The Usage of Coenzyme Q10 on Skin Aging: A Systematic Review on Animal and Clinical Study

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Abstract

Skin aging is a multifactorial problem which involves free radical, cell cycle, and glycation mechanism. Hence, antioxidants become a prominent solution to this problem. Supplementation of Coenzyme Q10 as a promising antioxidant for skin aging has not been widely discussed. Thus, a systematic review was conducted following the 2020 Preferred Reporting Itemsfor Systematic Reviews and Meta-analyses (PRISMA) guideline and critically appraised. Ten studies focusing on efficacy and dose of CoQ10 for skin aging through oral and topical route were included in this systematic review. Studies were categorised into 3 animal study, 3 clinical stand-alone CoQ10 study, and 4 clinical CoQ10 combination study. In this review, it was confirmed that CoQ10 benefits the skin through reduction of wrinkle and fine lines, overall signs of photoaging, and inflammatory cytokines' activity. Further study needs to be conducted on ideal oral and topical dose along with safety and tolerability of topical CoQ10.

Keywords: aging, coenzyme Q10, skin

Introduction

Aging as a time-related deterioration of human physiological function, affects all individuals.[1] In particular skin aging is expressed intrinsically through smooth, thinned, dry skin with prominent expression lines; and expressed extrinsically through photodamage including wrinkles, actinic keratoses, patchy hypopigmentation, and pigmented lesions.[2]Due to poor hydration, dermis and epidermal junction disintegration, and loss of body mass, aging process occurs. Several endogenous factors including gene mutation, hormonal factor, cell metabolism; and exogenous factors including ultraviolet ray, pollutants, toxins, and chemicals have been reported to speed up skin aging through various mechanisms including free radical, glycation, cell cycle, and others.[3]

Over the years, therapeutic modalities to improve skin aging has been conducted through photoprotection and administration of a range of antioxidants and retinoids.Coenzyme Q10 (CoQ10) is one of the antioxidants which function to enhance antiaging effect.[2] Itis a lipid-soluble antioxidant that works on lipoprotein and plasma membrane and also function as an essential component at the mitochondrial electron transport chain. With aging process, biosynthesis of CoQ10 reduced and resulted in increased lipid oxidative damage.[4] Thus, CoQ10 replenishment through supplementation is needed.As the third most consumed supplement, CoQ10 has been used as treatment in numerous aging diseases such as cardiovascular and kidney diseases, diabetes, metabolic syndromes, neurodegenerative disease and fertility.[4,5]The supplementation of CoQ10 has been established as a supporting therapy that positively improve disease outcome.[4]

However, application of CoQ10 for skin aging have not been discussed as widely as other type of antioxidants and effective therapeutic dose has not been determined. Thus, this systematic review aimed to determine the efficacy and dosage of CoQ10 adjuvant in prevention against skin aging.

Methods

Study design

This systematic review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and following the Oxford Centre of Evidence-Based Medicine (CEBM) critical appraisal checklist to review the studies included. We aimed to describe the utilization of coenzyme Q10 in various applications in dermatology through this review.

Inclusion and exclusion criteria

To obtain a comprehensive searching result, both animal models and clinical trial results are included, thus any experimental study, case-control, cohort study, and randomized controlled trials (RCTs) are eligible. All studies in English language, published until 19/01/2024, and reported quantitative primary outcome of skin aging, wrinkles, and skin roughness are included. Studies focusing on other subjects and report only qualitative outcomes are excluded.

Search Strategy

Study searching was done by going through electronic journal databases: PubMed, Cochrane Library, Ebsco, and ProQuest using search terms: ("coenzyme Q10" OR "coQ10") AND ("skin" OR "dermatology") AND ("wrinkle" OR "aging"). Additionally, hand searching was conducted with Google Scholar using the same keywords. ___ conducted the search strategy as independent researchers by filtering them with the eligibility criteria for search refining.

Study Selection

Study articles were individually screened for titles and abstract to select studies suitable with the requirements. Then, the full-text of each potential studies were screened and appraised, only those which met the eligibility criteria were selected. Any discrepancy between author findings were discussed to reach an agreement.

Data Extraction and Synthesis

In order to extract necessary information from the selected studies, we presented a table with following data: first author and year of publication, type of study, number of samples, gender and mean age (years) (for clinical trial only), form and dose of coenzyme Q10 given, duration of treatment, measuring instruments, relevant statistical results, and the principal outcomes. Based on provided statistical report, studies were critically appraised and effect size were calculated for data synthesis.

