



The effect of topical ascorbic acid on cutaneous healing

O efeito do ácido ascórbico tópico na cicatrização cutânea

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■ ABSTRACT

Introduction: The surgical wound has high levels of free radicals in response to skin damage, which raises the hypothesis of a possible benefit from using antioxidants in repairing these wounds, such as the topical application of ascorbic acid. However, recent research has found conflicting conclusions about this type of treatment. The objective is to evaluate the effect of topical ascorbic acid on skin healing through a scope review. **Methods:** The scope review was carried out in the Medline, Lilacs and Cochrane databases, with the descriptors: ascorbic acid, skin cream, and wound healing. Inclusion criteria were defined as randomized clinical trials, observational and systematic reviews, in humans, with a publication date of up to 5 years, in English, Portuguese or Spanish. The following were excluded: narrative reviews, dissertations, theses, editorials, in vitro and animal studies. Finally, the studies were classified using the GRADE methodology. **Results:** 83 studies were found, and six articles were selected after screening. The use of ascorbic acid in the concentration of 5 to 20% and its derivatives (0.075% to 9.55%) stood out. The outcomes presented a moderate GRADE quality: increased skin firmness and reduced redness, and high quality: improved hydration, elasticity, colorimetry of the stains and improved wound closure. **Conclusion:** Ascorbic acid promotes better skin elasticity, reduced erythema and better wound closure. Despite these strong indications, randomized clinical trials with a lower risk of measurement bias and greater casuistry are still necessary.

Keywords: Ascorbic acid; Skin; skin cream; GRADE approach; Antioxidants; Wound healing.

■ RESUMO

Introdução: A ferida cirúrgica apresenta altos níveis de radicais livres em resposta ao dano cutâneo, o que gera a hipótese de um possível benefício do uso de antioxidantes no reparo destas feridas, tal como a aplicação tópica do ácido ascórbico. No entanto, pesquisas recentes obtiveram conclusões discrepantes para este tipo de tratamento. O objetivo é avaliar o efeito do ácido ascórbico tópico na cicatrização cutânea por meio de uma revisão de escopo. **Métodos:** A revisão de escopo foi realizada na base de dados Medline, Lilacs e Cochrane, com os descritores: ácido ascórbico, creme para a pele e cicatrização de feridas. Foram definidos como critérios de inclusão: ensaios clínicos randomizados, observacionais e revisões sistemáticas, em humanos, com data de publicação de até 5 anos, nas línguas inglesa, portuguesa ou espanhola. Foram excluídas: revisões narrativas, dissertações, teses, editoriais, estudos *in vitro* e em animais. Por fim, foi realizada a classificação dos estudos através da metodologia GRADE. **Resultados:** Foram encontrados 83 estudos e, após triagem, seis artigos foram selecionados. Destacou-se o uso do ácido ascórbico na concentração de 5 a 20% e de seus derivados (0,075% a 9,55%). Apresentaram a qualidade GRADE moderada os desfechos: aumento da firmeza cutânea e redução da vermelhidão, e alta qualidade: melhora na hidratação, elasticidade, colorimetria das manchas e melhora do fechamento das feridas. **Conclusão:** O ácido ascórbico

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promove melhor elasticidade cutânea, diminuição do eritema e melhor fechamento das feridas. Apesar destes fortes indícios, ensaios clínicos randomizados com menor risco de viés de aferição e com maior casuística ainda se fazem necessários.

Descritores: Ácido ascórbico; Pele; Creme para a pele; Abordagem GRADE; Antioxidantes; Cicatrização.

INTRODUCTION

Healing is a sequence of wound repair events, followed by inflammation, cell proliferation, remodeling, wound contraction, and finally, epithelialization. The surgical wound has increasing levels of free radicals in response to skin damage. Neutrophils release these molecules, which can impair the healing process at high levels. Due to this physiological process, it is hypothesized that antioxidants may assist wound repair by reducing the damage caused by free radicals^{1,2}.

Ascorbic acid (AA) - or vitamin C - is a potent antioxidant and cofactor in collagen biosynthesis, acting in transcription, RNA stabilization, translation, hydroxylation and secretion. Therefore, the topical application of this product would potentially promote improvement in skin healing through its antioxidant properties, participation in collagen synthesis, and/or its ability to stimulate the proliferation of fibroblasts during the wound healing process^{3,4}.

