ISSN: 2230-9926

*Available online at http://www.journalijdr.com*

IJDR

*International Journal of Development Research*
*Vol. 10, Issue, 12, pp. 42521-42525, December, 2020*
https://doi.org/10.37118/ijdr.20504.12.2020

RESEARCH ARTICLE OPEN ACCESS

# RESVERATROL IN TOPIC PREPARATION AS A PREVENTIVE TO SKIN PHOTOAGING: A SYSTEMATIC REVIEW

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**ARTICLE INFO**

***Article History:***
Received 14th September, 2020
Received in revised form
19th October, 2020
Accepted 20th November, 2020
Published online 30th December, 2020

***Key Words:***
Polyphenols,
Trans-Resveratrol,
Antioxidant, Physiology of the Skin.

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**ABSTRACT**

**Background:** The increase in research in the cosmetic area on resveratrol, mainly due to its antioxidant action and the existence of few in vivo studies proving its effective action against topical skin photoaging, are the antecedents of this research. **Aims:** To evaluate, through systematic review, scientific evidence that proves the antioxidant activity of resveratrol in preparation for topical use as a preventive to photoaging. **Methodology:** The research was carried out in the Cochrane, Scielo, Science Direct, Pubmed, Web of Science, and Scopus databases, using in vitro and in vivo studies with topical resveratrol application. Data published from 1999 to March 2020 were considered. **Results:** Through the search strategies presented, 714 articles were found in the databases searched. Of these, 29 were duplicated, leaving 685 articles. After reading the title and summary of these articles by two reviewers, 30 articles partially met the inclusion criteria and were selected for a full reading. Of these, 9 met all criteria and were included for data extraction. **Conclusion:** Topical preparations added with RSV acted as a preventive to photoaging, and the primary prevention mechanism, in general, is linked to its antioxidant activity. It was also shown that this antioxidant action could be higher when RSV is applied in formulations associated with other antioxidants and in their synthesized analogous forms.



**Citation:** ***Bruna Aparecida dos Santos Marubayashi, Suelen Eloise Simoni, Suzana Bender, Andréia Cristina Conegero Sanches and Luciana Oliveira de Fariña.*** "Resveratrol in topic preparation as a preventive to skin photoaging: a systematic review*", International Journal of Development Research*, 10, (12), 42521-42525.

## INTRODUCTION

Resveratrol, or 3,5,4'-trihydroxystilbene (RSV), is a polyphenol found naturally in various fruits such as grapes, nuts, pomegranates, wild fruits, jackfruit and peanuts, and in plants such as eucalyptus, *Ko-jo-kon*, and white hellebore[1,2]. It is also a phytoalexin, that is, an enzyme that has the function of protecting fruits and plants from bacteria, fungi, irradiation, heat, toxins, and pathogens[3]. RSV was first isolated in the 1940s from white hellebore roots and in 1963 from Japanese knotweed roots (*Polygonumcuspidatum*var.*japonicus*)[4]. Several studies have shown that RSV can prevent or slow the progression of a wide variety of human diseases, such as cancer, by observing effects against precancerous cells, on which it acts in the 3 (three) distinct phases of carcinogenesis (initiation, promotion, and progression)[1,5,6]. RSV can also prevent cardiovascular diseases and ischemic injuries, promoting anti-inflammatory and neuroprotective effects, with increased resistance to oxidative stress[1,7].RSV consumption can occur through food, supplementation of the isolated substance, and the use of topical products. It is noteworthy that, in the last 20 years, the number of searches on the asset, in general, has had a considerable increase[6,8].Photoaging is a cumulative process, related to the degree of sun exposure in which the skin becomes wrinkled, yellowish, and atrophic, with the possibility of developing carcinogenic lesions. Our body has defense systems that include free radical detoxifying enzymes and antioxidant molecules[2,9]. Glutathione and uric acid are examples of endogenous sources in our skin, but they are not always sufficient against oxidative stress and the formation of free radicals. Obtaining substances with the same effect, such as vitamins A, C, and E, in addition to polyphenolic compounds, such as RSV, can also take place exogenously (orally or topically)[4,10]. The use of antioxidant cosmetics is one of the ways to prevent photoaging due to protection against free radicals[3,11,12]. This study aimed to

evaluate, through a systematic review, scientific evidence that proves the antioxidant activity of RSV in preparation for topical use as a preventive of photoaging of the skin.