Result

In total, we found 244 journal articles from the database. After duplicated articles were removed, there were 240 articles available for title and abstract analysis.Based on title and abstract 13 studies pass through the screening of which five are animal study and eight are clinical study. In the next step, full text from each study was analysed.Two articles from animal study and one article from clinical study were removed from analysis due to full-text unavailability or unrelated content, leaving 10 articles in final analyses.

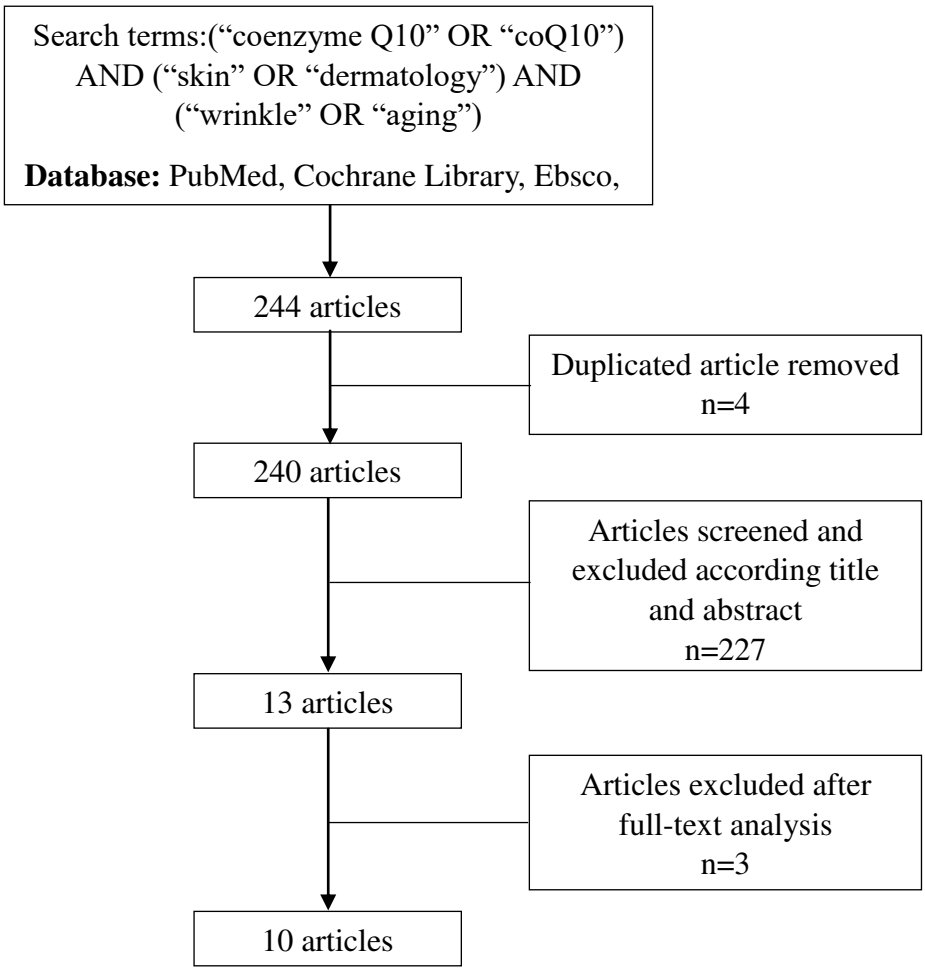

Figure 1. PRISMA diagram of the assessment method

Chosen articles were then analysed for risk of bias with Version 2 of Cochrane Risk of Bias Tool for Randomized Trial (RoB-2) as seen in Table 1. Three of ten articles have moderate risk of bias while the others have low risk of bias. Although these three articles raise some concerns, they are still acceptable and thus not excluded

Table 1. Version 2 of Cochrane Risk of Bias Tool for Randomized Trial Assessment for Chosen Articles

