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Anti-aging properties of extracts from *Ziziphus mauritiana* leaves. A comprehensive systematic review and meta-analysis

Właściwości przeciwstarzeniowe ekstraktów z liści *Ziziphus mauritiana*. Kompleksowy przegląd systematyczny i metaanaliza

ABSTRACT

With growing awareness of the transformations occurring in the body due to aging, these changes have become the subject of research by many scientists. Attempts are being made to halt this process naturally, using the potential of various herbs.

This study aimed to present the potency of extracts from the leaves of the plant *Ziziphus mauritiana* as an anti-aging agent, by its antioxidant and anti-inflammatory properties.

A systematic review and meta-analysis were performed using the PRISMA guidelines based on studies retrieved from PubMed, Science Direct, and the Cochrane Library that met the inclusion criteria up to March 2025. Variables, including antioxidant, anti-inflammatory, and anti-aging properties, were extracted and then analyzed descriptively and quantitatively. The study demonstrated the potential of *Ziziphus mauritiana* leaf extract to increase endogenous antioxidants, inhibit inflammation, increase collagen density, elasticity, hydration, and skin brightness, and reduce sebum levels, erythema, fibroblast numbers, and improve wound healing.

Keywords: antioxidant, leaf extract, *Ziziphus mauritiana*, aging processes, inflammation

STRESZCZENIE

Rosnąca świadomość zmian zachodzących w organizmie człowieka z wiekiem sprawiła, że temat ten zaczął interesować wielu naukowców. Poszukiwane są naturalne sposoby spowolnienia procesów starzenia, m.in. poprzez wykorzystanie właściwości ziół.

Celem pracy było wskazanie, że ekstrakty z liści *Ziziphus mauritiana* mogą działać przeciwstarzeniowo dzięki swoim właściwościom przeciwutleniającym i przeciwzapalnym.

Dokonano przeglądu systematycznego i metaanalizy przy użyciu wytycznych PRISMA na podstawie badań pobranych z PubMed, Science Direct i Cochrane Library, które spełniały kryteria włączenia do marca 2025 roku. Wyodrębniono zmienne, w tym przeciwutleniające, przeciwzapalne i przeciwstarzeniowe, a następnie przeanalizowano je opisowo i ilościowo. Badania wykazały potencjał ekstraktu z liści *Ziziphus mauritiana* w zwiększaniu ilości endogennych przeciwutleniaczy, hamowaniu stanów zapalnych, zwiększaniu gęstości kolagenu, elastyczności, nawilżenia, jasności skóry oraz zmniejszaniu poziomu sebum, rumienia, liczby fibroblastów i poprawie gojenia się ran.

Słowa kluczowe: przeciwutleniacz, ekstrakt z liści, *Ziziphus mauritiana*, procesy starzenia stan zapalny



INTRODUCTION

Increased life expectancy correlates with a growing elderly population and an escalation in age-related issues. Efforts to slow down aging process have become a significant research trend related to these demographic changes [1]. Baby-soft skin has long been considered as the ideal skin type. The elderly group and older adults are the main consumers of anti-aging products, but recent trends show a growing interest of young people to seek preventive measures [2]. Understanding the etiopathogenesis of skin aging is important in cosmetic dermatology to create innovative and effective skin care products that prevent and reduce the visible signs of aging, thereby improving quality of life and self-confidence [3]. Topical use of cosmetic products containing antioxidants can counteract free radicals and enhance natural skin defense mechanisms. Topical products derived from synthetic sources in the cosmetic industry could be associated with adverse effects on the skin and are capable of triggering allergic reactions. This has led to the development of pharmaceutical formulations derived from natural sources, referred to as green cosmeceuticals, and considered a promising alternative therapy [4]. Natural ingredients derived from plants or botanicals, minerals, and other natural sources are believed to be healthier and have minimal side effects on the skin [5].

Botanical extracts have been used in cosmetics, and skincare products for thousands of years, and their use as anti-aging products continues to grow [2]. Several studies have addressed the content and effects of bioactive ingredients of botanical extracts in cosmetic preparations for skin care, such as flavonoids, polyphenols, and vitamins, with antioxidant capacity, collagen synthesis, and modulation of enzymes involved in extracellular matrix formation [5]. *Ziziphus mauritiana*, commonly known as bidara, is an herbal plant found in tropical and subtropical areas and has various pharmacological activities [6]. *Ziziphus mauritiana* leaf extracts consist of many phytochemical compounds, including flavonoids, phenolic acids, alkaloids, phytosterols, terpenoids, amino acids, and proteins [7]. *Ziziphus spp.* is a genus of about 40 species of thorny shrubs and small trees of the family *Rhamnaceae*, distributed in warm temperate and subtropical regions around the world. *Ziziphus* species contain several minerals, such as vitamin C, phosphorus, calcium, and iron, amino acids (asparagine, glutamic acid, arginine, aspartic acid, serine, glycine, threonine), and sugars (sucrose, fructose, glucose, starch) [8]. Phytochemicals are the main metabolite content in plants, which consists of two groups, namely primary and secondary metabolites [2, 9]. Secondary metabolites are structurally and chemically much more diverse than primary metabolites and refer to compounds that are present in cells and are not directly important for metabolism, photosynthesis, or respiration, but are necessary for plant survival in the environment [10]. Secondary metabolites in

plants have been recognised as high-value cosmeceutical ingredients, due to the presence of phytochemicals, such as phenolic acids, flavonoids, and terpenoids [5].

Several studies have reported that *Ziziphus mauritiana* leaf extract is a potential extract as an antiseptic and can accelerate wound healing. Recent studies have shown that *Ziziphus mauritiana* leaf extract has high antioxidant and anti-inflammatory activities. This is represented by the ability to increase endogenous antioxidant enzymes (including superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), glutathione peroxidase (GPx)) and inhibit pro-inflammatory mediators (interleukin-6 (IL-6), tumor necrotizing factor alpha (TNF- α), and C-reactive protein (CRP)) so that it has the potential as an anti-aging agent [7, 11].

