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Curcuminoids and Skin Depigmentation: A Comprehensive Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 April 2025 and was last updated on 28 April 2025.

INTRODUCTION

Review question / Objective Hyperpigmentation, a condition characterized by excessive melanin production, is a prevalent dermatological concern affecting individuals globally. While, Conventional treatments, including tyrosinase inhibitors such as hydroquinone, kojic acid, and arbutin, as well as procedural interventions like chemical peels and laser therapies, are frequently associated with adverse effects, including skin irritation, cytotoxicity, and potential recurrence of pigmentation. Curcuminoids, particularly curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC) were the principal bioactive polyphenols in C. longa and related species. They have garnered increasing scientific attention for their multifaceted pharmacological properties. Despite the promising ethnomedicinal background and emerging cosmeceutical applications, there are few in vivo or clinical studies on the use of curcuminoids in pigmentation management. Besides, the data from in vitro studies need to be systematized reviewed due to fragmented researches, variations in formulation strategies, and inconsistencies in tyrosinase inhibition assays.

Condition being studied Hyperpigmentation, a condition characterized by excessive melanin production, is a prevalent dermatological concern affecting individuals globally. While melanin plays a crucial role in protecting the body from ultraviolet (UV) radiation and environmental stressors, an excessive amount of its production can lead to hyperpigmentation disorders such as melasma, post-inflammatory hyperpigmentation, and solar lentigines, which in turn, may contribute to psychological stress. The cosmetic industry has long sought safe and effective agents to combat these conditions, with particular attention to depigmentation agents that target melanogenesis. The global demand for skin-brightening agents has

surged, driven by both cosmetic and therapeutic needs. Conventional treatments, including tyrosinase inhibitors such as hydroquinone, kojic acid, and arbutin, as well as procedural interventions like chemical peels and laser therapies, are frequently associated with adverse effects, including skin irritation, cytotoxicity, and potential recurrence of pigmentation. Consequently, the search for safer, naturally derived depigmenting compounds has intensified, particularly within the field of ethnopharmacology.

METHODS

Search strategy Three primary databases Sci-Finder, Web of Science (WoS), and Scopus were searched up to 27 August 2024 using the following keywords, the first set (curcuminoids AND curcuma) was combined systematically using the Boolean operator AND with the second set, (nanoemulsion OR formulation OR pigmentation OR *anti AND aging* OR melanin OR tyrosinase OR cosmetics OR skin OR toxicity).

Participant or population Original research articles (in vitro, in vivo, clinical trials) that provide quantitative data on melanin production or pigmentation reduction of curcuminoids or curcumin-based substances.

Intervention Curcuminoids and conventional therapy in different indicators against pigmentation.

Comparator The conventional therapy to brighten the skin, Kojic acid or Arbutin.

Study designs to be included Publication language was limited to English-language studies only. Publication type was limited to article, and research area was excluded the topics irrelevant to chemistry on each database automatically. All of the results were imported to excel and conducted deduplication. The studies were screened one by one in Excel to exclude ones irrelevant to the topic “skin activities” by paired reviewers independently, based on title and abstract. Disagreements were resolved by consensus.

Eligibility criteria Only include original research articles (in vitro, in vivo, clinical trials) that provide quantitative data on melanin production or pigmentation reduction of curcuminoids or curcumin-based substances. Only include studies that use curcuminoids or analogues in any topical formulation (creams, gels, patches, nanoemulsions) aimed at reducing pigmentation. Outcome measures only include studies where the primary or secondary outcomes involve melanin reduction, skin lightening, or inhibition of melanogenesis or tyrosinase activity. The studies that focus on outcomes unrelated to pigmentation, like anti-aging, acne treatment, anti-wrinkle, skin disorder or general skin conditions, unless pigmentation is a specific part of the outcome, or studies that do not provide measurable or statistical data on pigmentation outcomes would be excluded.

Information sources Three primary databases Sci-Finder, Web of Science (WoS), and Scopus were searched up to 27 August 2024 using the following keywords, the first set (curcuminoids AND curcuma) was combined systematically using the Boolean operator AND with the second set, (nanoemulsion OR formulation OR pigmentation OR *anti AND aging* OR melanin OR tyrosinase OR cosmetics OR skin OR toxicity).

Main outcome(s) Effect of crude extracts on anti-tyrosinase. Effect of curcuminoids on anti-tyrosinase. Effect of curcuminoids on anti-skin cancer activity. Effect of curcuminoids on melanogenesis inhibition.

Quality assessment / Risk of bias analysis Two researchers independently assessed the risk of bias using the ToxRTool evaluation. If there was any ambiguity, it can be resolved through discussion and third-party negotiation. The assessment results were grouped into three categories: reliable without restrictions (for in vitro studies with 15–18 points), reliable with restrictions (for in vitro studies with 11–14 points), and not reliableTwo researchers independently assess the risk of bias using the ToxRTool evaluation. If there is any ambiguity, it can be resolved through discussion and third-party negotiation. The assessment results will group into three categories: reliable without restrictions (for in vitro studies with 15–18 points), reliable with restrictions (for in vitro studies with 11–14 points), and not reliable (for in vitro studies less than 11 points).

Strategy of data synthesis Statistical analysis will be performed using the RevMan 5.4. For continuous data indicators IC50 values, the standardized mean difference (SMD) and mean difference (MD) with 95% confidence interval (CI) will be used. The overall effects will be estimated with the Z-test and $P<0.05$ will be considered as statistically significant. The chi-square tests will be used to examine difference among included studies, and $P < 0.10$ will be considered significant. The heterogeneity will be assessed by

the inconsistency. The publication bias will be described by funnel plot.

Subgroup analysis Subgroup analysis will be conduct on different curcuminoids analogs.

Sensitivity analysis Assess the robustness of the analysis results by leave-one-out strategy throughout the sensitivity analysis.

Country(ies) involved Malaysia.

Keywords Curcuminoids, Anti-pigmentation, Tyrosinase, Melanin, Systematic review, Meta-analysis.

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