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The protective effect of lycopene-rich products on skin photodamage: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Ultraviolet (UV) radiation has known as a major cause of photodamage, photoaging, and skin cancer as it involves in reactive oxygen species generation. Several natural antioxidants, including lycopene, have been suggested for photoprotection. However, the protective effect of lycopene on skin photodamage is still controversial. **Objective**: The objective of this study was to evaluate the protective effect of lycopene-rich product on skin photodamage. **Materials and Methods**: A systematic literature search was conducted in PubMed, Scopus, CINAHL, and Cochrane Library from inceptions to March 2018. Randomized placebo-controlled trials determining the effect of lycopene-rich products on photodamage in healthy volunteer were included in the study. Studies adding other antioxidants except carotenoids were excluded from the study. Risk of bias version 2.0 was used to assess the quality of included studies. Primary outcome was intensity of skin erythema formation. Meta-analysis was performed using random-effects model. **Results**: A total of four studies were included in this systematic review with a total of 99 participants. Only two studies were included in a meta-analysis. Lycopene-rich products with the lycopene content of 8–20 mg/day significantly reduced skin erythema formation, with mean difference of −2.35 units when compared to control (95% confidence interval; −3.65–−1.05, I2 = 0.0%). At molecular level, lycopene significantly inhibited UV radiation-induced expression of matrix metalloproteinase-1, heme oxygenase 1, and intercellular adhesion molecule 1 (ICAM-1) compared to olive or soybean oil ($P < 0.05$). **Conclusions**: Lycopene-rich products had a potential to be developed as a nutraceutical for photoprotection as it showed protective effects on skin photodamage.

Keywords: Lycopene, photodamage, photoprotection, tomato, ultraviolet radiation

INTRODUCTION

Ultraviolet (UV) radiation that naturally obtained from sunlight has been known as a major cause of photodamage, photoaging, and skin cancer.[1,2] The long wavelength UVA is a detrimental factor for long-term photodamage such as skin cancer, while the medium wave UVB is related to acute photodamage such as sunburn or erythema. The main mechanism which UV radiation causes skin damage involved the generation of reactive oxygen species (ROS), oxidative stress, or indirect DNA damage.[2,3] Protective clothing or sunscreen is generally used as photoprotective option.[4,5] However, the effectiveness of such photoprotections on skin damage is heavily depended on human behavior and correct usage. An alternative photoprotection method which has been increasingly used is natural antioxidants.

One of the natural antioxidants that have been studied for UVB photoprotection is carotenoid, especially β-carotene, lutein, and lycopene.[6-8] However, the ability to neutralize ROS and free radical varies among these carotenoids. Lycopene is a natural red carotenoid pigment accounted for approximately

80–90% of total carotenoid in ripe tomatoes[9] and presents in process tomato-based products such as ketchup and tomato juice.[9,10] It is the most effective carotenoid to scavenge ROS[10-13] and hence has been used as a nutraceutical for several health conditions including cardiovascular disease, cancer, and photoprotection.[10,14,15] Considering its effect on photoprotection, a previous clinical study[13] showed that lycopene-rich product could decrease the intensity of erythema formation and increase lycopene level in both serum and skin. However, another recent study[16] revealed that lycopene-rich products in either pill or natural product had no photoprotective effect. These contradicted findings indicate that evidence on the effect of lycopene on skin photodamage protection is still controversial. Summarizing such evidence is truly needed to determine whether lycopene could be further developed as a supplementary product to aid protecting individuals from sunlight.

The present study aims to summarize the protective effect of lycopene-rich products compared to placebo on skin photodamage in healthy subjects by systematically reviewing the current clinical literature with high level of evidence. Findings from this study are useful for people to decide whether to use lycopene-rich products for sun protection.

MATERIALS AND METHODS

Search Strategies and Study Selection

A total of four electronic databases including PubMed, Scopus, CINAHL, and Cochrane Library were searched from inceptions to March 2018 without any restriction. The followings were key words used in literature searches: (Tomato OR tomato paste OR lycopene OR carotene*) and (sun protect* OR erythema OR UV light OR irritat* OR aging OR photoprotect* OR photoaging OR photodamage) (Table A1). The inclusion criteria were as follows: (1) Randomized placebo-controlled trials, (2) studies determining the effect of lycopene-rich products on skin photodamage, and (3) studies conducted in healthy volunteer. Studies which investigated products that combined with other antioxidants apart from carotenoids were excluded because it might confound the effect of lycopene on photodamage. The bibliographies of retrieved articles which met the above inclusion criteria were also screened to determine other relevant studies. The title and abstracts of all retrieved articles were screened to see whether the articles met our inclusion criteria by WD. Full text of the potential articles which were likely to meet the inclusion criteria was reviewed by WD and verified by PD. Any disagreements between the investigators were solved by a consensus.