SOD, CAT, GPx, and GSH are key components in the body's defense system against oxidative stress. SOD converts superoxide radicals into hydrogen peroxide and oxygen. This hydrogen peroxide is then broken down by CAT into water and oxygen, or by GPx into water with the help of GSH as a cofactor. The increased activity of these four enzymes indicates an increase in the body's ability to fight oxidative stress, which is important for maintaining cell redox balance. Flavonoids in *Ziziphus mauritiana* leaf extract, such as quercetin and rutin, can stimulate the activity of nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 is a transcription factor that plays an important role in regulating the production of antioxidant enzymes. When Nrf2 is active, the production of SOD, CAT, and GPx increases, as does the availability of GSH [12, 13]. In addition, the polyphenol content in this extract can act directly as a free radical scavenger, thereby reducing oxidative stress in cells. In addition to flavonoids, *Ziziphus mauritiana* leaves also contain alkaloids that help maintain cell membrane stability and prevent damage from lipid peroxidation. This is important for protecting cell structures from oxidative damage [7, 11]. However, until now, there has been no detailed evaluation compiling studies related to the anti-aging potential of *Ziziphus mauritiana* leaf extract. Based on this, this article aims to discuss the potency of *Ziziphus mauritiana* leaf extracts as an anti-aging agent through antioxidant enhancement and inflammatory inhibition activity.

MATERIAL AND METHODS

Study design

This systematic review and meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, with the overall literature selection as represented in fig. 1. A thorough selection of available medical research in the form of original articles was made, and exclusion and inclusion criteria were applied. Then, a thorough analysis of the studies accepted for this study was carried out, which were accompanied by an appropriate statistical analysis (by using qualitative

standardised mean differences (SMD) comparison in Review Manager 5.4 software) and discussion indicating the antioxidant potential of the extract from *Ziziphus mauritiana* leaf extracts as anti-aging agent. Literature searches were conducted in credible scientific databases, including PubMed, ScienceDirect, and the Cochrane Library, with a search period until March 25, 2025 by involving studies published in the last 20 years. The keywords used in the article search included English and used the Boolean Operators “AND” and “OR”. The keywords used include: (*Ziziphus mauritiana* OR Bidara leaf extract) and (Anti-aging OR Aging inhibition OR Inflammatory inhibition OR Anti-inflammatory OR Antioxidant activity OR Oxidative stress reduction).

Study eligibility

Study selection was carried out by considering the established inclusion and exclusion criteria. Studies that met the inclusion criteria were written in English, examining the effects of *Ziziphus mauritiana* leaf extract as an anti-aging agent and/or inflammation inhibition and/or increased antioxidant activity, and had results that could be extracted and analysed statistically. Meanwhile, studies that were excluded were those that were not available in full-text, were not original research articles (such as reviews, comments, or editorials), and were included in gray literature (articles without a peer-review process).

The quality of the included studies was assessed using the SYRCLE’s Risk of Bias (RoB) scale developed for *in vivo* studies and Risk of Bias (RoB2) tools for clinical research. The assessment was carried out based on seven main domains, including selection, performance, detection, attrition, reporting, and other biases. The overall bias score was determined by the personal decision of the author.

Data extraction, analysis, and interpretation

Data extraction was carried out systematically by collecting key information from each studies, including study identity (name of main author, year of publication, and study design), characteristics of subjects (species, age, and number of samples), dose and duration of administration of *Ziziphus mauritiana* extract, inflammatory parameters measured

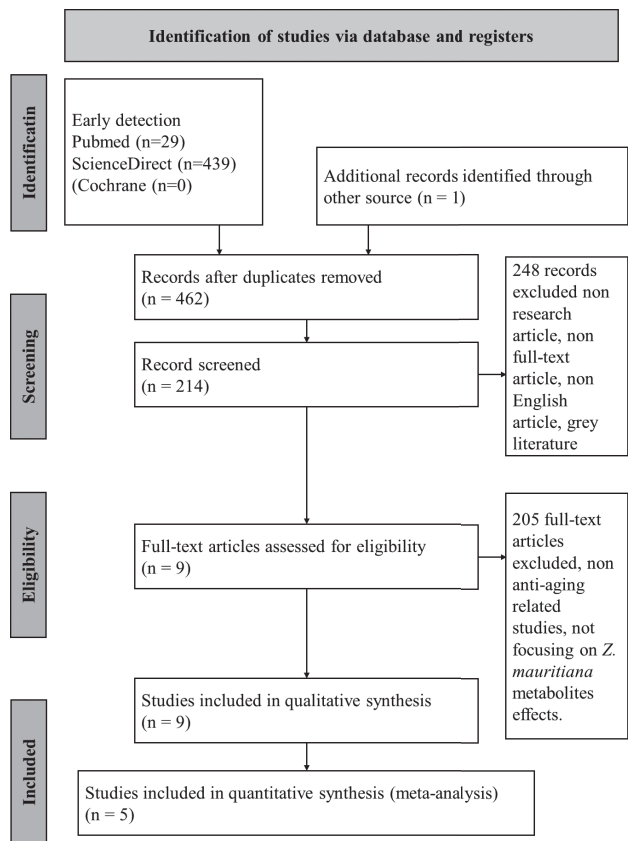


Fig. 1 PRISMA flowchart for study selection of *Ziziphus mauritiana*'s anti-aging activity
Source: Own elaboration

(TNF- α , IL-6, CRP and paw diameter (which is defined as the diameter of the rat paw induced by carrageenan (water-soluble sulfated galactans) to experience inflammation so that it can be used as a model of inflammatory conditions; the bigger the diameter is, the more inflammatory conditions occur), antioxidant activity parameters (SOD, CAT, GSH, and GPx), and main results related to anti-aging potential.

Data analysis was performed qualitatively and quantitatively. In qualitative analysis, the results are described in table 1. While the qualitative analysis, Review Manager 5.4 software (Cochrane Collaborator, UK) was used. The results were analysed in the form of Standardized Mean Difference (SMD) with 95% Confidence Interval (CI), and heterogeneity between

Table 1 Characteristics of included studies Source: Own elaboration

Study	Methods	Population	Intervention	Outcome	Follow-Up Duration	RoB
Anggraeny et al. (2021) [14]	Randomized posttest-only control group design study	30 female Wistar strain rats (<i>R. norvegicus</i>) with aging induced by UVB and cigarette smoke	<ul style="list-style-type: none"> Group I was not treated (C) Group II was given base cream + UVB exposure + cigarette smoke Group III was given <i>Ziziphus mauritiana</i> leaf extract cream with 7.5% UVB exposure + cigarette smoke 	<ul style="list-style-type: none"> MMP-1 levels were lowest in group I (4.64 ± 0.04) and group III (6.50 ± 0.25) Collagen composition was highest in group III (80.15) 	4 weeks	Moderate

