
Manuscript Submission

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10 Maret 2020 12.07

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Dear Editor
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We wish to submit a new manuscript entitled **“Clinical Outcomes of Stem Cell Metabolites Formula Derived from Placenta for Skin Regeneration”** for consideration by your journal.

We confirm that this work is original and has not been published elsewhere nor is it currently under consideration for publication elsewhere.

This study is focusing on clinical application of stem cell metabolites derived from placenta for skin regeneration. This study is an advanced stage by focusing on clinical trial in 30 patients who met the inclusion and exclusion criteria to be applied with stem cell metabolites on their face. The paper should be of interest to readers in the areas of stem cell research including stem cell research and therapy.

Please address all correspondence concerning this manuscript to me at purwati@fk.unair.ac.id.

Thank you for your consideration of this manuscript.

Sincerely,

Dr. Purwati, dr., Sp.PD, K-PTI, FINASIM
Stem Cell Research and Development Center
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Surabaya, Indonesia



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ISSN: 0975-8542

JGPT Elsevier Indexed link: <http://www.scimagojr.com/journalsearch.php?q=19700200708&tip=sid&clean=0>

Manuscript ID: 2020JGPT142

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CLINICAL OUTCOMES OF STEM CELL METABOLITES FORMULA DERIVED FROM PLACENTA FOR SKIN REGENERATION

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Abstract

Previous research focuses on in vitro and animal study of stem cell metabolites formula derived from placenta for skin regeneration. This study is an advanced stage by focusing on clinical trial in 30 patients who met the inclusion and exclusion criteria to be applied with stem cell metabolites on their face. Previously, subjects were examined their face conditions by using janus skin analyzer to see markers on their skin. Subjects were then applied stem cell metabolites formula in their face twice per day, at day and night with single-use doses of three pumping. Evaluation was carried out before and after application of stem cell metabolites using janus in three months. The results of the janus examination evaluated were Spot, Pore, Roughness, Wrinkle, UV Acne, UV Spot and UV Moisture. The percentage of spot, pore, roughness, wrinkle, UV acne and UV spots are decreased, while the percentage of UV moisture is increased in almost all subjects who were evaluated for three months. In qualitative, almost 90%

subjects are satisfied with the results of stem cell metabolites. The subjects felt that facial wrinkles were reduced, the face was smoother and supple, and pigmentation was reduced. It can be conclude that stem cell metabolites formula are effective and efficient in skin regeneration.

Keywords: stem cell metabolites, formula, placenta, skin regeneration, clinical outcomes

Introduction

Aging in human is a gradual and continuous process of natural change, a decreasing process the ability of tissue to replace and maintain its normal functions involving every molecule, cell and organ in the body.^{[1][2]} In adult, individuals experience many changes, both physically and mentally, especially setbacks in various functions and abilities they have ever had. The decrease is related to various systems in the body such as decreased memory, muscle weakness, hearing, vision, feelings and changing

physical appearance and other biological functions.^{[3][4]}

Skin aging is a natural process where the process of renewing skin cells and collagen production slows down, as well as the weakening of the internal support structure and the natural protective layer of the skin. The deterioration of the skin renewal process, combined with environmental and lifestyle factors, such as pollution can cause signs of aging to appear earlier.^[5] Basically, premature aging often occurs in someone who has a dry skin type because sebum which is an oil content to protect the skin from pollution and moisturizes the skin is very lacking.

There are several anti-aging therapies that are widely used in dealing with aging, include cosmetological treatments such as protective cosmetics from UVA and UVB; Topical agents such as tretinoin to stimulate the synthesis of type I collagen and vitamin C for antioxidants; Systemic agents which include vitamins C and E, glutathione, polyphenols, melatonin and selenium; and Procedural Therapy which offers services such as physician-performed or device-driven procedures such as laser therapy.^{[6][7]}

Stem cell therapy was initially carried out to treat degenerative diseases. The role of stem cell metabolites in skin aging is to repair injured tissue or replace other cells in programmed cell death. Stem cell metabolites are rich in growth factors such as cytokines IL-10, IL-4, EGF, GM-CSF, and TGF- β . These cytokines can penetrate the skin layer to stimulate the growth of new cells and increase nutrition, accelerate skin metabolism to inhibit premature aging, stimulate the skin to produce new proteins, collagen and elastic fibers, also reduce black pigments and induces basal cells to proliferate resulting in the growth of epidermal keratinocytes.^{[8][9][10][11]} In this

way, stem cells keep us healthy and prevent us from premature aging. These stem cells act like our own microscopic doctor forces.^{[12][13]}