Despite some positive results from using AA in skin healing, there are conflicting results in the current scientific literature on the effectiveness of both AA and its derivatives in skin healing.

OBJECTIVE

Given this scenario, the objective of this study is to map the key concepts, main sources and types of evidence available on the effect of topical vitamin C (AA) on skin healing through a scoping review.

METHODS

Research design

This is a scope review of primary studies to assess the effect of topical AA use on skin healing⁵⁻⁷.

Ethical aspects

This review was developed with the support of the Postgraduate Program in Translational Surgery - Professional Master's in Management, Innovation and Technology in Tissue Regeneration at the Universidade Federal de São Paulo - UNIFESP, and is part of the research project entitled "Topic care in Aesthetic Plastic Surgery: elaboration and validation of a book"

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Search strategy

The literature search strategy was based on the descriptors obtained by the acronym PICO - P: population and problem (Adult women and men over 18 years old); I: intervention (topical administration of vitamin C); C: comparison (patients who did not receive topical administration of vitamin C); O) outcomes (improvement and/or acceleration of skin healing)⁵⁻⁷. A bibliographic survey was carried out in Medline, Lilacs and Cochrane databases. The following Medical Subject Heading (MeSH) descriptors were used: ascorbic acid, l-ascorbic acid, skin, skin cream, antioxidants, wound healing, healing; administration, oral and the Health Sciences (DeCS) descriptors: ascorbic acid, l-ascorbic acid, skin, skin cream, antioxidants, wound healing, healing and oral administration, combined with boolean operators (AND, OR).

Selection of studies

Inclusion criteria were: randomized clinical trial, systematic review or observational study in humans, age over 18 years, publication date up to 5 years, in English, Portuguese and Spanish, and studies with relevant outcomes concerning wound healing. Publications such as narrative literature reviews, dissertations, theses, editorials, in vitro and animal studies, or those that did not have outcomes relevant to the proposed theme were excluded.

The articles included in this study analyzed the methodology's quality through GRADE - Grading of Recommendations Assessment, Development and Evaluation⁸⁻¹⁰.

RESULTS

The search strategy resulted in 83 articles, 33 in Medline, 22 in Lilacs and 28 in Cochrane. After the screening, six studies were selected that met all eligibility criteria (Figure 1). These six studies encompassed 129 patients aged between 21 and 70 years. The studies found are described in Chart 1, which details the authors, study design, location, sample, methodology, intervention and main findings.

The selected studies were analyzed according to the GRADE methodology - Grading of Recommendations Assessment, Development and Evaluation (Chart 2). Used by the World Health Organization (WHO), this methodology provides clear and concise information on the evidence's quality and the strength of the recommendation⁸⁻¹⁰.

In an observational, prospective, open-label, uncontrolled clinical trial carried out in this review, a nighttime facial serum containing melatonin, *bakuchiol* (plant extract - 0.5%) and ascorbyl tetraisopalmitate (undisclosed dose-response gradient), which was evaluated in 39 healthy women aged 40 to 65 years who had moderate skin aging. After 12 weeks, a decrease in wrinkles was observed (11%, $p < 0.01$, Dermatop scan); an increase in skin firmness (8%, $p < 0.01$) and a reduction in redness (70%; $p < 0.01$, Bazin score). The outcomes presented in this study obtained moderate-quality evidence according to the GRADE⁸⁻¹¹ analysis.

In a randomized, controlled clinical trial, the efficacy of microneedle mesotherapy in combination with the application of a serum containing 2.5 ml of L-ascorbic acid (20%, pH 3.5, treated group) to the right half of the face versus needle-free mesotherapy with the application of the same serum as the treated group, applied to the left half of the face (control group), in 17 healthy volunteers aged between 45 and 70 years. Four treatment sessions were performed, with an interval of 10 days between sessions. In the treated group, there was an improvement in skin hydration ($p < 0.0001$, Corneometer[®]); improvement in skin firmness ($p < 0.0001$, Cutometer[®]); improvement in skin elasticity ($p < 0.002$, Cutometer[®]); and decreased erythema ($p < 0.001$, Mexameter[®]). In the control group (mesotherapy without needle), there was improvement only in skin hydration ($p < 0.001$, Corneometer[®]) and decreased erythema ($p < 0.001$, Mexameter[®]). In summary, the results were more expressive in the