Study	Methods	Population	Intervention	Outcome	Follow-Up Duration	RoB
Ma'ruf et al. (2021) [15]	<i>In vivo</i> experimental laboratory with a post-test-only control group design	40 male Wistar strain rats (<i>R. norvegicus</i>) with gingival incision	<ul style="list-style-type: none"> Group I was given 70% <i>Ziziphus mauritiana</i> leaf extract gel + gingival incision Group II was given 80% <i>Ziziphus mauritiana</i> leaf extract gel + gingival incision Group III was given 100% <i>Ziziphus mauritiana</i> leaf extract gel + gingival incision Group IV was given Povidone-iodine 10% + gingival incision 	The highest number of fibroblast cells in group III (1597±743)	8 days	Low
Akhtar et al. (2016) [16]	Clinical experimental study	13 healthy human volunteers. All volunteers were healthy non-smoking males with ages ranging from 25 to 35 years	<ul style="list-style-type: none"> Placebo (base) without any plant extract and formulation with 4% <i>Ziziphus mauritiana</i> extract Skin rejuvenation was evaluated using 13 healthy human volunteers 	Leaf extract of <i>Z. mauritiana</i> ameliorated the skin aging parameters, such as erythema, melanin level, moisture content, elasticity, sebum content	8 weeks	Low
Rajan et al. (2013) [17]	<i>In vivo</i> experimental laboratory with a post-test-only control group design	24 male Wistar albino rats (<i>R. norvegicus</i>)	<ul style="list-style-type: none"> Group I was given base ointment + incision Group II was given 5% <i>Ziziphus mauritiana</i> leaf ethanol extract ointment + incision Group III was given 5% <i>Ziziphus mauritiana</i> leaf aqua extract ointment + incision Group IV was given nitrofurazone ointment + incision 	<i>Ziziphus mauritiana</i> leaves 5% ethanol extract ointment induced wound contraction and reduced wound closure time, which has a similar effect to nitrofurazone.	16 days	Moderate
Dahiru et al. (2008) [18]	<i>In-vivo</i> pre- and post-test with control group design study	36 male Wistar albino rats (<i>R. norvegicus</i>) with alcohol-induced liver damage	<ul style="list-style-type: none"> Group I was given normal saline Group II was given a 40% alcohol solution Group III was given <i>Ziziphus mauritiana</i> leaf extract 200 mg/kg/orally + 40% alcohol solution Group IV was given <i>Ziziphus mauritiana</i> leaf extract 400 mg/kg/orally + 40% alcohol solution Group V was administered silimarin 100 mg/kg/orally + 40% alcohol solution Group VI was given <i>Ziziphus mauritiana</i> leaf extract 400 mg/kg/orally + normal saline 	<ul style="list-style-type: none"> Group IV had a significant decrease in AST, ALT, ALP, and tuberculosis (TB) levels Group IV had a significant increase in endogenous antioxidant enzyme levels (GR, GPx, SOD, and CAT) 	6 weeks	Moderate
Alsawayt, et al. (2025) [19]	<i>In vivo</i> experimental post-test only with the control group	24 Male Sprague Dawley rats with acute inflammatory condition (paw edema) include by carrageenan injection	<ul style="list-style-type: none"> Group I: DC (Disease control group received 0.1 ml of 1% carrageenan) Group II: PC (Positive control group received a standard dose of indomethacin 10 mg/kg) Group III: EAF-250 (Ethyl acetate fraction of combined ZMZS leaves extract at 250 mg/kg) Group IV: EAF-500 (Ethyl acetate fraction of combined ZMZS leaves extract at 500 mg/kg) 	<ul style="list-style-type: none"> Group IV had a significantly higher level of SOD, GPx, and CAT compared to group I (p<0.05) Group IV also had significantly lower levels of paw diameter, IL-6, TNF-α, and CRP 	2 weeks	Low

Study	Methods	Population	Intervention	Outcome	Follow-Up Duration	RoB
Asely, et al. (2020) [20]	<i>In vivo</i> experimental post-test only with the control group	260 healthy Nile tilapia (<i>Oreochromis niloticus</i>) with inflammation induced by <i>Aeromonas hydrophila</i> infection	<ul style="list-style-type: none"> Group I: disease control without intervention Group II: infected fish with 5 grams of <i>Ziziphis mauritiana</i> powder Group III: infected fish with 10 grams of <i>Ziziphis mauritiana</i> powder Group III: infected fish with 20 grams of <i>Ziziphis mauritiana</i> powder 	<ul style="list-style-type: none"> Group III had a significantly higher level of SOD and GSH (p<0.05) 	2 weeks	Moderate
Khanam, et al. (2025) [21]	<i>In vivo</i> experimental post-test only with the control group	42 Male Wistar rats with acute inflammatory conditions induced by carrageenan injection	<ul style="list-style-type: none"> Group I: The normal control (NC) group (received no specific treatment). Group II: The disease control (DC) group (received an injection of 0.1 mL (1 %) of freshly prepared carrageenan). Group III: The positive control (PC) group (received a standard dose of indomethacin 10 mg/kgBW). Group IV: SZML-250 (received seedless <i>Ziziphis mauritiana</i> leaves extract 250 mg/kgBW) Group IV: SZML-500 (received seedless <i>Ziziphis mauritiana</i> leaves extract 500 mg/kgBW) Group VI: SZMF-250 (received Seedless <i>Ziziphis mauritiana</i> fruit extract 250 mg/kgBW) Group VII: SZMF-500 (received seedless <i>Ziziphis mauritiana</i> fruit extract 500 mg/kgBW). 	<ul style="list-style-type: none"> Group IV had a higher level of SOD< CAT, MDA, GPx, and GSH (p<0.05) significantly compared to group II. Group IV had a lower level of paw diameter, IL-6, TNF-α, and CRP significantly compared to group II (p<0.05). 	2 weeks	Low
Mohankumar, et al. (2022) [22]	<i>In vivo</i> experimental post-test only with the control group	24 Male Wistar rats with acute inflammatory conditions induced by carrageenan injection	<ul style="list-style-type: none"> Group I: the normal control (inflammation without treatment) Group II: inflammation group treated by indomethacin Group III: inflammation group treated by <i>Ziziphis mauritiana</i> leaves 250mg/kgBW Group IV: inflammation group treated by <i>Ziziphis mauritiana</i> leaves 500mg/kgBW 	<ul style="list-style-type: none"> Group IV had the paw volume, SGPT, SGOT, ALP, IL-6, and TNF-α significantly lower compared to group I (p<0.05) Group IV had a higher level of SOD, CAT, and GSH compared to group I (p<0.05). 	2 weeks	Low

Risk of Bias (RoB). Reduced glutathione (GSH). Superoxide dismutase (SOD). Glutathione Peroxidase (GPx). Catalase (CAT). Interleukin-6 (IL-6). Tumor Necrotizing Factor- α (TNF- α). C-Reactive Protein (CRP)

Source: Own elaboration

studies was calculated using the I² statistic. The results of the meta-analysis are presented in the form of a Forest Plot. In addition, publication bias was evaluated qualitatively using Begg's Funnel Plot, with an indication of low bias if the graph shows a symmetrical distribution. P-value <0.05 indicates that the result is statistically significant.