In this study, stem cell metabolites formula were taken from human placenta. Placenta contains more hematopoietic stem cell populations and mesenchymal precursor cells when compared to adult blood or bone marrow. Validation of stem cell metabolites formula are conducted before use includes plasticity, purity and contamination. Cells must be free of infectious diseases such as HIV, herpes, hepatitis, BSE, gonorrhoe, and cancer cells. In addition, the level of cell viability and cell phenotype must also be in accordance with the desired target.^[14]

Previous research focuses on in vitro and animal study of stem cell metabolites formula derived from placenta for skin regeneration. Characterization in vitro were conducted, include cytotoxicity assay, cytokine detection assay and apoptosis assay. From the study, it can be conclude that stem cell metabolites formula are not toxic in terms of the toxicity test results with a percentage of cell viability that exceeds 50%. Stem cell metabolites formula do not cause any systemic immune response to surrounding tissue in terms of decreased levels of cytokine release. They also do not induce apoptosis in terms of the increased percentage of expression of Hsp70 (anti-apoptotic gene) and the decrease in the percentage of expression of p53 and caspase-3 (pro-apoptotic gene) in the treated sample (with metabolites) compared to controls.^[15]

An advanced stage are animal trial focusing on the efficiency and efficacy of stem cell metabolites formula in rats (*Rattus norvegicus*). Rats were injured in the anterior and posterior back skin with a small incision wound, with control group (without injecting stem cell metabolites formula) and rats

treated with intra-muscular injection of stem cell metabolites formula. Samples were observed for blood levels using ELISA IL-4, ELISA IL-10, and ELISA TNF- α , and integument histology at pre-injection, day 1, day 3, and day 6 to compare the development of inflammatory cells, which are polymorphonuclear (PMN) and monocytes (MN) between groups. From the results, it can be concluded that stem cell metabolites formula are effective and efficient significantly inhibiting the inflammatory process in the tissues in terms of the blood levels examination in rats with ELISA IL-4, IL-10 and TNF- α . IL-4 and IL-10 (anti-inflammatory) tend to decrease significantly in the treatment group, while TNF- α (pro-inflammation) tends to be high in the control group. Histology results showed a decrease in the number of PMN and MN inflammatory cells in the treatment group compared to control which indicated that stem cell metabolites formula were able to significantly inhibit the inflammatory process.^[16]

In this study, we are focusing on clinical trial in 30 patients who met the inclusion and exclusion criteria to be applied with stem cell metabolites formula on the face. Previously, subjects will be examined their face conditions by using janus skin analyzer to see markers on their skin. They will be applied stem cell metabolites formula twice per day, at day and night with single-use doses of three pumping. Evaluation was carried out before and after application of stem cell metabolites formula using janus. The results of the janus examination evaluated were Spot, Pore, Roughness, Wrinkle, UV Acne, UV Spot and UV Moisture.

Methods

This study received ethical clearance from the law and medical research ethics

committees of Universitas Airlangga Hospital, Surabaya, Indonesia, following the regulatory guidelines of the country. Clinical trial registration number is 101/KEH/2019. Prior to the study, informed consent documents, details of the medical treatment and other necessary approval documents were delivered to all subjects involved in the study. Study analysed data from 19 men and 11 women in various aged between 40-70. The following inclusion and exclusion criteria were used for the subjects.

Inclusion Criteria:

- Subjects are men or women
- Aged 40 or above
- Having no infectious diseases
- Having no allergic diseases
- Willing to be a donor as evidenced by the signing of informed consent

Exclusion Criteria:

- Using another skin care during the study
- Not willing to sign an informed consent

Procedure

Previously, subjects were examined their face conditions by using janus skin analyzer to see markers on their skin. Subjects were then applied stem cell metabolites formula in the face twice per day, at day and night with single-use doses of three pumping. Evaluation was carried out before and after application of stem cell metabolites formula using janus in three months, with three times repetition of evaluation per two weeks. The results of the janus examination evaluated were Spot, Pore, Roughness, Wrinkle, UV Acne, UV Spot and UV Moisture.

Statistical Analysis

Data analysis performed using SPSS Statistics. Data in ratio expressed in mean, standard deviation, frequency distribution, and percent on descriptive analysis and frequency. Data normality test performed by

Kolmogorov-Smirnov Z statistics. Variable paired comparison performed by T-test if data were normally distributed or two related samples (Chi-Square test) if data distribution was abnormal. Significance limit is that if $p < 0.05$ with 95% confidence interval.^[16]

Results

We performed statistical data analysis to evaluate the differences of subject's skin

condition include Spot, Pore, Roughness, Wrinkle, UV Acne, UV Spot and UV Moisture before and after treatment of metabolites stem cell formula in three months. Evaluation conducted three times per month. Data are presented in Table 1.

