGI: Patient Global Impression of Change; BPI: Brief Pain Inventory; BDI: Beck Depression Inventory; SF-36: short form 36; ND: not described.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – J.F.C.; Design – J.F.C.; Supervision – J.F.C.; Resources – J.F.C.; Materials – J.F.C.; Data Collection and/or Processing – J.F.C., T.F.S.; Analysis and/or Interpretation – J.F.C., T.F.S.; Literature Search – J.F.C., T.F.S.; Writing Manuscript – J.F.C., T.F.S.; Critical Review – J.F.C., T.F.S.

Declaration of Interests: The authors have no conflict of interest to declare.

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