RESULT

Characteristics of the included studies

This systematic review and meta-analysis involved 9 studies to be analysed descriptively qualitatively in a systematic review, as shown in table 1 below. Of the total included studies, there were 8 studies with *in vivo* designs and 1 clinical experimental

study. The *in vivo* study involved 196 Wistar rats (*Rattus norvegicus*) and 260 Nile tilapia (*Oreochromis niloticus*). While the clinical experiment involved 13 healthy volunteers. The preparations of *Ziziphis mauritiana* leaves used were aqueous, ethanolic, methanolic extract or powder with concentrations ranging from 100 mg/kg body weight (kgBW) to 20 grams per research subject. The evaluation was carried out ranging from 8 days to 8 weeks. The parameters tested include anti-aging effects played by antioxidant markers (SOD, CAT, GPx, GSH, malondialdehyde (MDA)), anti-inflammation markers (paw diameter, IL-6, TNF- α , CRP), collagen density, skin elasticity, moisture, skin brightness, and a decrease in sebum levels, erythema, number of fibroblast, and improving wound healing in the skin. This study also conducted a quality

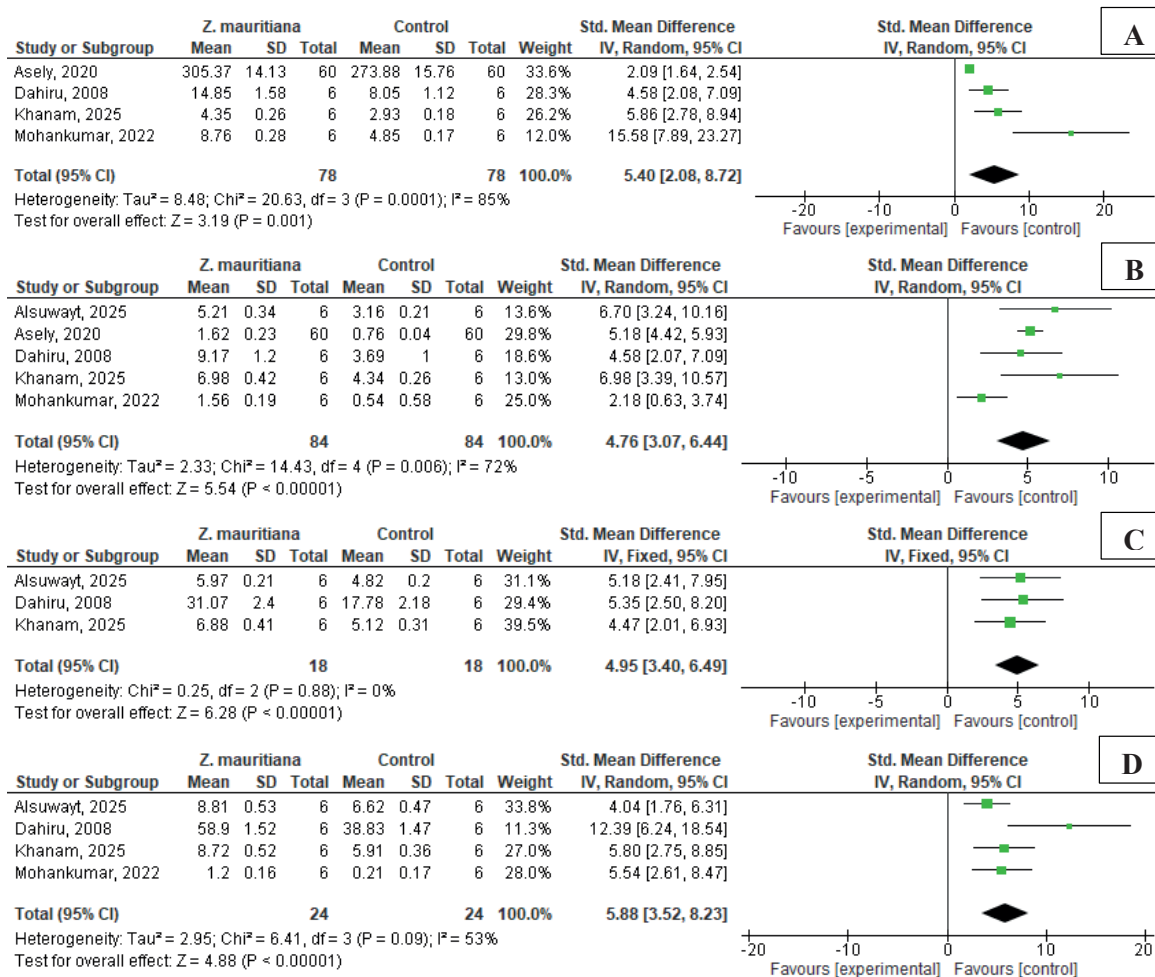


Fig. 2 Forest plot result of antioxidant activity analysis of *Ziziphus mauritiana*. Reduced glutathione/GSH (A). Superoxide dismutase/SOD (B). Glutathione Peroxidase/GPx (C). Catalase/CAT (D) Source: Own elaboration

analysis and potential bias, which showed that there were 6 studies with low potential bias and 3 studies with moderate potential bias.

Antioxidant activity of *Ziziphus mauritiana*

The results of data analysis in this study showed that intervention through the administration of *Ziziphus mauritiana* leaf extract can significantly increase the activity of the body's endogenous antioxidant enzymes. This is expressed through increased levels of SO and CA) with standardised SMD reaching 4.76 (95%CI: 3.07 - 6.44; $p < 0.001$) and 5.88 (95%CI: 3.52 - 8.23; $p < 0.001$) respectively. In addition, supplementation of *Ziziphus mauritiana* leaf extract can also significantly increase the levels of GSH and GPx with SMD reaching 5.40 (95%CI: 2.08 - 8.72; $p = 0.001$) and 4.95 (95%CI: 3.40 - 6.49; $p < 0.001$). The results of the analysis are presented in fig. 2.