## METHODOLOGY

**Search Strategy:** The research used virtual files from databases such as Cochrane, Scielo, Science Direct, Pubmed, Web of Science and Scopus, and manual searches were carried out on review articles and unpublished articles. The search terms used the descriptors or Mesh Terms: "Antioxidants" AND "Resveratrol" OR "Trans-Resveratrol" AND "Photoaging." The data found were evaluated using bibliography management software for publishing scientific articles.

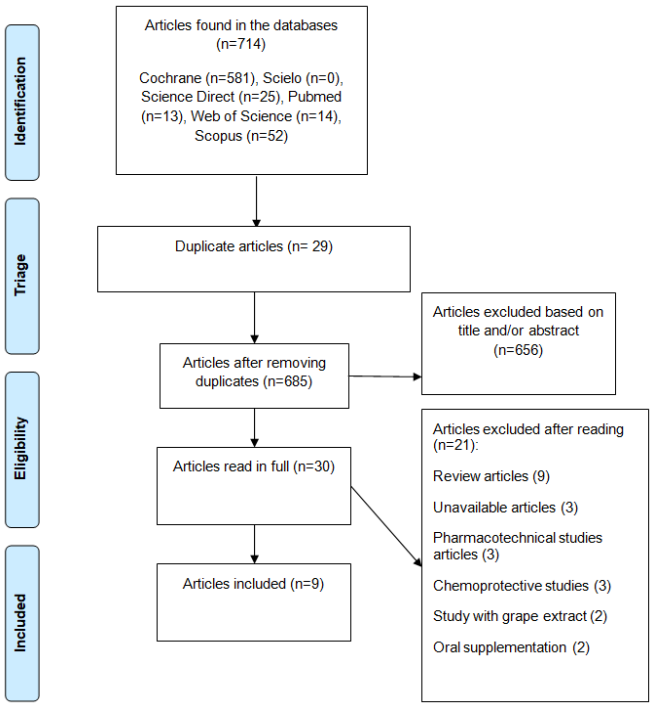


**Figure 1. Flowchart of the article selection process (data from the authors)**

**Inclusion Criteria:** The retrieved articles were analyzed using titles and abstracts and evaluated to meet the pre-established inclusion criteria, which were publications with *in vitro* and *in vivo* tests of individuals without comorbidities in the skin and exclusive topical resveratrol supplementation as prevention to photoaging by antioxidant mechanisms.

**Data Extraction:** The evaluation of titles, abstracts, and articles in full was carried out by two reviewers (B.A.S.M. and S.E.S.), and the doubts were resolved with the help of the third reviewer (S.B.). The data were extracted in previously prepared tables in Microsoft Office Word 2010. The data collected consisted of references, date of publication of the study, country of origin of the research, objective, methods of analysis, and results of the study.

## RESULTS

**Description of Selected Studies:** Through the search strategies presented, 714 articles were found in the databases. Of these, 29 were duplicates, leaving 685 remaining articles. After the reading of the title and summary of these articles by two reviewers, 30 articles met the inclusion criteria and were selected for reading in full. Of these, 9 were included for data extraction. Figure 1.describes the study selection process according to the inclusion and exclusion criteria

**Included Studies:** The 9 (nine) articles included presented the established criteria, as they dealt with the topical use of RSV as a photoprotection factor or against photoaging. They were organized in Table 1, Tabel 2, and Tabel 3, according to the research designs.

**Quality assessment of selected studies and publication bias:** The suggestion offered by the Cochrane Foundation for assessing the quality of studies does not materialize in a checklist or scale. Its approach constitutes a domain-based evaluation, which allows evaluating the influence of potential biases in the studies (by types of biases)., each potential is evaluated and classified in: low risk, high risk, and unclear risk[19,20]. The tool from the Systematic Review Center for Laboratory animal Experimentation (SYRCLE) is based on the Cochrane RoB tool and has been adjusted for particular aspects of bias that play a role in animal intervention studies[21].