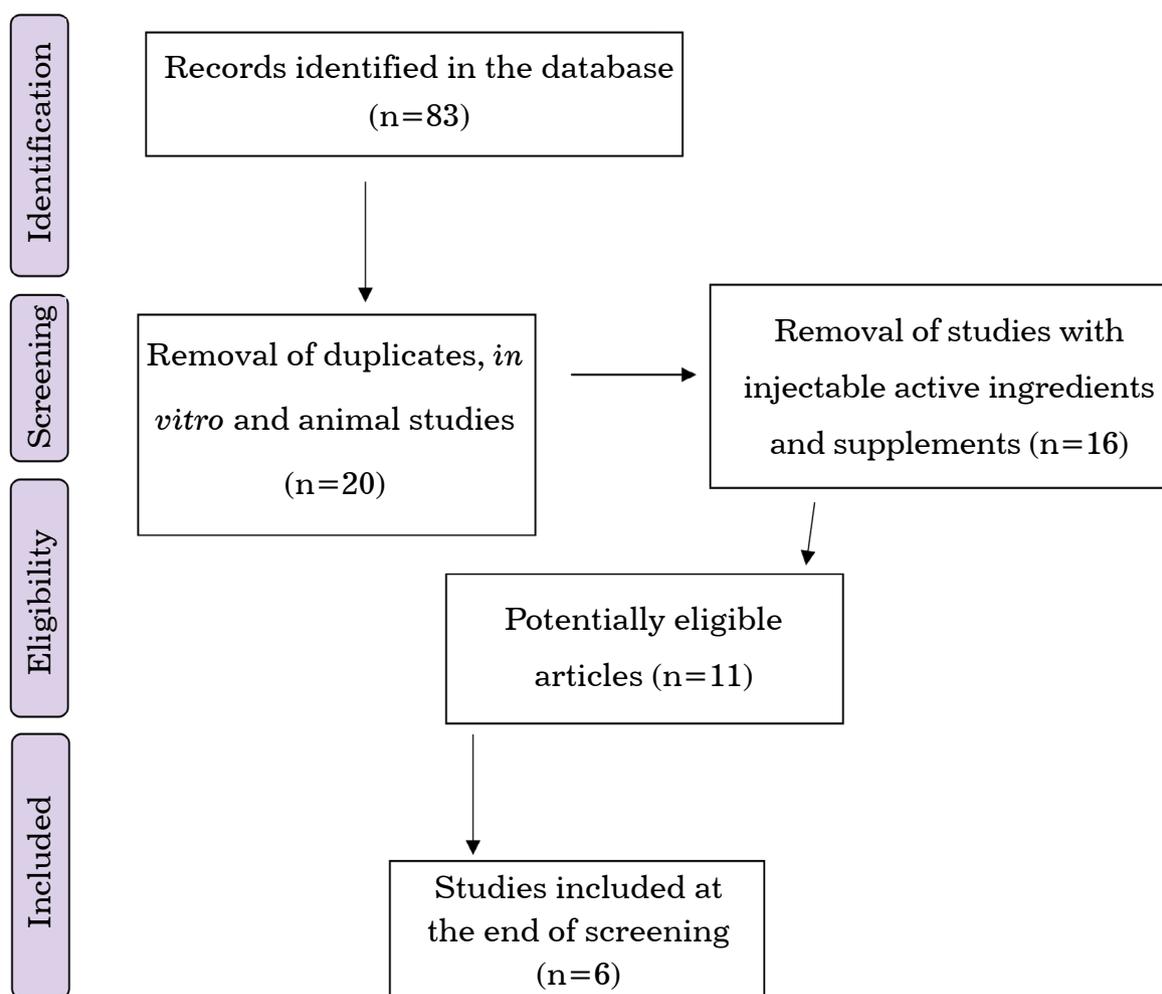


Figure 1. Flowchart of the article review process.

Chart 1. List of authors, study design and sample, methodology and outcomes of the randomized controlled trial and observational studies included in this study.