Anti-inflammatory activity of *Ziziphus mauritiana*

This systematic review and meta-analysis also analysed the anti-inflammatory activity exhibited by *Ziziphus mauritiana*

leaf extract supplementation. The results are presented in fig. 3. In the analysis results, macroscopically (by the paw diameter measurement) it was found that supplementation of *Ziziphus mauritiana* leaf extract could reduce inflammation which was indicated by a decrease in paw size in experimental animals with a SMD reaching -6.42 (95%CI: -10.48 to -2.36; $p = 0.002$). Meanwhile, biomolecular analysis results showed that supplementation of *Ziziphus mauritiana* leaf extract could reduce inflammatory markers, including a decrease in IL-6, TNF- α , CRP with SMD values respectively reaching -8.73 (95%CI: -16.66 to -0.80; $p = 0.03$); -10.67 (95%CI: -17.91 to -3.44; $p = 0.004$); and -6.38 (95%CI: -8.72 to -4.03; $p < 0.001$).

Publication bias

This systematic review and meta-analysis also conducted a qualitative publication bias test through Begg's Funnel Plot with the results of the analysis are shown in fig 4. The results of the analysis showed that the parameters of GSH, SOD, IL-6, and TNF- α levels had a relatively symmetrical distribution of studies in the funnel plot indicating relatively low publication bias.

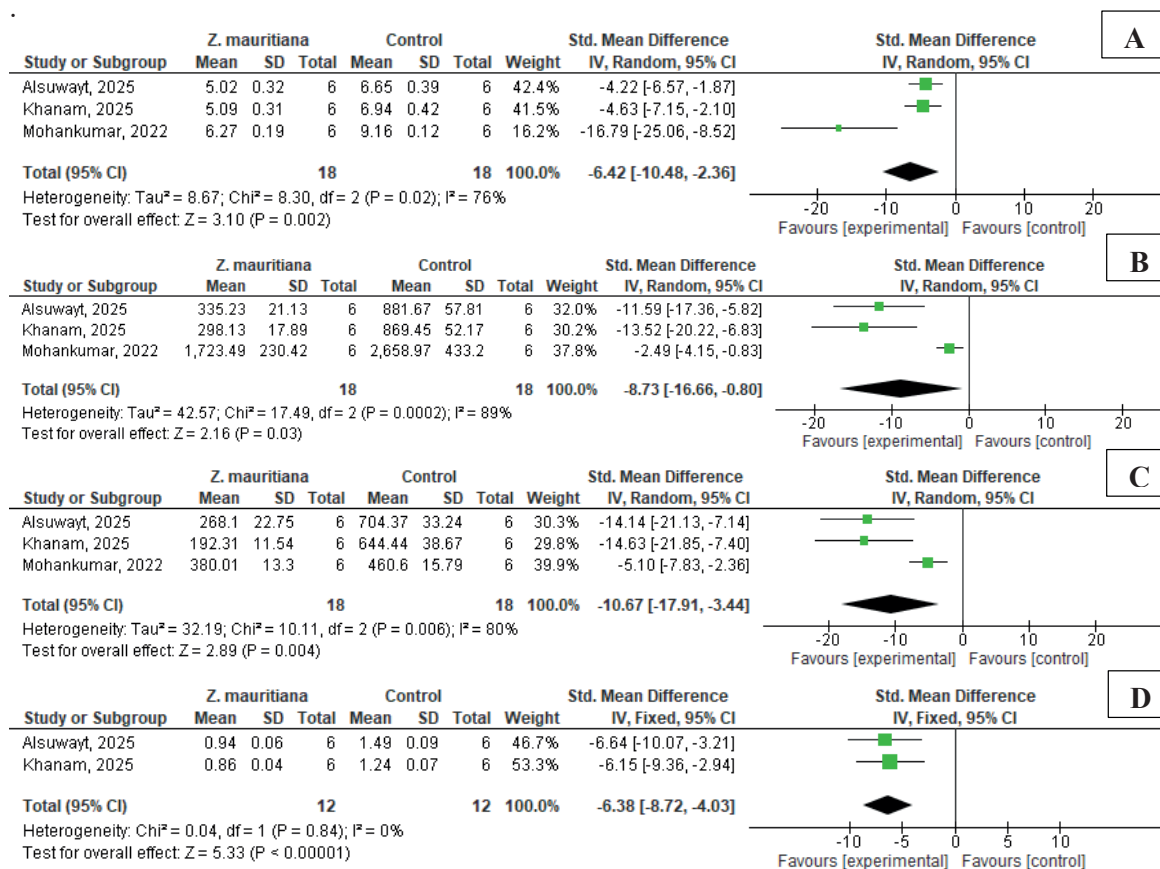


Fig. 3 Forest plot result of anti-inflammatory activity analysis of *Ziziphus mauritiana*. Paw size (A). Interleukin-6/IL-6 (B). Tumor Necrotizing Factor- α /TNF- α (C). C-Reactive Protein/CRP (D). Source: Own elaboration

DISCUSSION

Anti-oxidant activity of *Ziziphus mauritiana* leaf extract

The results of data analysis showed that supplementation of *Ziziphus mauritiana* leaf extract was able to increase endogenous antioxidant levels in the body. This is expressed through increased levels of SOD and CAT with SMD reaching 4.76 ($p < 0.001$) and 5.88 ($p < 0.001$) and levels of GSH and GPx with SMD reaching 5.40 ($p = 0.001$) and 4.95 ($p < 0.001$). These results are in line with previous research conducted by Khanam, et al. (2025) which showed that supplementation of *Ziziphus mauritiana* leaves extracts 250 mg/kg body weight (BW) can increase GSH and SOD levels in male Wistar rats with acute inflammatory conditions induced by carrageenan injection with a comparison of average levels of 4.35 ± 0.26 vs 2.93 ± 0.18 ($p < 0.05$) and 6.98 ± 0.42 vs 4.34 ± 0.26 ($p < 0.05$) respectively [21]. These results were further strengthened by previous research conducted by Dahiru, et al. showed that supplementation of *Ziziphus mauritiana* leaf extract 400 mg/kgBW orally can increase CAT levels in male Wistar rats with alcohol-induced liver damage with a ratio of 58.90 ± 1.52 vs 38.83 ± 1.47 ($p < 0.05$) [18].