## DISCUSSION

In the experiments carried out with HaCaT cells, the observed results are promising regarding the antioxidant effect of RSV with an emphasis on the preventive activity of photoaging. This cellular model represents an efficient way to reproduce human skin in the laboratory since it preserves the characteristics of basal cells[23].*In vivo* experiments were based on the analysis of the physical aspect of the volunteers' skin after a period of topical applications of an RSV derivative. In these, it was demonstrated that the skins submitted to topical RSV had less erythema, even when induced to it, and reduced development of pigmentation[24]. Also, RSV associated with other antioxidants potentiated its action, in addition to an apparent improvement of the effects of aging, which configure an analysis of corneometry, colorimetry, and elastometry[15].A clinical trial carried out by L'Oréal's Research and Innovation Group evaluated clinically the effects of RSV at 0.25% associated with tocopherol and baicalin, in comparison to the formulation containing only the vehicle, on the back of the arm of 40 volunteers (45-65 years) to check the skin density. After the applications, 2 (two) times a day for 3 (three) months, a DensiScore® was used for measurement (evaluation of the degree of skin folds using a 6-point photographic scale), and a significant decrease in the score was observed (-0.43) in the arm where the RSV was applied in comparison with the one that only contained the vehicle (P ¼.032)[25].Although the different research focuses on each experiment analyzed, the results indicate that RSV has antioxidant activity when used topically, demonstrated in several ways, such as the reduction of the expression of genes responsible for skin aging and the increased production and expression of the genes responsible for collagen production[17].Oral supplementation showed similar results to those of topical use concerning skin aging. RSV and grape peel extract (GPE) provide adequate protection against UV-induced skin wrinkles[18]. The administration was 2g of GPE or 2mg of RSV per kg of body weight in mice, three times a week for two weeks., the results showed that the supplementation attenuated the epidermal thickening induced by UVB (in 63% and 55% in comparison with the control group) and had a protective effect on the formation of wrinkles[18].

**Table 1.Experimental studies performed on cells related to antioxidant properties against topical RSV photoaging.**

| Reference | Country | Objective | Study target | Results |
|---|---|---|---|---|
| Park and Lee, 2008[13] | Korea | Skin photoprotection | HaCaT Cell Culture | Decrease in the production of reactive oxygen by the application of RSV. |
| Fabbrocini*et al.*, 2010[14] | Italy | Antioxidant activity on the skin | HaCaT Cell Culture | RSV induced phosphorylation of the Ser-36 residue of the p66Shc gene[1]. |
| Moyano-Mendez *et al.*, 2014[15] | Italy | To analyze trans-resveratrol activity topically *in vivo* and *in vitro* | HaCaT Cell Culture | Significant reduction of ROS production induced by $H_2O_2$, mainly with the association of bCD. |
| Soeur*et al*., 2015[16] | France | Antioxidant activity on the skin | Normal human keratinocytes and reconstructed human skin received concentrations of RSV | RSV increased glutathione concentrations (85% to 10 and 20 mM) in keratolytic cells and 55% in the three-dimensional model at a concentration of 100 mmol. |
| Lephart., Sommerfeldt., Andrus, 2014[17] | USA | Antioxidant activity on the skin | HaCaT Cell Culture | RSV increased the production and expression of the SIRT1[2] gene by approximately 180% compared to controls and type IV collagen by 16%. |
| Zhou *et al*., 2018[3] | China | Skin photoprotection | HaCaT Cell Culture | RSV inhibited apoptosis induction by increasing HSP27 expression, reducing the production of proapoptotic proteins, such as p65, Bax, and cleaved caspase-3. |
| Kim *et al.*, 2019[18] | Korea | Skin photoprotection | HaCaT Cell Culture | Treatment with RSV or GPE increased the expression of HO-1 and Nrf2 in human HaCaT keratinocytes exposed to UVB. |

Source: data by the authors. [1]Shc p66 protein kinase is involved with collagen metabolism and antioxidant activities. [2] SRT1 gene, or sirtuin 1, is responsible for the expression of proteins that increase the production of collagen cells. HaCaT: human immortalized keratinocytes., UVB: ultraviolet B rays., p66Shc: Shc p66 protein kinase., ROS: reactive oxygen species., bCD: b-cyclodextrin., SIRT 1: sirtuin 1., HSP27: heat shock protein 27., p65: transcription factor 65., Bax: apoptosis regulator., Caspase., GPE: grape peel extract, HO-1: hemeoxigenase 1., Nrf2: nuclear factor erythroid 2.

**Table 2. Experimental studies carried out in animals regarding the antioxidant properties against the photoaging of topical RSV**

| **Reference** | **Country** | **Objective** | **Study population** | **Results** |
|---|---|---|---|---|
| Afaq*et al*., 2003[19] | USA | Skin photoprotection | Female rats, absence of hair at the application site | RSV showed significant inhibition of $H_2O_2$ levels under UVB radiation.,<br>RSV reduced the peroxidation of fats*. |

Source: data by the authors. UVB: ultraviolet B rays., $H_2O_2$: hydrogen peroxide. *Evaluation of the level of peroxidation of fats is also a mechanism for the generation of reactive oxygen.