Data Extraction and Quality Assessment

Data were extracted using a standardized data extraction form. The extracted data were study design, country of origin, subject characteristics, intervention characteristics (lycopene preparation, lycopene content, and regimen), control, outcomes, and findings. The primary outcome of interest was intensity of erythema formation which was a measurement of photodamage. Secondary outcomes were other outcomes related to photodamage. Quality of the included studies was assessed by the revised Cochrane risk of bias tool version 2.0.[17] All data extraction was performed by WD and verified by PD, and quality assessment was performed by PD and TD, independently.

Data Analysis

Mean difference of each outcome between lycopene and control with its corresponding standard deviation was calculated when it was not originally reported. Independent *t*-test was also used to assess statistical difference of each continuous outcome.

The pooled mean difference and its corresponding 95% confidence interval were estimated to determine the effect of lycopene-rich products on erythema formation. The meta-analysis was performed by a random-effects model using DerSimonian and Laird method.[18] Heterogeneity among included studies was assessed using Cochrane Chi-square and I^2 statistic. The Cochrane Chi-square of 0.10 indicated the statistically significant heterogeneity and I^2 statistic <30% denoted the minimal heterogeneity.[19] The analysis was performed using STATA version 15.0.

RESULTS

Search Results

A total of 5496 articles were retrieved from database searches. Of those, 884 were removed because of the duplication. Thus, 4612 articles were screened and only four randomized controlled trials (RCTs)[13,20-22] with a total of 99 participants included in the study. Two of the four included studies did not report an outcome (differences of a-value [Δa-value]) which could be used in meta-analysis;[20,22] therefore, only two studies were included in the meta-analysis [Figure 1].[13,21]

Study Characteristics

All included studies were conducted in Europe (two in Germany,[20,21] one in the Netherland,[13] and another one in the United Kingdom[21]). Participants involved in the studies aged 18–67 years. Two studies used tomato paste as the lycopene-rich products in a comparison with olive oil,[13,22] while other two studies used lycopene softgel capsule and compared with soybean oil.[20,21] The lycopene content ranged from 5 to 16 mg with the percentages of 33.3–96.4% of total carotenoids in the products. The daily dose of lycopene ranged from 8 to 20 mg for a treatment duration between 10 and 12 weeks. The outcomes reported in the included studies were erythema formation, lycopene level, minimal erythema dose (MED), and biomolecular markers such as protein expression of procollagen type I (PCI), fibrillin-1, and mitochondrial DNA (mtDNA) damage. A study characteristics in details are presented in Table 1.

The Effect of Lycopene-rich Products on Intensity of Skin Erythema Formation

Of the three studies that reported skin erythema formation,[13,21,22] only two[13,21] measured the intensity of skin erythema formation with chromametry using the three-dimensional color system. The differences of a-value (Δa-value), which is a parameter of