Type of study	Study (year)	D1	D2	D3	D4	D5	Overal l
Animal	Yadav et al (2015)[6]	+	+	+	+	+	+
	Nayak et al (2017)[7]	+	+	+	+	+	+
	Wu et al (2020)[8]	+	+	+	+	+	+
Human	Inui et al (2008)[9]	+	+	?	+	+	?
	Udompataikul (2009)[10]	+	+	+	+	+	+
	Di Cerbo et al (2015)[11]	+	+	+	+	+	+
	Knott et al (2015)[12]	?	+	?	+	?	?
	Herndon Jr et al (2015)[13]	+	-	+	?	?	?
	Zmitek et al (2017)[14]	+	+	+	+	+	+
	Zmitek et al (2020)[15]	+	+	+	+	+	+

D1: Risk of bias arising from the randomization process	+	low risk of bias
D2: Risk of bias due to deviation from the intended interventions (effect of assignment to intervention)	?	unclear risk of bias
D3: Missing outcome data	-	high risk of bias
D4: Risk of bias in measurement of outcome		
D5: Risk of bias in selection of the reported result		

Due to variation in subject and intervention methods, we divide the articles into three categories. First, intervention conducted through animal study; second, intervention conducted in clinical setting with only CoQ10; and third, intervention conducted in clinical setting with CoQ10 in combination with other pharmaceuticals. Characteristics of studies from each category can be observed in Table 2, Table 3, and Table 4 respectively.

Table 2. Characteristics of selected animal study

Study	Number of samples	Gender - animal	Drug dose (topical)	Treatment duration	Outcome
Yadav et al (2015)[6]	4 for negative control 4 for negative control 4 gotproniosomal (PN) gel 4 got conventional gel	Female – swiss albino mice	- UV radiation only +5 mg CoQ10 +5 mg CoQ10 Once daily, 5 days a week	4 weeks	CoQ10 application reduced skin pinch recovery time compared to UV treated group. PN gel showed better reduction of visual skin grading score compared to conventional gel. CoQ10 application increased antioxidant activity of superoxide dismutase ($p<0.01$) and

					catalase($p<0.05$) while decreasing activity of malondialdehyde ($p<0.001$) compared to positive control, but not as good as negative control group. PN gel showed better antioxidant activity than conventional gel.
Nayak et al (2017)[7]	6 for negative controls 6 for positive controls 6 for marketed formulation 6 for free retinaldehyde (RAL) gel 6 for free CoQ10 gel 6 for free RAL+CoQ10 gel 6 for RAL nanostructured lipid carrier (NLC) gel 6 for CoQ10 NLC gel 6 for RAL+CoQ10 NLC gel	Female – swiss albino mice	- UV radiation only + CoQ10, dosage not disclosed + 0,25 mg RAL + 1 mg CoQ10 + 0,25 mg RAL + 1 mg CoQ10 0,25 mg RAL + 1 mg CoQ10 + 0,25 mg RAL + 1 mg CoQ10 Once daily; dose for each 10 mL	3 weeks	Wrinkle reduction potential best observed in RAL+CoQ10 NLC gel and CoQ10 NLC gel All NLC groups showed skin recovery ability and skin epidermal thickness alteration comparable to the negative control group ($p>0.05$ compared to negative control) RAL+CoQ10 NLC gel was reduces collagen and elastin changes due to UV exposure All NLC groups were able to revert UV-caused photoaging
Wu et al (2020)[8]	9 for negative control 9 for positive control 9 for TiO_2suncreen 9 for CoQ10 suncreen	Female – pathogen-free Kunming mice	- UV-B radiation only +TiO_2 50 mg/g +CoQ10 10 mg/g Once daily	8 weeks	CoQ10 increased antioxidant activity of superoxide dismutase ($p<0.05$) and glutathione peroxidase ($p<0.05$) while decreasing activity of malondialdehyde ($p<0.05$) Dermal thickness significantly improves with CoQ10 sunscreen compared to positive control ($p<0.05$) CoQ10 sunscreen reducecollagen degradation

					proven through significant reduction of MMP-1 mRNA level. ($p<0.05$) CoQ10 sunscreen reduce photoaging effect proven through significant improvement of DNMT1 activity. ($p<0.05$)