Authorship	Study design and sample	Methodology	Main Findings
Goldberg et al. (2019) ¹¹	<ul style="list-style-type: none"> - Observational, single-center, prospective, open-label, uncontrolled clinical trial. - 39 healthy women aged between 40 and 65, with moderate skin aging. 	<ul style="list-style-type: none"> - Clinical evaluation of facial serum containing melatonin, bakuchiol (0.5%) and ascorbyl tetraisopalmitate for 12 weeks. - Corneometer®. - Mexameter®. 	<ul style="list-style-type: none"> - Decrease in wrinkles (11%, $p < 0.01$); increase in skin firmness (8%, $p < 0.01$); reduction in redness (70%; $p < 0.01$).
Zasada et al. (2019) ¹² .	<ul style="list-style-type: none"> - Randomized, controlled clinical trial. - 17 healthy volunteers aged between 45 and 70 years. 	<ul style="list-style-type: none"> - Efficacy of mesotherapy with needles and application of a serum containing 2.5 ml of L-ascorbic acid (20%, pH 3.5, treated group). - Mesotherapy without needles and application of a serum containing L-ascorbic acid (control group). - 4 treatment sessions. - Interval of 10 days. 	<ul style="list-style-type: none"> - Treated group: - Improved skin hydration ($p < 0.0001$); improvement in skin firmness ($p < 0.0001$); improvement in skin elasticity ($p < 0.002$) and decrease in skin erythema ($p < 0.001$). - Control group: improvement in skin hydration ($p < 0.001$) and reduction of erythema ($p < 0.001$).
Humbert et al. (2018) ¹	<ul style="list-style-type: none"> - Randomized, double-blind clinical trial. - 22 patients over 60 years old with senile purpura. 	<ul style="list-style-type: none"> - Topical application of 5% vitamin C (treated group) versus neutral cream (control group) for 12 weeks. - Colorimetry assessment (macrophotography – FUJI S2 camera, 60 mm Micro Nikkor lens). 	<ul style="list-style-type: none"> - Improvement in the colorimetry of the spots ($p < 0.0001$, treated group).
Prakoeswa et al. (2018) ²	<ul style="list-style-type: none"> - Randomized, controlled, open-label clinical trial. - 13 women and 9 men - Leprosy ulcers. 	<ul style="list-style-type: none"> - Application of medication (hAMMSC-CM - 5.05mg/ml), for up to 8 weeks, group control. - Application of medication (hAMMSC-CM - 5.05mg/ml and sodium ascorbyl phosphate - 8.76%±9.55%), treated group for up to 8 weeks. - Spectrophotometry. 	<ul style="list-style-type: none"> - Improvement in ulcer closure and depth in the treated group (4th week 22%, $p < 0.005$).
Kim et al. (2017) ¹³	<ul style="list-style-type: none"> - Randomized, double-blind clinical trial. - 21 healthy Korean women aged between 41 and 55. 	<ul style="list-style-type: none"> - Topical application of Palm-KVK-AA (0.075%) for 12 weeks versus placebo (neutral cream). - Visiometer. - DermascanC. 	<ul style="list-style-type: none"> - Treated group: improvement in skin roughness ($p < 0.001$), improvement in skin roughness ($p < 0.05$).
Waibel et al. (2016) ¹⁴	<ul style="list-style-type: none"> - Randomized, double-blind, single-center, prospective clinical trial. - 15 healthy men and women aged 30 to 55. 	<ul style="list-style-type: none"> - Application of vitamin C (15%), vitamin E (1.0%) and ferulic acid (0.5%) versus neutral solution after application of the ablative CO₂ laser and daily until the seventh day - Photography from the first to the seventh day, application of a questionnaire and molecular evaluation. - Pre-auricular biopsies on the fifth day and 3 months after laser treatment. 	<ul style="list-style-type: none"> - There was no significant reduction in skin edema and erythema.

Source: Authors.

Chart 2. List of authors, outcomes and strength of recommendation according to the GRADE methodology, which includes randomized and observational clinical trials included in this study.

