Topical melatonin, resveratrol, and rapamycin for skin anti-aging: a systematic review

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BACKGROUND

- With an abundance of skincare products available today claiming to slow or reverse signs of aging, patients may feel overwhelmed selecting products.
- Topical melatonin, resveratrol, and rapamycin have recently emerged as potential off-label treatments for skin aging.

OBJECTIVE

The purpose of this systematic review was to perform a comprehensive review of the literature on these three agents when used for the reduction of the symptoms of aged skin, and their corresponding effectiveness, or lack thereof.

METHODS

Search Strategy & Study Selection

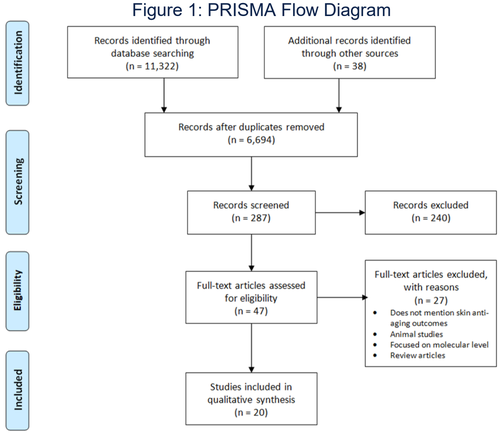
- A comprehensive search strategy using a combination of controlled vocabulary and keywords for 'topical melatonin,' 'resveratrol,' 'rapamycin,' and 'skin aging' was developed with the expertise of an experienced health sciences librarian.
- Articles were identified through a systematic search of the following bibliographic databases: PubMed/Medline (NLM), Embase (Elsevier), Cochrane Library (Wiley), International Pharmaceutical Abstracts (Ovid), Web of Science (Clarivate Analytics), and Scopus (Elsevier), along with citation searches of key articles, and grey literature.
- Three investigators individually assessed each of the studies based on the study design, intervention, participants, outcomes, and results, determining relevance for inclusion.
- Human studies published up to September 2019 were included if at least one group received topical melatonin, resveratrol, or rapamycin, and at least one outcome related to skin anti-aging was reported.
- Disagreements on inclusion were resolved through consensus generation with an additional reviewer, and bias assessment was performed.

Risk of Bias Assessment

Bias was assessed using one of two tools, depending on study type:

- Cochrane Risk of Bias (RoB) tool for randomized controlled trials
- Cochrane Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) tool for all other study designs.