Table 1. The average of subject's skin condition before and after treatment with metabolites stem cell

Group	$\bar{x} \pm SD$ (%)						
	Spot	Pore	Roughness	Wrinkle	UV Acne	UV Spot	UV Moisture
Pre	68,16 ^a ± 20,67	97,53 ^a ± 0,97	96,73 ^a ± 1,59	73,30 ^a ± 17,82	45,96 ^a ± 9,30	75,70 ^a ± 19,83	70,53 ^a ± 7,17
Post 1	57,96 ^b ± 25,81	95,56 ^b ± 1,92	96,10 ^b ± 1,47	65,63 ^b ± 22,42	35,30 ^b ± 9,89	70,46 ^b ± 21,84	86,66 ^b ± 8,57
Post 2	54,16 ^c ± 26,04	90,53 ^c ± 1,92	91,00 ^c ± 1,59	61,16 ^c ± 22,50	33,93 ^c ± 13,72	66,20 ^c ± 21,65	90,56 ^c ± 7,13
Post 3	49,73 ^d ± 24,69	85,86 ^d ± 2,77	86,20 ^d ± 2,29	56,26 ^d ± 22,69	30,66 ^d ± 13,13	62,23 ^d ± 21,85	94,00 ^d ± 5,81

a,b,c,d indicates data between pre treatment and 3x post treatment are statistically significant difference

Discussion

Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth so that rejuvenation process occurs. Metabolite products are produced by stem cells. In the process, the cell will produce metabolite materials that are rich in growth factors. This process can be repeated several times for taking the supernatant. This metabolite is then used as the main ingredient in topical preparations. Gradually, stem cell metabolites reduce dull skin and wrinkled due to decreasing in collagen production by degenerative process. Some practitioners claim that stem cell metabolites will produce

more elastic skin and reduce pigmentation so that the appearance is looking much better.^[8]

In this study, stem cell metabolites taken from human placenta which contains more hematopoietic stem cell populations and mesenchymal precursor cells when compared to adult blood or bone marrow. Stem cell metabolites are rich in growth factors including Interleukin-10, Interleukin-4, EGF (Epidermal Growth Factor), GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor), and TGF- β (Transforming Growth Factor Beta). These growth factors making the skin produce protein and elastic fibers and new proteins, so that skin returns to elastic, reduces black pigments and induces basal cells to

proliferate resulting in the growth of epidermal keratinocytes.^{[9][10][11]}

Previous research focuses on in vitro and animal study of stem cell metabolites derived from placenta for skin regeneration. Characterization of stem cell metabolites in vitro were conducted, include cytotoxicity, cytokine detection and apoptosis assay. From the study, it can be conclude that stem cell metabolites are not toxic in terms of the toxicity test results with a percentage of cell viability that exceeds 50%. Stem cell metabolites do not cause any systemic immune response to surrounding tissue in terms of decreased levels of cytokine release. Stem cell metabolites also do not induce apoptosis in terms of the increased percentage of expression of Hsp70 (anti-apoptotic gene) and decreased percentage of expression of p53 and caspase-3 (pro-apoptotic gene) in the treatment groups (with metabolites) compared to control.^[13]

In animal study, we are focusing on the efficiency and efficacy of stem cell metabolites in rats (*Rattus norvegicus*). Rats were injured in the anterior and posterior back skin with a small incision wound, with control group (without injecting stem cell metabolites) and rats with intra-muscular injections of stem cell metabolites. Samples were observed for blood levels using ELISA IL-4, ELISA IL-10, and ELISA TNF- α , and integument histology at pre-injection, day 1, day 3, and day 6 to compare the development of inflammatory cells, which are polymorphonuclear (PMN) and monocytes (MN) between groups. From the results, it can be conclude that stem cell metabolites are effective and efficient significantly inhibiting the inflammatory process in the tissues in terms of blood levels examination in rats with ELISA IL-4, IL-10 and TNF- α . IL-4 and IL-10 (anti-inflammatory) tend to decrease significantly in the treatment group, while TNF- α (pro-inflammation) tends to be

high in the control group. Histology results showed a decrease in the number of PMN and MN inflammatory cells in the treatment group compared to control which indicated that stem cell metabolites were able to significantly inhibit the inflammatory process.