Several studies have shown that supplementation of *Z. mauritiana* extract can increase total antioxidant capacity

so that the body is better prepared to deal with exposure to free radicals from the environment and metabolic processes. Another mechanism of this extract in fighting oxidative stress involves increasing the activity of phase II enzymes, such as glutathione S-transferase (GST), which plays a role in detoxifying xenobiotics and oxidative compounds. This strengthens the role of *Ziziphus mauritiana* extract in maintaining redox balance and protecting cells from damage [12]. In comparison, previous research conducted by Haritha, et al. showed that administration of *Aloe vera* extract in rats with hyperglycemia only increased GSH by 1.11 U/mg and had an insignificant value indicating the superior potential of *Ziziphus mauritiana* [23]. This finding is also supported by other research conducted by Mandal, et al. showing that supplementation of green tea extract (*Camellia sinensis*) increased SOD levels by only 0.35 U/mg which was slightly higher than the control group (0.27 U/mg; $p < 0.05$). These results still show the good potential of *Ziziphus mauritiana* [24].

Anti-inflammatory activity of *Ziziphus mauritiana* leaf extract

The results of data analysis also showed that *Ziziphus mauritiana* leaf extract has the potential to prevent inflammation. This is indicated by a decrease in paw size

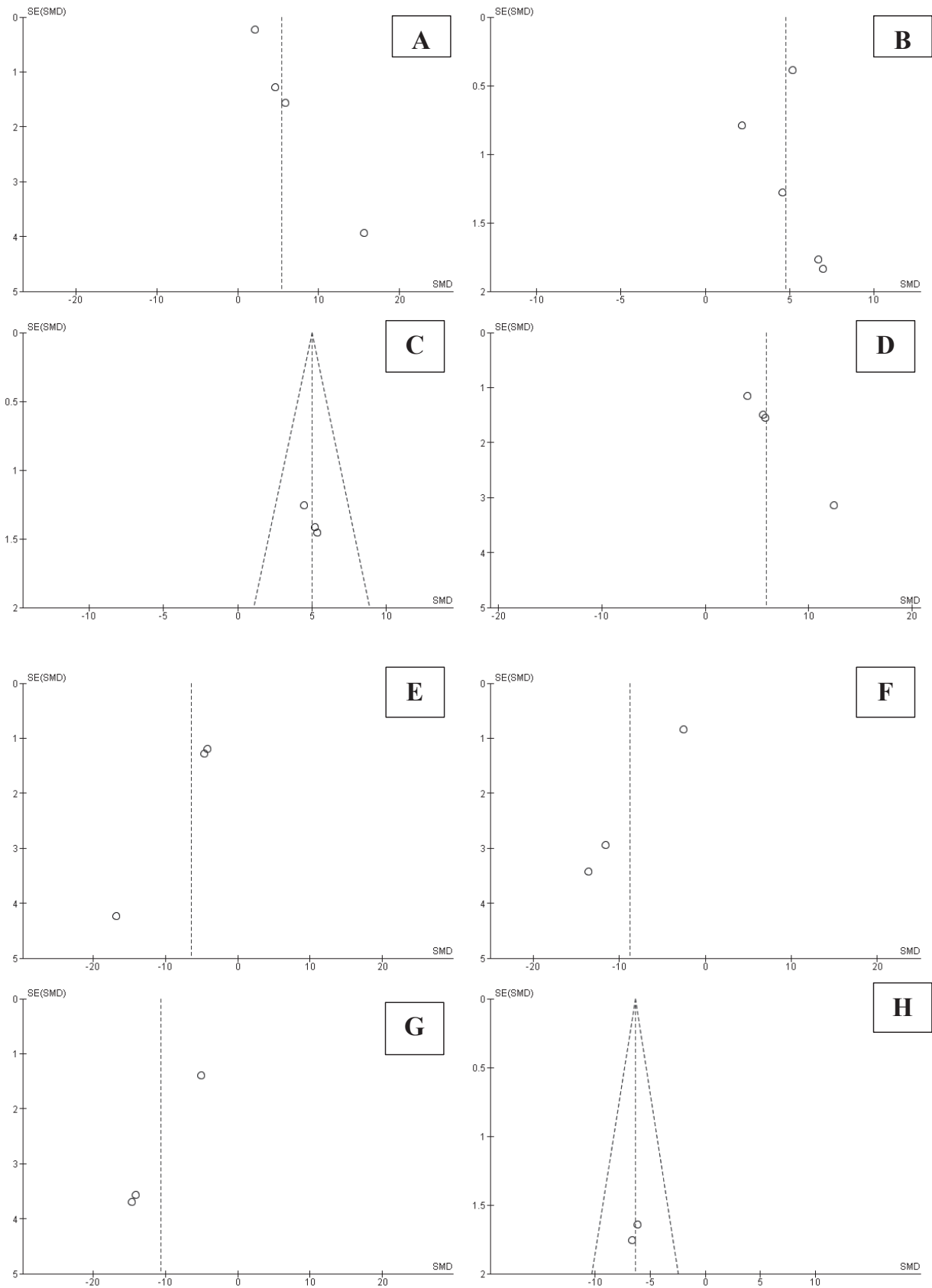


Fig. 4 Funnel plot publication bias analysis result of antioxidant, anti-inflammatory, and anti-aging activity of *Ziziphus mauritiana*. Reduced glutathione/GSH (A). Superoxide dismutase/SOD (B). Glutathione Peroxidase/GPx (C). Catalase/CAT (D). Paw size (E). Interleukin-6/IL-6 (F). Tumor Necrotizing Factor- α /TNF- α (G). C-Reactive Protein/CRP (H) **Source:** Own elaboration

(edema), IL-6, TNF- α , and CRP levels, which respectively had SMD of -6.42 ($p = 0.002$); -8.73 ($p = 0.03$); -10.67 ($p = 0.004$); and -6.38 ($p < 0.001$). These results are in line with previous research conducted by Mohankumar, et al. which showed that oral supplementation of *Ziziphus mauritiana* leaf extract 500 mg/kg can reduce IL-6 levels of the paw tissue in male Wistar rats with acute inflammatory condition (paw edema) induced by carrageenan injection with a comparison of 1723.49 ± 230.42 vs 2658.97 ± 433.20 (in the disease control group, $p < 0.05$) [18]. In addition, previous research conducted by Khanam, et al. showed that supplementation of *Ziziphus mauritiana* leaves extracts 250 mg/kgBW can reduce TNF- α levels of blood serum in male Wistar rats with acute inflammatory condition induced by carrageenan injection with a comparison of average levels of 192.31 ± 11.54 vs 644.44 ± 38.67 (in the disease control group; $p < 0.05$). The extract's potential as an anti-inflammatory is directly linked to its antioxidant properties. Increased oxidative stress through pro-oxidant components, such as reactive oxygen species (ROS), causes systemic inflammation in the body, which is characterized by increased pro-inflammatory mediators. Through inhibition of oxidative stress, inflammation can also be reduced. In addition to increasing endogenous antioxidant enzymes, *Ziziphus mauritiana* also has the potential as an exogenous antioxidant agent that reduces ROS levels in the body [21].