Figure 1: PRISMA Flow Diagram

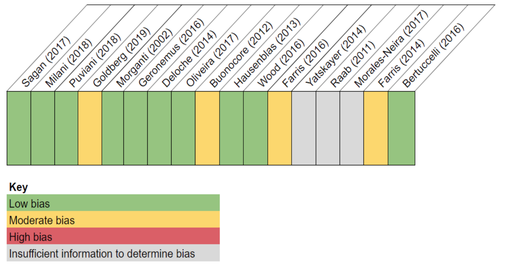


CHARACTERISTICS OF INCLUDED STUDIES & RESULTS

Table 1: Data Extraction Table

Author (year)	Intervention	Comparator	Duration	Design	Subject Baseline Characteristics	Outcome Results
Topical Melatonin						
Sagan (2017)	Topical melatonin 1% daily	Restructurer 5 mL topically daily	4 weeks	RCT	Not mentioned	• Increase in sebum • No change in skin pigmentation
Morganti (2002)	Topical melatonin + others BID	Carrier + oral supplement BID Carrier + supplement control BID	8 weeks	RCT	Dry skin with moderate xerosis and photoaging	In subjects that received oral supplement and topical product: • Lipids increased from about 40 to 70% • Hydration increased from 55% to >100%
Puviani (2018)	Topical melatonin 0.1%, 2 fingertip units BID	No treatment	2 months	Split-face	Moderate-severe facial aging	• Decreased coarse wrinkle volume (-31%) • Decreased fine wrinkles (-18%) • Decreased melanin content (-17%) • Reduced periorbital wrinkle volume (-17%)
Milani (2018)	Topical melatonin 0.1% BID	No treatment	3 months	Pre-post	Moderate-severe skin aging	• Reduction in crow's feet (-15%) • Surface microrelief (- 26.5%) • Reduction in skin profilometry (-13%): -13% reduction in roughness, –13% reduction in wrinkles' maximum depth and –7.2% reduction in total wrinkles' height in comparison with baseline and control sides • Reduction in skin tonicity (+30%) • Reduction skin dryness (-59.9%)
Goldberg (2019)	Topical melatonin + others qHS	No treatment	3 months	Pre-post	Moderate facial aging with crow's feet wrinkles and ≥1 pigmented spot	• Decrease in wrinkles (-11%) • Increase in skin firmness (-8%) • Reduction in redness (-70%) • Overall improvement in skin quality and complexion
Resveratrol						
Oliveira (2017)	Topical resveratrol BID	No treatment	45 days	Pre-post	Not mentioned	• Progressive reduction in pore size on forehead (79%) and on cheeks (58%) • Decrease in pigmentation on forehead (29%) and on cheek (16%) • Increase in pigmentation in forehead in 4/24 and in cheek in 5/24 • No significant change in wrinkles and expression lines • Non-significant decrease in transepidermal water loss
Wood (2016)	Oral resveratrol 30 mg + others	No treatment	8 weeks	Pre-post	Non-smokers with moderate signs of skin aging based on a dermatologist assessment, Fitzpatrick skin types I and II	• Increased skin carotenoid concentrations, skin elasticity, and transepidermal water loss • Improvements in skin radiance, texture, and overall appearance, as evaluated by a dermatologist • Improvements in skin firmness and radiance based on participants' self assessments • No changes in texture, lines, firmness, fine lines, or overall appearance
Buonocore (2012)	Oral resveratrol + others daily	Placebo	60 days	RCT	Dull complexion, 60% with cutaneous dyschromia/brown spots	• Improvements in skin moisture and skin elasticity • Decrease in skin roughness, wrinkle depth • Decrease in intensity of age spots
Farris (2016)	Topical resveratrol 1% + others 2-3 times per week, then qHS	No treatment	10 weeks	Pre-post	Mild-moderate hyperpigmentation with other clinical signs of skin aging	• Improvements in fine lines, radiance, and skin smoothness as early as week 2 and in hyperpigmentation, overall skin clarity, skin tone/evenness, and wrinkles by week 6
Yatskayer (2014)	Topical resveratrol + others qHS	No treatment	12 weeks	Pre-post	Clinically determined mild to moderate photodamaged facial skin	• Improvements in fine lines and wrinkles in the periorbital area, firmness/elasticity, skin laxity, density, skin radiance, skin tone evenness, skin roughness, hyperpigmentation, and the overall skin appearance as assessed by expert clinical grading • Improvement in skin density shown with bioinstrumentation measurements
Raab (2011)	Topical resveratrol + others BID	No treatment	12 weeks	Pre-post	Clinically determined mild to moderate photodamaged facial skin	• Improvements in fine lines and coarse wrinkles in the periorbital area, firmness/elasticity, toned/resiliency, defined contours, density, skin radiance, skin tone evenness, skin roughness, skin hyperpigmentation, the overall appearance of skin condition at all time points • Improvement in firmness, hydration, and skin barrier function shown with bioinstrumentation measurements
Farris (2014)	Topical resveratrol 1% + others qHS	No treatment	12 weeks	Pre-post	Mild to moderate facial lines, wrinkles, hyperpigmentation, and skin laxity	• Improvements in fine lines and wrinkles, skin firmness, skin elasticity, skin laxity, hyperpigmentation, radiance, skin roughness, and in dermal thickness of the periorbital area (average 18.9%)
Bertucelli (2016)	Oral trans-resveratrol 10 mg + others BID	Oral fermented papaya preparation BID	90 days	RCT	Clinical signs of skin aging: wrinkles, dull complexion and brown spots	• No effect on skin moisturization or skin elasticity • No change in skin roughness, wrinkle depth, skin tone evenness, or darkness of brown spots
Deloche (2014)	Topical resveratrol 0.25% once to BID	No treatment	2-3 months	RCT	Not mentioned	• More important DensiScore decrease in treated arm (skin density) • Significantly improved skin firmness immediately after application of the product • Significantly reduced skin wrinkles as early as 1 month later
Geronemus (2016)	Topical resveratrol 1.0% + others	Supportive materials: Topical vitamin C, vitamin E, ferulic acid	24 weeks	Split-face	Moderate hyperpigmentation, lentigines, moderate periorbital wrinkles	Greater improvement in: • Hyperpigmentation (26.1% vs. 16.7%) • Lentigenes (21.0% vs. 11.0%) • Overall skin appearance (26.8% vs. 12.6%) • Skin texture (36.3% vs. 22.0%) • Skin tone evenness (27.4% vs. 14.3%) • Periorbital wrinkles (15.7% vs. 9.4%) • Global face wrinkles (18.7% vs. 13.7%)
Hausenblas (2013)	Oral trans-resveratrol 50 mg + others daily	No treatment	6 months	Pre-post	Visible signs of skin aging	• Reduction in facial pores and in UV spots • No changes in skin tone, wrinkles, and polarized spots • Self-reported changes of improved skin tone, lighter age spots, softer skin, diminished wrinkles and fine lines
Rapamycin						
Morales-Neira (2017)	Rapamycin	Placebo	240 days	Pre-post	Not mentioned	• Improved dermal thickness, diameter and density of the collagen fiber bundles

Figure 2: Risk of Bias Assessment



RESULTS

- The majority of selected studies were pre-post design and enrolled female patients aged 40-65 years.
- 11 studies included the agents of interest as components of a combination regimen.
- In the 5 studies involving topical melatonin, positive outcomes included skin wrinkle reduction, increased skin hydration, and improved skin tonicity or complexion.
- In the 11 studies involving resveratrol, positive outcomes included reduction in skin wrinkles, hyperpigmentation, or age spots, and improvement in skin elasticity and tonicity or complexion.
- Only one article on rapamycin met inclusion criteria and the positive outcomes of this study included an increase in dermal thickness, diameter, and density of collagen fibers.

DISCUSSION & CONCLUSIONS

- Available studies identified through this systematic review suggest that resveratrol and topical melatonin appear to be modestly effective at reducing the appearance of aged skin.
- While a body of literature exists that examines rapamycin on a molecular level, more human studies must be carried out in order to gain a better understanding of its potential benefits on skin aging.
- Further research should be focused on the individual drugs to determine the extent of skin anti-aging effects, without additional active ingredients that may contribute to skin anti-aging and therefore, confound results.

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