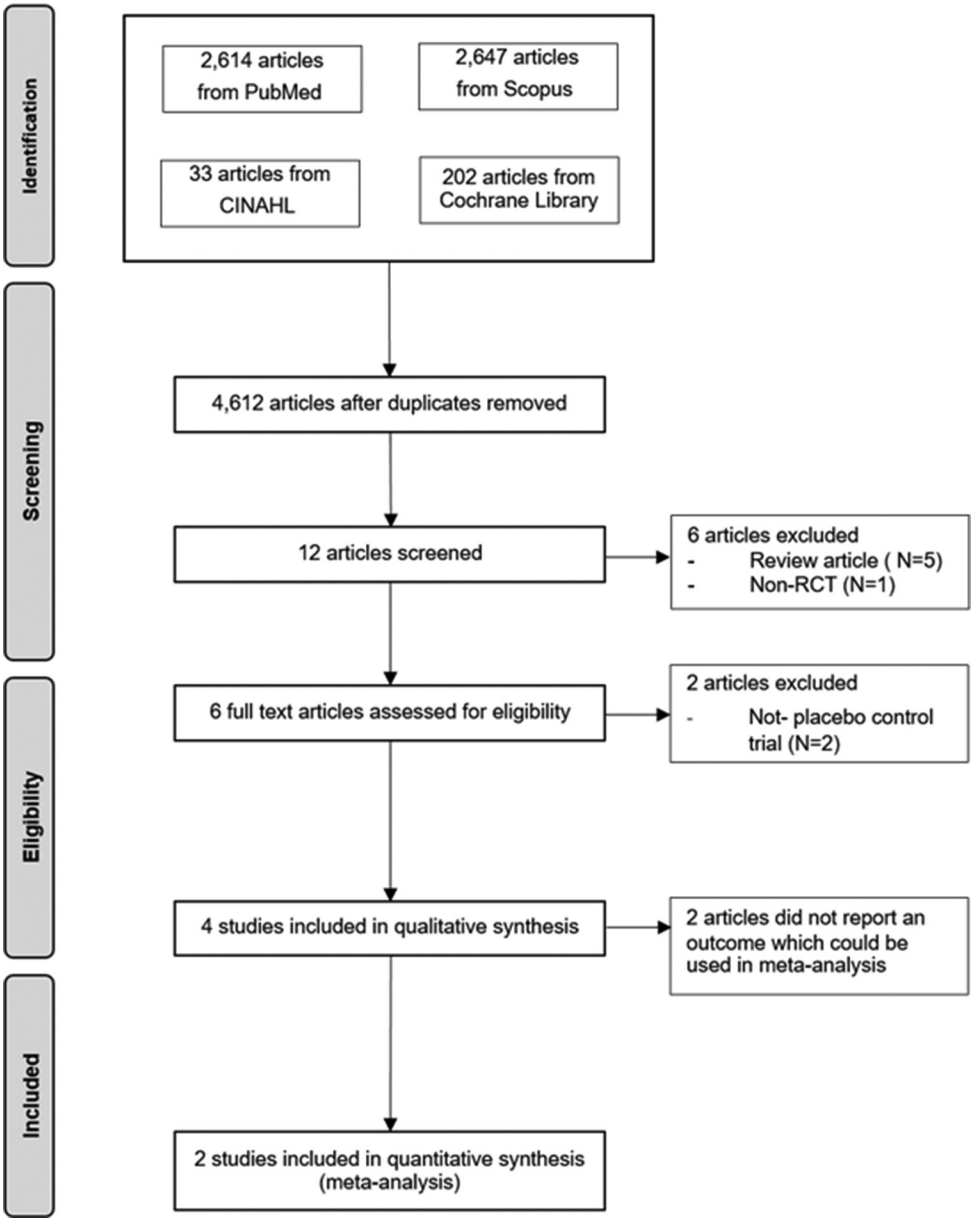

Figure 1: PRISMA flow diagram of included articles

erythema formation, was used to quantify the skin response to UV irradiation by comparing a-value between before and 24 h after UV irradiation. The lower Δa-value indicated the better effect of intervention on photodamage protection.

The study by Stahl *et al*.[13] reported that the Δa-value in lycopene group was 2.5 ± 5.5 units lower than control group at 10 weeks after expose to 1.25 individual MED of UV light at dorsal skin, and the study by Heinrich *et al*.[21] found that the Δa-value in lycopene group was 2.3 ± 3.7 units lower than control group at 12 weeks after irradiated with 1.25 individual MED at dorsal skin (Table 2). The pooled mean difference calculated by meta-analysis under a random-effects model was −2.35 units (95% confidence interval; −3.65–−1.05, I^2 = 0.0%) [Figure 2].

Another study by Rizwan *et al*.[22] determined the effect of lycopene-rich product on photodamage using MED of UV radiation that could produce a perceptible erythema as the outcome. The higher MED indicated better effect of intervention on photodamage protection. This study showed that subjects with lycopene-rich products had higher increased MED than those with controls (42.2 ± 11.3 mJ/cm^2 vs. 32.6 ± 9.6 mJ/cm^2) compared to before supplementation at the skin of upper buttock. However, the difference was not statistically significant between groups [Table 2].