This study is an advanced stage that focusing on clinical trial in 30 patients who met the inclusion and exclusion criteria as mentioned in the methods section to be applied with stem cell metabolites on the face. Evaluation was carried out before and after application of stem cell metabolites using janus skin analyzer. After analysis, subjects will know their specific skin problems and determine the severity, the analysis of each representative of the indicators mean, and how to recommend a suitable course of treatment. There are 7 skin problems: for surface, there are spot, pore, roughness and wrinkle, and for deep skin problem, there are UV acne, UV spot and UV moisture. The percentage represent the degree of skin problem. The higher the number is, the worse the skin condition will be, except for UV moisture.^[17]

In surface skin problems, normal value of **RGB Spot** is in 30%, indicate that the spots of surface skin is in normal state; if 30%-70%, indicate that in the excess state from medium to serious; if over 70%, indicate that in serious state, need to do freckles removal treatment urgently. For **RGB Pore**, normal value is in 80%, this value is a little special, as everyone have pores, so the value is high, we detect the degree of clogged pores. 80%-90% indicate that in medium state; over 90%, indicate in serious state. **RGB Roughness** is relative with Pore, so the value indication is similar with pore. 80%-90% is medium state, over 90% is serious state, at same time, it's closely connect with habits and dehydration. Generally, **RGB Wrinkle** in 30% is fine lines, no need to pay much

attention, as adult's every movement of face, will have fine lines. Over 40%, fine lines quantity increased, when the blue points on detect pictures together into a line, this is authenticity wrinkles, over 70% is in serious state, need to do anti-aging treatment.^[16]

In deep skin problems, normal value of *UV Acne* is in 30%, 30%-70% is in medium state, need to do moisturizing, deep cleaning treatment often; if over 70%, indicate that in serious state, remind customers do course of moisturizing, oxygen therapy and deep cleaning treatment. For *UV Spot*, normal value is in 30%, 30%-70% is in medium state, need use products of promote metabolism often; if over 70%, indicate that in serious state, remind customers do course of promote metabolism. The value of *UV Moisture* is a little special. Normal value is in 80%, as everyone's face need large amounts of moisture, so everyone has lack moisture problem. 80%-90% is medium state, over 90% is serious state, need do moisturizing treatment urgently.^[18]

From the study results, it was found that stem cell metabolites formula are effective and efficient in overcoming aging as evidenced by the decrease of percentage in spot, pore, roughness, wrinkle, UV acne and UV spots, while the increase happen in the percentage of UV moisture. This result was experienced by almost all subjects who were evaluated for 6 weeks. In qualitative, almost 90% subjects are subjectively satisfied with the results of the application of stem cell metabolites formula. The subjects felt that facial wrinkles were reduced, the face was smoother and supple, and pigmentation was reduced.

Conclusion

It can be conclude that stem cell metabolites formula are effective and efficient in overcoming aging as evidenced by the decrease of percentage in spot, pore,

roughness, wrinkle, UV acne and UV spots, and the increase of percentage in UV moisture. This result was experienced by almost all subjects who were evaluated for 6 weeks. In qualitative, almost 90% subjects are satisfied with the results of the application of stem cell metabolites formula. The subjects felt that facial wrinkles were reduced, the face was smoother and supple, and pigmentation was reduced.

Declarations

Ethics approval

This study received ethical clearance with No. 101/KEH/2019 from the law and medical research ethics committees of Universitas Airlangga Hospital, Surabaya, Indonesia, following the regulatory guidelines of the country.

Competing interests

The authors report no conflicts of interest in this work.

Funding

The authors received no specific funding for this work.

Authors' contributions

Purwati: stem cell metabolites preparation, manuscript preparation

Afif Nurul H: data analysis, discussion

M. Yulianto Listiawan: clinician, study literature, discussion

Ernawati: data analysis, discussion

Fedik A. Rantam: stem cell metabolites preparation

Medhi Denisa Alinda: clinician, data analysis, discussion

Novianti Risky Reza: clinician, data analysis, discussion

Ardhiah Iswanda P: clinician, study literature, manuscript preparation

Imam Susilo: stem cell metabolites validation

Diah Puspita Rini: stem cell metabolites validation
Afriyanti Sandhi: clinician, data analysis, discussion
Prasasta Adhistana: clinician, data analysis, discussion

Acknowledgements

We would like to acknowledge the support of all laboratory technicians in Stem Cell Research and Development Center, Universitas Airlangga, Surabaya, Indonesia and all functional medical staff of Department of Obstetrics and Gynecology, Universitas Airlangga Hospital, Surabaya, Indonesia.

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Abbreviations:

IL-4: Interleukin-4

IL-10: Interleukin-10

TNF- α : tumor necrosis factor-alpha

EGF: Epidermal Growth Factor

GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor

TGF- β : Transforming Growth Factor Beta

RGB: red, green, blue; the color values

UV: Ultra-Violet



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