Table 3. Characteristics of selected clinical study with CoQ10 only intervention

Study	Type of study	Number of samples	Gender	Age	CoQ10 Dose and form	Treatment duration	Randomization	Outcome
Inui et al (2008)[9]	In vitro + Prospective cohort study	31 participants	Female	27-61 years old	1% CoQ10 cream twice daily	5 months	Single-blind	In-vitro experiment showed reduction in UV induced cytokines IL-6 ($p<0.05$) and MMP-1 ($p<0.01$) activity in cultured fibroblast treated with 20 uM CoQ10. Reduced wrinkle grade score in treatment group (not significant statistically)
Knott et al (2015)[12]	Prospective cohort study	73 participants, each with 3 test area: untreated, with CoQ10 cream, and with CoQ10 serum	Female	20-66 years old	Cream: 348 uM; Serum: 870 uM Twice daily	2 weeks	None	Both groups of CoQ10 therapy significantly increase quinone levels lines ($p<0.05$) in epidermis end dermis, increase energy metabolism in epidermis ($p<0.05$), and improve antioxidant properties in stressed skin ($p<0.05$) Both dose shows similar result

Zmitek et al (2017)[14]	RCT	33 participants: 11 – placebo 11 – CoQ10 (A) 11 – CoQ10 (B)	Female	45-60 years old (52.6± 4.2 years old)	A: 50 mg tablet; B: 150 mg tablet Once daily	12 weeks	Double-blind	CoQ10 supplementation improves wrinkles and fine lines ($p<0.05$), microrelief lines ($p<0.05$), skin smoothness and firmness ($p<0.01$). Minimal UV induced erythema, dermal thickness, skin elasticity and hydration do not improve with CoQ10 supplementation. Both dosage shows similar result.

Table 4. Characteristics of selected clinical study with CoQ10 in combination with other pharmaceuticals

Study	**Type of study**	**Number of samples**	**gender**	**Age**	**CoQ10 Dose and form**	**Other active ingredients**	**Treatment duration**	**Rando-mization**	**Outcome**
Udompataikul et al (2009)[10]	RCT	60 participants: 30 in placebo group 30 in supplement group	Female	35-60 years old 36-60 (46.23) years old 35-59 (43.10) years old	15 mg capsule Once daily	*Camellia sinensis* leaf extract 150 mg, demineralised fish proteoglycan extract 105 mg, *Dunaliella salina* fresh cell 75 mg, zinc 14 mg, *Vitis vinifera* seed extract 25 mg *Pinus*	12 weeks	Double-blind	Treatment group showed significant depth of skin roughness and wrinkles ($p=0.048$) compared to placebo group. Compared to to baseline, wrinkle depth improved by 21.22%($p=0.000$) Treatment participants are

						pinaster bark extract 20 mg, selenium 26 ug, vitamin E 7.36 mg			significantly satisfied with reduction of pore size and wrinkles.
Di Cerbo (2014)[11]	RCT	30 participants: 15 in placebo group 15 in Viscoderm©supplement group	Female	43.6±1.2 years old	10 mg capsule 3 times a day With standardized diet	Hydrolysed collagen 200 mg, Pycnogenol 15 mg	2 weeks	double-blind	Significant improvement in VAS photoaging score ($p<0.0001$), facial sebum ($p<0.0001$), hydration ($p<0.0001$), and tonicity ($p<0.05$) Supplementation increased serum fibronectin ($p<0.001$) and serum hyaluronic acid ($p<0.001$); and decrease in serum neutrophil elastase 2 ($p<0.001$), and serum carbonylated proteins ($p<0.0001$)
Herndon Jr et al (2015)[13]	Prospective study	37 participants	Female	35-60 years old (52.1 ± 6.4 years)	Dose not disclosed, topical (oil-in water moisturizer) twice daily	*Astragalus membranaceus* root extract, palmitoyl tripeptide-38, ursolic acid, THD ascorbate	12 weeks	none	Multidrug moisturizer improves signs of skin aging ($p<0.001$) (fine lines, wrinkle, skin clarity, visual roughness, tactile roughness, redness, skin tone, and overall appearance)
Zmitek (2020	RCT	34 participants:	Female	40-65 years old (54.4±6.	Water solub	Hydrolysed fish collagen 40 mg,	12 weeks	Double-blind	Dermis density ($p<0.0001$ to baseline and

)[15]		17 in placebo group 17 in supplement group		8 years old)	le CoQ 10 50 mg syrup Once daily	vitamin c 80 mg, vitamin A 920 ug, biotin 150 ug			p<0.001 to placebo group) and winkle area fraction (p<0.0001 to baseline and p<0.0001 to placebo group) improved significantly with supplementation Dermis thickness, skin viscoelasticity, skin hydration, trans epidermal water loss, skin smoothness and microrelief do not improve significantly.