The Effect of Lycopene-rich Products on Biomolecular Markers of Photodamage

Two studies reported the effect of lycopene-rich products on biomolecular markers of photodamage.[20,22] The study by Rizwan *et al*.[22] measured the effect of lycopene-rich products with several biomolecular markers including pCI, fibrillin-1,

Table 1: Demographic characteristic of included study

Study	Country	Number of patient (female)	Age (year)	Skin type	Study design	Intervention	Lycopene content	% Lycopene	Comparator	Regimen	Treatment period (week)	Follow-up duration (week)	Outcomes
Stahl *et al*., 2001[13]	The Netherland	22 (63.64)	26–67	Type II	RCT (parallel)	Tomato paste	16 mg	96.4	Olive oil	1 pack of tomato paste once daily	10	0, 4, 10	Erythema formation
Heinrich *et al*., 2003[21]	Germany	24 (NA)	22–55	Type II	RCT (parallel)	Lycopene softgel capsule	8 mg	33.3	Soybean oil	1 capsule once daily	12	0, 6, 12	Erythema formation
Rizwan *et al*., 2011[22]	UK	20 (100)	21–47	Type I or II	RCT (parallel)	Tomato paste	16 mg	91.8	Olive oil	1 pack of tomato paste once daily	12	0, 12	• MED • Protein expression of PCI, Fibrillin-1, MMP-1 • mtDNA damage
Grether-Beck *et al*., 2017[20]	Germany	33 (15.15)	18–60	No report	RCT (cross-over)	Lycopene softgel capsule	5 mg	NA	Soybean oil	2 capsules twice daily	12	0, 12	• mRNA expression of HO-1, MMP-1 and ICAM-1

MMP-1: Matrix metalloproteinase-1, mtDNA: Mitochondrial DNA, HO-1: Heme oxygenase 1, ICAM-1: Intercellular adhesion molecules 1, MED: Minimal erythema dose, PCI: Procollagen type I

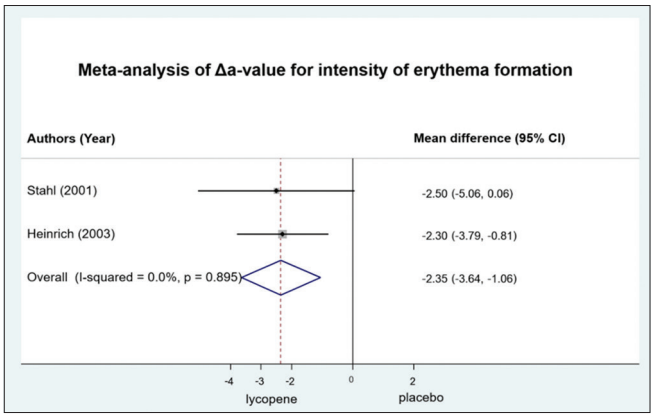

Figure 2: Meta-analysis of Δa-value for intensity of erythema formation

matrix metalloproteinase-1 (MMP-1), and mtDNA, while a study by Grether-Beck *et al*.[20] measured the effect of lycopene on heme oxygenase-1 (HO-1), MMP-1, and intercellular adhesion molecules-1 (ICAM-1).

Rizwan's *et al*. study[22] investigated the changes in pCI expression using immunohistochemistry, the higher pCI staining indicated better effect on photodamage protection. The result showed that lycopene-rich products significantly increase pCI staining in the papillary dermis at 12 weeks of treatment from baseline, although this was not different compared to placebo (0.66 ± 0.49 vs. 0.08 ± 0.75, $P > 0.05$). Similarly, the differences of changes in fibrillin-1 and mtDNA were not observed when compared to placebo, even lycopene-rich product was significantly reduced mtDNA damage from baseline**.** MMP-1 expression was the only biomolecular marker that expressed the difference between lycopene and control groups (11.44 ± 2.73 vs. 15.28 ± 4.19, $P = 0.04$) [Table 3].

Another study by Grether-Beck *et al*.[20] revealed that lycopene-rich products significantly inhibited UV radiation-induced mRNA expression of HO-1, MMP-1, and ICAM-1 compared to placebo, which indicated that lycopene-rich products had photodamage protective effect [Table 3].

Quality Assessment

Three of four included studies appeared to have some concerns risk of bias,[13,21,22] while only one study had low risk of bias.[20] Among the studies with some concerns risk of bias, two of them did not report the randomization process and allocation concealment.[13,21] Moreover, all three studies had some concerns risk of bias due to the deviations of intended intervention.[13,21,22] However, all four included studies had low risk of bias in other domains based on Cochrane risk of bias version 2.0 [Table 4].

DISCUSSION

The present study provided a comprehensive evidence that lycopene-rich products with the lycopene content of 8–20 mg/day could protect skin photodamage according to the effects on erythema formation and biomolecular markers of skin photodamage.