Authorship	Outcomes	GRADE rating
Goldberg et al. (2019) ¹¹	- Decrease in wrinkles - Increase in firmness - Reduction in redness	⊕⊕⊕○ MODERATE
Zasada et al. (2019) ¹²	- Improved hydration - Improved firmness - Improved elasticity - Decreased erythema	⊕⊕⊕⊕ HIGH
Humbert et al. (2018) ¹	- Improvement in the colorimetry of the spots	⊕⊕⊕⊕ HIGH
Prakoeswa et al. (2018) ²	- Improved closure and depth of ulcers	⊕⊕⊕⊕ HIGH
Kim et al. (2017) ¹³	- Improvement in skin roughness - Improvement in skin roughness	⊕⊕⊕⊕ HIGH
Waibel et al. (2016) ¹⁴	- Decreased edema - Decreased erythema	⊕⊕⊕○ LOW

Source: Authors.

treated group, and there was high-quality evidence for these outcomes, according to the GRADE analysis^{8-10,12}.

In a randomized, double-blind clinical trial, the results of topical application of a cream with 5% vitamin C (L-ascorbic acid - pH 6.0, treated group) were evaluated compared to the application of a neutral cream (control group) in 18 patients over 60 years with senile purpura for 12 weeks. The study showed improvement in the colorimetry of the spots (macrophotography - Fuji S2 camera, 60 mm Micro Nikkor lens, $p < 0.0001$) in 15 patients (88%) of the treated group compared to eight patients (47%) of the control group, with high-quality evidence for improvement of skin blemishes, according to GRADE analysis^{1,8-10}.

In a randomized, controlled, open-label clinical trial, 22 patients (13 women and 9 men) who had chronic plantar ulcers resulting from leprosy underwent treatment with the application of a drug/gel containing mesenchymal stem cells from the human amniotic membrane (hAMMSC-CM, 5.05mg/ml, control group) versus application of hAMMSC-CM, 5.05mg/ml associated with sodium ascorbyl phosphate (vitamin C derivative, concentration between 8.76%±9.55%, treated group). The gel was applied in the inflammatory phase, every 3 days until the ulcer closed or for a maximum period of 8 weeks. There was an improvement in ulcer closure and depth from the fourth week onwards in the treated group (spectrophotometry, 22%, $p < 0.005$, fourth week). There was high-quality evidence for this outcome in the GRADE analysis^{2,8-10}.

In a randomized, double-blind clinical trial, the effect of the ascorbic acid derivative (Palm-KVK-AA - 0.075%) was evaluated versus neutral cream in 21 healthy South Korean women aged between 41 and

55 years, applied to each half of the participants' faces, twice a day, for 12 weeks. The results show improvement in skin roughness ($p < 0.001$) and improvement in skin roughness ($p < 0.05$) in the treated group, obtained through analysis by Dermascan C and Visiometer. There was high-quality evidence for this outcome, according to GRADE analysis^{8-10,13}.

In a randomized, double-blind, single-center, prospective clinical trial, wound healing after applying ablative CO2 laser in the face region was investigated in 15 patients aged between 30 and 55 years with moderate photodamage (Scale of Glogau 3). Immediately after laser application, two solutions were applied: a topical solution (15% vitamin C, 1.0% vitamin E, 0.5% ferulic acid) on one side of the face (treated group) and a neutral solution on the other side (control group), allocated randomly. Both solutions were applied daily for seven days. Photographs and a healing process questionnaire were taken every two days a week. On the fifth day and three months after treatment (n=5), pre-auricular biopsies and analysis of metalloproteinase biomarkers (MMP-1, Applied Biosystems) were performed. The results were not statistically significant regarding the decrease in edema ($p > 0.05$) and decrease in erythema in the treated group compared to the control group. ($p > 0.05$). These outcomes were qualified as low quality by GRADE analysis^{8-10,14}.

DISCUSSION

The present scope review found beneficial effects of topical use of AA on skin healing, such as improved wound closure and depth, improved stain colorimetry, improved skin hydration, firmness, elasticity, decreased erythema and reduction in skin redness.

Scope reviews allow descriptively mapping scientific data, particularly useful when many results are different but applicable. Although the quality of scientific evidence is not required in a scope review⁵⁻⁷, the use of the GRADE methodology was used in this review, in which the quality of evidence can be classified as “High,” “Moderate,” “Low,” or “Very Low,” this classification being defined from the study design.