Discussion and Conclusion

According to our findings, usage of CoQ10 has been assessed for topical application in animal study and for oral and topical application in clinical trials. In addition to chosen studies, multiple in vitro studies had also presented evidence of effectivity of CoQ10 therapy as antioxidant to relief oxidative stress, as treatment for photoaging, and to improve mitochondrial function.[16-20]

Overall, both oral and topical CoQ10 provide varying degree of improvement of skin aging signs including wrinkles and fine lines. Interestingly, several parameters result from stand-aloneoral CoQ10 therapy are significantly different compared with result in oral combination therapy. Stand-alone oral CoQ10 treatment did not show any improvement in dermis thickness, skin smoothness, elasticity, and hydration while these parameters were improved two studies experimenting on combination therapy with hydrolysed collagen and combination of other antioxidants.[11,14,15]

Oral CoQ10 supplementation ranges from 15 to 150 mg daily, yet only Zmitek et al (2017) reported dose comparison in which they have two groups of intervention with 50 mg CoQ10 and 150 mg CoQ10 each. According to their result, both groups showed similar improvement within the 12 weeks of therapy.[14] However, it should be noted that their study was only conducted with 11 subjects in each group and do not assess for other dose. Hence, we can only conclude that oral dose of 50 mg CoQ10 can already adequately improve skin aging. We can not conclude whether lower dosesof oral CoQ10 were able to show similar result given that all report for lower doses are in combination with other active ingredients. [10,11] In proceeding study, Zmitek et al (2020) experimented with 50 mg CoQ10, this time in combination with hydrolysed fish collagen, vitamin A and C, and biotin. They again, find no significant difference in dermis thickness, skin hydration, and elasticity in this newer study.[15]

Three studies reported no treatment side effects for oral consumption of CoQ10 while the other two do not address safety and tolerability of oral CoQ10.[10,14,15] Yet, this do not impose as a problem as safety and tolerability of CoQ10 is well established. In 2010, a study conducted with a maximum dose of 3600 mg of

daily oral CoQ10 reported to be well tolerated with some gastrointestinal symptoms in healthy subjects and in patient with Huntington's disease.[21]

While all topical therapy regime also reported improved signs of wrinkle and fine lines, some specifically reported other mechanism of aging improvement especially while in combination with other active ingredient including through cytokine activity, reduction of collagen degradation, and other parameters improvement such as skin tone, redness, and clarity.[6-9,12,13]Each study proposed different doses of CoQ10 in different vehicle. Based on information from PubChem that CoQ10 molecular weight is 863.3 g/mol;[22] we calculated that topical dose range varies approximately from 0.1 mg/mL to 10 mg/mL in animal study and from 0.3 mg/mL to 10 mg/mL in clinical trial. Additionally, the vehicle varies in consistency from liquid serum, gel, to emulsion (cream and sunscreen), used different base, and some even with advanced base (proniosomal (PN)gel and nanostructured lipid carrier (NCL) gel). Thus, the studies are incomparable with each other. None of three clinical studies addressed about safety and tolerability of topical CoQ10.[9,12,13]

Despite the limitation, we can conclude that topically applied CoQ10 has better penetration when delivered as a smaller structure such as with PN and NCL compared to when delivered as free structure. This finding is supported by multiple other in vitro studies with similar report. Ayunin et al (2022) reported improvement of anti-aging activity with protransfersome-loaded emulgel whereas Schwarz et al (2013) and Lohan et al (2015) reported improvement on CoQ10 dermal delivery and penetration with ultra-small NLC.[23-25] In the past decade, NLC has especially gained a place in the cosmetic industry due to capability to enhance drug penetration, increase skin hydration; in addition to control release of actives, target drugs, and good occlusion; along with its excellent tolerability.[26]In the future, NLC and other type of more advanced technology can possibly be the way for pharmaceutical company to produce CoQ10 contained topical treatment for global consumer.

Due to limitations presented in available studies, we recommend further experimentation to be conducted to determine ideal CoQ10 usage dose for skin aging orally and topically. In addition, further studies need to also consider safety and tolerability of topical CoQ10.

Conflict of Interest

There was no conflict of interest in the making of this systematic review.

Acknowledgement

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