Table 2: Effect of lycopene on skin erythema formation

Study	Outcome	At endpoint (mean±SD)		
		Lycopene group	Placebo	Difference
Stahl *et al*., 2001[13]	Δa-value#	3.8±3.3	6.3±2.2	−2.5±5.5*
Heinrich *et al*., 2003[21]	Δa-value#	5.2±2.1	7.5±1.6	−2.3±3.7**
Rizwan *et al*., 2011[22]	Post-supplement MED	42.2±11.3 mJ/cm^2	32.6±9.6 mJ/cm^2	9.6±21.1 mJ/cm^2

UV: Ultraviolet, MED: Minimal erythema dose, #Δa-value: Difference of a-value (red/green color evaluated by chromatometry) before and 24 h after irradiation, *significantly different to control, P=0.02, **significantly different to control; P=0.006

Table 3: Effect of lycopene on biomolecular markers of photodamage

Biomarkers	Effect of UV on biomarkers of photodamage	Effects of lycopene compared with controls	References
PCI	Downregulation	0.58±1.24 (P=0.07)	Rizwan *et al*., 2011[22]
Fibrillin-1	Downregulation	−0.21±1.28 (P=0.51)	Rizwan *et al*., 2011[22]
mtDNA damage	Increase	0.0129±0.0990 (P=0.61)	Rizwan *et al*., 2011[22]
MMP-1 (protein expression)	Upregulation	−3.84±3.49 (P=0.04)	Rizwan *et al*., 2011[22]
MMP-1 (mRNA expression)	Upregulation	Significantly inhibited mRNA expression (P<0.05)	Grether-Beck *et al*., 2017[20]
HO-1	Upregulation	Significantly inhibited mRNA expression (P<0.05)	Grether-Beck *et al*., 2017[20]
ICAM-1	Upregulation	Significantly inhibited mRNA expression (P<0.05)	Grether-Beck *et al*., 2017[20]

MMP-1: Matrix metalloproteinase-1, mtDNA: Mitochondrial DNA, HO-1, mRNA: Messenger ribonucleic acid, ICAM-1: Intercellular adhesion molecules 1, PCI: Procollagen type I

Table 4: Quality assessment

Study	Risk of bias domain					Overall risk of bias
	Randomization process	Deviation of intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Stahl *et al*., 2001	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns
Heinrich *et al*., 2003	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns
Rizwan *et al*., 2011	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Grether-Beck *et al*., 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

UV radiation causes erythema formation, a sign of acute photodamage, by enhancing histamine-stimulated prostaglandin synthesis, which leads to inflammation. Another possible mechanism of UV-associated erythema formation is that UVB could produce ROS which, in turns, cause lipid peroxidation. The lipid peroxidation has been linked to increase the formation of inflammatory cytokines such as prostaglandins that lead to erythema formation.[23,24] The protective effect of lycopene on intensity of erythema formation is likely due to its potent scavenging ROS activities. Lycopene could also inhibit ROS production which leads to the reduction of ROS-producing enzymes such as cyclooxygenase-2. Eventually, it could reduce lipid peroxidation and inflammatory cytokine production which resulted in lowering erythema formation. [25,26]

The MMP-1 upregulation is caused by UV radiation-generated oxidative stress[27] and leads to degradation of extracellular matrix proteins such as collagen. The MMP-1 plays an important role in photodamage and photoaging.[28-30] Results from the included studies indicated that lycopene significantly decreases the MMP-1 production after UV irradiation. This finding possibly due to the potential effect of carotenoids (such as lycopene, β-carotene, or astaxanthin) on the suppression of UV radiation-induced MMP-1 upregulation. [22,31,32]

The meta-analysis of lycopene-rich products on intensity of erythema formation was based on the findings from only two small studies which were conducted with different proportion of lycopene content, i.e. 33% with other carotenoids[21] and 96%.[13] This difference might affect the pooled estimate identified in this study. However, the objective of this systematic review and meta-analysis was to determine the effect of lycopene-rich products with no restriction on the amount of lycopene used. In addition, the mean difference of lycopene-rich products and control in Stahl

et al.'s study and that in Heinrich *et al*.'s study was similar with no statistical heterogeneity as showed by I^2 statistic. Therefore, the pooled mean difference from both studies could be used to determine the protective effect of lycopene-rich products on skin photodamage.