Ziziphus extracts have a strong antioxidant activity due to the high content of phenolic compounds and flavonoids, bioactive molecules capable of neutralising ROS by donating hydrogen atoms or electrons. These properties help prevent oxidative stress and protect cells from damage to the underlying mechanisms involved in various chronic diseases, including the skin aging process [25]. Abalaka et al. conducted an *in vitro* study to assess the antioxidant activity of ethanol and hexane extracts of *Ziziphus mauritiana* and *Z. spina-christi* leaves using 2,2-Diphenyl-1-picrylhydrazyl (DPPH) method. The results showed that ethanol extracts of *Ziziphus mauritiana* leaves, *Z. spina-christi*, and ascorbic acid as a positive control, had values of 18.13 ppm, 101.02 ppm, and 78.12 ppm, respectively. The highest antioxidant content was obtained in the ethanol extract of *Ziziphus mauritiana* leaves. The same study was also conducted to measure antioxidant activity using the hydroxyl radical method, the lowest IC50 result was found in the ethanol extract of *Z. spina-christi* leaves, which was 198.34 g compared to *Ziziphus mauritiana* (357.23 g) and ascorbic acid (219.31 g) [28]. Jha et al. also conducted a study on the toxicological profile and antioxidant potential of ethanol extract of *Ziziphus mauritiana* leaves using the DPPH method compared to ascorbic acid. The results showed IC50 values of ethanol extract of *Ziziphus mauritiana* leaves and ascorbic acid of 128.7 and 24.96 $\mu\text{g/mL}$, respectively. The ethanol extract of *Ziziphus mauritiana* leaves showed strong potential antioxidant activity, thus supporting its use as a natural

antioxidant in medicinal applications [25]. Mokhtar et al. also conducted IC50 tests on the methanol extract of *Ziziphus mauritiana* leaves and ascorbic acid with the DPPH method, which showed values of 10.57 and 4.19 $\mu\text{g/mL}$, respectively [27].

The potencies of *Ziziphus mauritiana* leaf extract in anti-aging skin therapy

Skin aging is influenced by two main factors: intrinsic factors, such as genetics and cellular metabolism, and extrinsic factors like environmental exposures and lifestyle. Intrinsic or chronologic skin aging refers to the unavoidable physiological changes in the skin that occur over time [3, 26]. Extrinsic skin aging is the physiological and histological changes of the skin caused by environmental factors, including ultraviolet (UV) radiation, also known as photoaging [1]. Structural and functional changes in the skin mediated by UV radiation involve several mechanisms, including oxidative stress, deoxyribonucleic acid (DNA) damage, inflammation, and matrix metalloproteinase (MMP) upregulation [3]. Intrinsic and extrinsic skin aging manifestations can be differentiated based on clinical and histopathological features [1, 26]. Cosmeceuticals are cosmetic products that contain biologically active ingredients that provide cosmetic and pharmaceutical benefits. These ingredients consist of vitamins, plant phytochemicals, bioactive peptides, polyunsaturated fatty acids (PUFA), polysaccharides, or anti-inflammatory agents. They are claimed to improve skin regeneration, elasticity, and moisture, and induce a more even skin tone. All these biological properties synergistically provide anti-aging benefits, such as reducing or preventing the appearance of wrinkles and fine lines. *Ziziphus mauritiana* is unique as an active cosmetic ingredient due to its bioactive compound content such as flavonoids, saponins, and ascorbic acid, which have antioxidant, anti-inflammatory, and photoprotective properties, so it has the potential to support skin regeneration, inhibit premature aging, and protect against damage due to UV exposure [4, 5].

Bidara leaves are often used in herbal medicine, either orally or topically. The leaf extract functions as an anti-inflammatory, antipyretic (reduce fever), and antioxidant. The antioxidant content of bidara, especially in the leaves, was found to be higher than in the seeds and stem bark. The highest antioxidant compounds in bidara leaves are flavonoids and tannins [29]. Another study showed the main antioxidants in *Ziziphus mauritiana* leaf extract were phenolic acids and flavonoids, with additional alkaloids, glycosides, terpenoids, saponins, and tannins [27]. Previous studies conducted by Khanam, et al. showed that extracts from *Ziziphus mauritiana* leaves have various secondary metabolite compounds that have the potential as cosmetic and anti-aging agents, including quercetin (356.64 ± 10.60 mg/kg); salicylic acid (1495.97 ± 44.88 mg/kg); rutin (50.54 ± 2.02 mg/kg); kaempferol (4.15 ± 0.17 mg/kg) and total phenolics and flavonoids

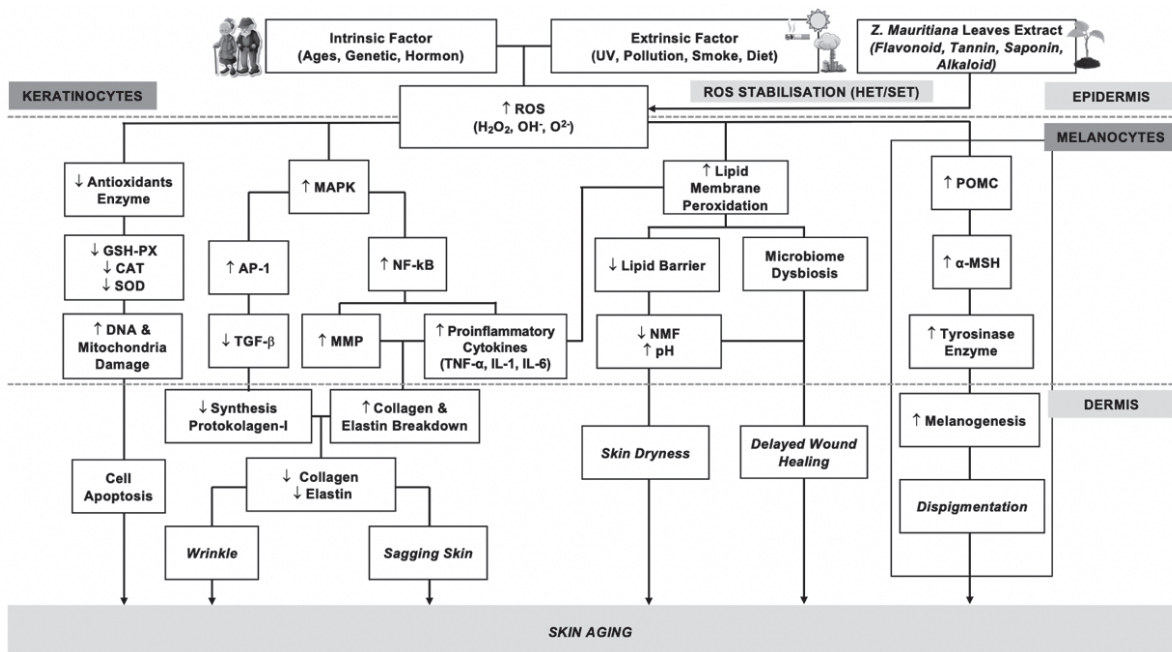


Fig. 5 The role of *Ziziphus mauritiana* leaf extract in anti-aging skin therapy Source: Own elaboration