For randomized controlled trials, the quality of the initial evidence is set as “High,” while for observational studies, the quality of evidence starts as “Low.” The characteristics of the study and its results allow reducing or increasing the level of this evidence, such as, for example, the methodological limitations that may be responsible for the reduction in the level of evidence. Factors such as the large magnitude of effect and dose-response gradient can increase confidence in the estimate, while studies that express recommendations based on expert opinions are classified with a “Very Low” level of evidence⁸⁻¹⁰.

Regarding the topical use of AA, widely commercialized in the Brazilian market, there is a growing list of ingredients, raw materials or active principles characterized as AA or derivatives used in cosmetic products. In this way, the standardization of topical AA and/or its derivatives for scientific studies becomes a challenge, emphasizing the need for a careful investigation of the scientific literature to determine the best way to treat patients^{15,16}.

According to Anvisa’s RDC No. 7/2015, cosmetics are preparations for external use exclusively. However, AA can be administered directly to wounds as medication to induce the healing of chronic plantar ulcers, for example. Therefore, the use of AA can be prescribed in cosmetic and drug formulations, depending on the treatment, the type of lesion and the stage at which it will be included in the treatment^{1,2}.

As for the cutaneous penetration of AA, despite the Technical Opinion No. 3, of 29 June, 2001 (updated on 06/28/2004) by Anvisa, considering good penetration of AA in concentrations of 10% and a maximum of 12%, in this research, scientific studies were found that used AA with a concentration of 20%, remembering that the higher the concentration of AA, whether in its pure or derived form, the greater the cost of the solution. Concerning the current Brazilian market, the pure form of AA is more easily found when compared to its derivatives, a fact that can be justified by the cost of the raw material and the technology required in preparing derivatives concerning pure AA.

Some limitations in the studies that composed this scoping review were observed. The sample size was small (ranging from 15 to 39 individuals); the outcomes were not standardized between the different studies, and the assessment tools and follow-up time (from 5

weeks to 12 weeks) were different. In addition, there was variation in the use of AA, with studies evaluating pure AA and its derivatives (ascorbyl tetraisopalmitate, sodium ascorbyl phosphate and palmitoyl-KVK aminopropyl ascorbyl phosphate). The concentration of pure AA ranged from 5 to 20%, while its derivatives ranged from 0.075% to 9.55%. Only two studies investigated the effects of pure and isolated AA, while in the other studies, AA was combined with other ingredients, such as Bakuchiol (0, 5%) and ascorbyl tetraisopalmitate (a derivative of AA). In these combinations, the authors did not report the dose-response ingredient of the AA derivatives, leading to confounding bias. Topical AA solution (15%) was combined with vitamin E (1.0%) and ferulic acid (0.5%). However, the authors “assume” that the improvement of the spots the elasticity and the thickness of the skin occurred mainly due to the action of AA as it is in a higher concentration, leading to a confounding bias^{1,11,12,14}.

Only two studies presented “skin healing” as a primary outcome; the others evaluated outcomes such as elasticity, cutaneous hydration and dermal density, which are also relevant in the cutaneous healing process^{2,14}.

CONCLUSION

According to the studies found in this scope review, the topical use of pure AA at concentrations between 5 and 20%, and its derivatives from 0.075% to 9.55%, promotes a decrease in wrinkles, an increase in firmness and a reduction in redness, the which presented moderate GRADE quality, as well as improvement in hydration, firmness, elasticity, stain colorimetry, roughness, skin roughness, reduction of erythema, improvement in wound closure and depth, which presented high GRADE quality. However, despite the strong positive evidence of the use of AA as an adjuvant factor in improving the quality and healing of the skin, randomized clinical trials with a lower risk of confounding bias and a larger sample are still needed.

COLLABORATIONS

- AVS** Analysis and/or interpretation of data, Data Collection, Conceptualization, Research, Methodology, Writing - Preparation of the original.
- JCMP** Final approval of the manuscript, Conception and design of the study, Project Management, Carrying out operations and/or experiments, Supervision.
- RAB** Final Manuscript Approval, Project Management, Writing - Review and Editing, Supervision.

- DOV** Data Collection, Investigation, Operations and/or Experiments.
- CCE** Data Collection, Investigation, Operations and/or Experiments.
- FOCP** Data Collection, Investigation, Operations and/or Experiments.

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