This systematic review included only RCTs which were related to the topic. We decided to not include observational studies in this systematic review because we would like to determine the efficacy of an intervention (lycopene-rich products). RCT is known as the study design which is able to provide such evidence, while observational studies could provide evidence on the effectiveness of an intervention when it is used in real-world setting. Those two study designs answer different questions. Although the number of included studies was small, we are certain that it is valid and represents the current available evidence in the field.

Our meta-analysis of the effect of lycopene-rich products on erythema formation was based on the secondary outcomes of the included studies.[13,21] In general, secondary outcomes are not the main purpose of studies. It might not represent the true effect of intervention as the study was not designed to detect the true effect of intervention on secondary outcome. However, similar to the issue on small sample size, if results from secondary outcomes exerted statistical power to detect difference among two studied groups, these outcomes should be considered as valid and could be used to generate a reliable evidence. Nonetheless, not all secondary outcomes from the included studies derived from appropriate sample size to detect the difference measured. Therefore, cautions should be exercised when interpreting the pooled effects of findings derived from secondary outcomes of some included studies.

The Food and Nutrition Board of the Institute of Medicine has not announced a recommended dietary allowance for lycopene.[33] Therefore, findings from this study might serve as an important evidence to consider the optimal daily dose of lycopene for photoprotection. Supplementation of lycopene 8–20 mg/day at least 10 weeks might be an effective regimen for skin photodamage protection. However, some information should be taken into account before making a decision on the use of lycopene-rich products. First, all studies included in this systematic review were from Europe. Individuals outside the continent should be used this evidence carefully because there might be other factors affecting the observed effect such as variations in exposed environment, the intensity of sunlight, and the use of other sun protection behavior. Second, most participants in the included studies had skin Type I or II, which were not or minimal tans. Lycopene-rich products might have different effect in individuals with other skin types. Third, the studies were conducted for 10–12 weeks. Short-term effects of the product have not been reported. Forth, the sample size in each study also appeared relatively low which might create concern regards to validity of the findings. Nonetheless, it appeared that the sample size used in most studies were sufficient to detect the effect of lycopene-rich products on skin photodamage as reported by several measures. Individuals who intend to use the product for short-term sun protection should be carefully interpreted our findings. Last, there were no adverse effects of the product reported.

Limitations of this study should be discussed. First, three out of four studies included in this systematic review had some concern risk of bias due to no information on randomization process or deviations from intended intervention. These might lead to less credibility of their findings. However, to the best of our knowledge, these studies were the most updated high-level evidence investigating the benefits of lycopene on photoprotection. Second, the meta-analysis was based on only two studies with small number of participants. Further, high-quality RCTs should be conducted to confirm such effects. Last, publication bias could not be statistically assessed in this review as it could be conducted only when the number of studies is at least 10 studies.

CONCLUSIONS

This systematic review and meta-analysis indicated that lycopene-rich products had protective effects against skin photodamage. Supplementation with lycopene-rich products could reduce intensity of erythema formation and decrease biomolecular markers for photodamage such as MMP1. Lycopene-rich products could be used as endogenous sun protection and also had high potential to be developed as a nutraceutical for sun protection.

ACKNOWLEDGMENTS

WD participated in the study concept and design, data acquisition, data analysis, data interpretation, manuscript drafting, and critical revision of the manuscript. TD participated in data, acquisition, quality assessment, data interpretation, manuscript drafting, critical revision of the manuscript, and the final review of the manuscript. PD participated in the study concept and design, quality assessment, data analysis, data interpretation, manuscript drafting, critical revision of the manuscript, and the final review of the manuscript.

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APPENDIX

Table A1: A search strategy in PubMed

Search	Query	Items found
#15	Search (((((((((sun protect*) OR erythema) OR UV light) OR irritat*) OR aging) OR photoprotect*) OR photoaging) OR photodamage)) AND ((((tomato) OR tomato paste) OR lycopene) OR caroten*)	2614
#14	Search (((((((sun protect*) OR erythema) OR uv light) OR irritat*) OR aging) OR photoprotect*) OR photoaging) OR photodamage	534501
#13	Search (((tomato) OR tomato paste) OR lycopene) OR caroten*	54422
#12	Search sun protect*	2781
#11	Search erythema	40020
#10	Search UV light	92190
#9	Search irritat*	26011
#8	Search aging	377468
#7	Search photoprotect*	3832
#6	Search photoaging	1862
#5	Search photodamage	2382
#4	Search caroten*	34121
#3	Search lycopene	4492
#2	Search tomato paste	209
#1	Search tomato	21414