of 177.6 mg/100 g and 46.2 mg/100 g respectively [21]. The increased DPPH radical-capturing ability of the plant leaf extracts is due to the high concentration of these organic compounds [28]. Flavonoids and tannins can inhibit the activation of transcription factors, such as AP-1 and NF-κB, resulting in decreased levels of MMP-1 and collagen degradation, thus preventing premature aging [29]. Based on our meta-analysis, *Ziziphus mauritiana* leaf extract can reduce inflammation and increase the intrinsic antioxidant activity that is involved in the inhibition of skin aging. Moreover, phenolic compounds in *Ziziphus mauritiana* leaf extracts exhibit a variety of effects on the skin, with their specific targets depending on the area of skin. The compounds can target various structures within the skin, including keratinocytes, fibroblasts, and the extracellular matrix. Some polyphenols also show the ability to inhibit melanin synthesis and transfer in the epidermis by suppressing alpha-melanocyte-stimulating hormone (α-MSH) activity, tyrosinase enzymes, and binding copper ions, thereby reducing hyperpigmentation and improving skin tone [30, 31].

Natural antioxidants derived from plants, including the *Ziziphus mauritiana* leaf extract, have shown promising effects in protecting the skin from damage caused by free radicals and UV radiation [9]. Phenolic compounds can absorb and neutralise free radicals through their primary antioxidant effects, which have a high affinity for collagen and elastin [32]. Antioxidants can activate complex cascade reactions to convert ROS into more stable molecules and to maintain ROS at low and non-toxic levels in tissues [33]. The antioxidant effect works through several mechanisms, including hydrogen atom transfer (HAT), single electron transfer (SET), or metal

ion chelation [9]. Polyphenols have a high hydroxyl content and can donate hydrogen or electrons to other molecules, such as ROS, thus preventing electron uptake by other biologically important molecules, such as proteins or DNA [32]. Phenolic compounds can also inhibit collagenase and elastase, which are enzymes responsible for the breakdown of collagen and elastin in the skin. Furthermore, phenolic compounds can also absorb UV radiation and blue light, which acts as a physical filter to protect the skin [30]. Antioxidants have a dual effect in various topical cosmetic formulations, namely protecting the cosmetic product from potential oxidation processes and the ability to prevent damage to the skin due to oxidative damage caused by UV radiation and the aging process [4] (fig. 5).

Studies on products that formulate leaf extracts from *Ziziphus mauritiana* and their effectiveness as anti-aging therapies are still limited (table 1). Anggraeny et al. reported the effectiveness of 7.5% *Ziziphus mauritiana* leaf extract cream on UVB and cigarette smoke-induced experimental animals for four weeks. The study results showed a decrease in MMP-1 levels and an increase in collagen density in the intervention group compared to placebo. The previous study reported better effectiveness of *Ziziphus mauritiana* leaf extract at 5% concentration compared to 2.5%, in inhibiting the increase in MMP-1 levels (3.057 ng/mL and 3.072 ng/mL) and collagen amount (76.6% and 65.7%). The antioxidant activity of phenolics may dissipate into prooxidants at very high concentrations [29]. Other studies by Rajan et al. and Ma'ruf et al. reported the successful administration of 5% ointment and 100% gel of *Ziziphus mauritiana* leaf extract to Wistar rats as wound healing therapy [7, 34]. Akhtar et al. conducted a study on emulsion formulation (W/O) containing 4% *Ziziphus mauritiana* extract

to assess the effectiveness of anti-aging parameters in 13 healthy respondents for eight weeks. The results showed an increase in elasticity, moisture, skin brightness, and a decrease in sebum levels, as well as erythema [35]. Dahiru et al. reported the antioxidant activity of *Ziziphus mauritiana* leaf extract orally on alcohol-induced Wistar rats [36].

The stability of cosmetic formulations is critical to ensure that the product remains safe and aesthetically effective throughout its storage life. Cosmetic products are formulated with various ingredients that can interact with each other, through chemical, and physical changes, or degradation over time. Such changes can reduce the effectiveness and potential safety of the product [30]. Stability testing of *Ziziphus mauritiana* leaf extract cream (W/O) formulations with a high oil phase composition, and under high temperature and humidity conditions ($45^{\circ}\text{C} \pm 70\% \text{RH}$) can cause the cream to become unstable. Considering the antioxidant and anti-inflammatory activities as well as anti-aging that can be played by *Ziziphus mauritiana* leaf extract, shows the potential of this material to be developed into a cosmetic material that can be used to inhibit skin aging in further studies [13]. This meta-analysis and literature review have limitations related to the number of available studies that discuss the potential of *Ziziphus mauritiana* leaf extract as an anti-aging agent, especially in inhibiting this process. Therefore, further research and updating of the meta-analysis are needed. The use of cosmetics based on *Ziziphus mauritiana* is generally safe, but in individuals with sensitive skin it can cause local irritation such as redness, itching, or dermatitis due to reactions to active compounds such as saponins or tannins. Contraindications for use include a history of hypersensitivity to plants of the *Rhamnaceae* family or the presence of open wounds and active infections on the skin that require special medical treatment [27].

CONCLUSION

This systematic review and meta-analysis showed that *Ziziphus mauritiana* leaf extract has potential as an anti-aging agent through increasing antioxidant enhancement (by boosting SOD, CAT, GSH, GPx levels), inflammatory inhibition (by decreasing paw size, IL-6, TNF- α , and CRP), and increasing collagen synthesis density, elasticity, moisture, skin brightness, and a decrease in sebum levels, erythema, fibroblast count, and improving wound healing in the skin. These results indicate that further studies related to *Ziziphus mauritiana* need to be evaluated further and have the potential to be developed into an anti-aging and cosmetic agent in the future.

CONFLICT OF INTEREST

We declare there is no conflict of interest in this article.

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None.

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