**Table 3. Clinical trials carried out on humans regarding the antioxidant properties against the photoaging of topical RSV**

| Reference | Country | Objective | Study population | Research design | Results |
|---|---|---|---|---|---|
| Moyano-Mendez *et al.*, 2014[15] | Italy | Antioxidant activity on the skin | Women between 40 and 70 years old | Application once a day of RSV-based cream. The evolution was based on corneometry, colorimetry, and elastometry criteria. | All patients showed a visible improvement in signs of aging. |

Source: data by the authors. ssUVR., bCD: b-cyclodextrin., UV.

**Table 4 Evaluation of the quality of studies, according to the SYRCLE scale, related to the antioxidant properties against the photoaging of topical RSV in animals**

| Year/Author | Selection bias | | | Performance bias | | Detection bias | | Attrition bias | Reporting bias | Other biases |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Afaq*et al*., 2003[19] | ? | Y | ? | N | ? | ? | N | ? | ? | ? |

Source: data by the authors. Y - yes (low risk of bias)., N - no (high risk of bias)., ? - unclear (unclear risk of bias). 1 – Sequence generation: random sequence generation No description on randomization., 2- Baseline characteristics: All animals receive the same type of diet and air conditioning., 3 – Allocation concealment: The article did not describe whether there was concealment in the allocation of case and control groups., 4 – Random housing: both case and control groups were exposed to the same conditions., 5 – Blinding: No data to determine whether the researcher would have knowledge about which animals received each type of intervention., 6 – Random outcome assessment: No article described whether the outcome assessment of the case and control groups was performed randomly., 7 – Blinding: The article described which groups received interventions., 8 – Incomplete outcome data: It is not evident whether animals are excluded in the outcome assessment., 9 – Selective reporting: There was no selective reporting of outcomes whose results were significant., 10 – Other bias: It was not possible to determine other sources of bias.

**Table 5. Cochrane tool for clinical trials performed on humans regarding the antioxidant properties against the photoaging of topical RSV**

| Year/Author | Selection bias | | Performance bias | Detection bias | Attrition bias | Reporting bias | Other biases |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Moyano-Mendez *et al.*, 2014[15] | ? | Y | N | ? | ? | Y | Y |

Source: data by the authors. S - yes (low risk of bias)., N - no (high risk of bias)., ? - unclear (unclear risk of bias). 1 – Random sequence generation: No description on randomization., 2- Allocation concealment: The cream containers were identified by letters., 3 - Blinding of participants and personnel: It was a single-blind study, that is, there was blinding only of the participants., 4 – Blinding of outcome assessment: No data., 5 – Incomplete outcome: No data., 6 – Selective reporting: Outcomes have not been pre-established., 7 – Other biases: The study appears to be free of other sources of bias.

Another study conducted of oral supplementation with 50 individuals (25 treated with supplements and 25 with placebo) for 60 days with RSV and procyanidin demonstrated an increase in the antioxidant power of the skin. Besides, hydration and elasticity improved, while skin roughness and depth of wrinkles decreased[26].Studies of oral RSV supplementation are the majority, probably due to the less laborious pharmacotechniques, differences between the epidermis of animals and humans, the cost of cell research, and the bureaucracy to conduct studies in humans. Thus, the low number of clinical trials made it impossible to obtain a volume of articles with considerable evidence for the development of a meta-analysis. The risk of bias became unclear, as the studies were predominantly experimental and carried out on cells, and there is currently no statistical evaluation tool that allows the analysis of these parameters. However, it can be seen that these studies present methods in which cells are treated with RSV, emission of UV radiation, and comparisons between the control and experimental groups. Also, HaCaT cells were used, and the results showed decreased cell apoptosis, activation of the SRT1, responsible for the expression of proteins that increase the production of collagen cells[14], the activation of the protein kinase Shc p66, which is involved with the metabolism of collagen, and antioxidant activities[14,18]. This effect decreases the production of collagen cells and increases the production of metalloproteinases (MMPs) that influence aging, decreased formation of ROS, and increased expression of HO-1 and Nrf2, which shows a decrease in oxidative stress[16].

**Conclusion**

Through this systematic review and according to the experimental conditions of the different studies evaluated, it was possible to gather scientific evidence that indicates that topical preparations added with RSV acted as a preventive to photoaging and that the primary prevention mechanism, in general, is linked to its antioxidant activity. It was also shown that this antioxidant action could become more significant when RSV is applied in formulations associated with other antioxidants and in their synthesized analogous forms. The studies evaluated in this review indicated that there is little research available on humans with standardized methodologies to enable the verification of the quality of scientific studies through meta-analysis.

## SUPPORT

CAPES - Coordination of Superior Level Staff Improvement.

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