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THERAPEUTIC EFFICIENCY OF PLACENTAL EXTRACTS

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ABSTRACT: Thanks to the valuable components placental extracts (PE) are used in different fields of medical sphere, however most of them investigated only in Asian countries. The current study aimed to assess of therapeutic effectiveness of placental extracts depends on diagnosis. A systematic search strategy was conducted to capture published preclinical and clinical studies of usage placental extracts as a treatment variety of diseases. Pubmed, Web of science and Cochrane library databases were searched to identify relevant studies.Two members of review independently extracted the data on participant characteristics, intervention details and outcomes measures.Our initial query yielded 1091 potentially relevant records, of which 118 were excluded for duplicate records and Inspection of the abstracts and titles led to 899 of these studies to be discarded. A total of 74 studies were assessed for eligibility after which 59 studies were included in qualitative synthesis.In 59 selectedarticle regarding therapeutic properties of placental extract, 23 studies were carried out in Korea, 17 studies were carried out in India. 13 and 2 studies were conducted in Japan and China, respectively. In Taiwan 2 investigations were conducted, also one study was performed in Iran and Yugoslavia. There were 35 preclinical studies identified in this systematic review. In 30 preclinical studies rats and mice model was used, in 3 preclinical studies a rabbit model was used and 2 study pigs model was used. All preclinical studies reported a beneficial therapeutic effect of PE. However 1 out of 35 investigation described therapeutic efficiency on co-administration with other methodology.Analysis of theselected studies in many cases prove the effectiveness of placental extract for various therapeutic purposes, however, many of them refer to non-clinical studies, which requires more in-depth studies for their introduction into clinical practice.

INTRODUCTION

The placenta is an important organ during pregnancy, which provides fetus with hormones, nutrients and oxygen [1]. For many years, clinicians and researchers have worked on the therapeutic use of the placenta, as extracts and in cell or tissue transplantation, thus gaining significant empirical experience [2]. Basically in Asian countries human placenta (HPE) has been used as a folk remedy[3]. Additionally, investigations reveal that animal placental extracts also can show a similar therapeutic properties as human placenta.

Placental extracts are widely used in various fields of medicine due to the fact that they do not contain cells, but are sufficiently rich in proteins, minerals, amino acids and steroid hormones [4, 5]. Anti-inflammatory[6], antioxidative[7], immunomodulatory[8, 9] properties of derivatives of the human and animals placenta demonstrate a large curative opportunities.

Thanks to the valuable components placental extracts are used in cosmetology[10], in the treatment of climacteric syndrome [11, 12], in wound healing. [5, 13]and chronic fatigue syndrome[14].

For a number of historical reasons and due to these works are still not translated to English, a significant number of full-text studies, unfortunately, are not included in modern international databases[2].

Therefore, in order to prove therapeutic efficiency , a systematic approach is required to review the current scientific evidence and to analyze and clarify whether the administration of placental extracts are effective in a variety of clinical illnesses.

The current study aimed to assess of therapeutic effectiveness of placental extracts depends on diagnosis. The following null hypothesis was tested(there is no difference in the proportion of patients with health improvement after treatment with placental extracts), against alternative hypotheses about higher effectiveness of placental extracts in treatments in comparison with placebo/ no treatment group or group receiving traditional therapy.

Methods

The study was performed in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0[15], and the findings were reported according to the guidelines of the preferred reporting items for

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systematic reviews and meta-analyses (PRISMA) statement, which is an evidence-based protocol describing a set of items for reporting in systematic reviews and meta-analyses [16].

Data Sources and Search Strategy

A systematic search strategy was conducted to capture published preclinical and clinical studies of usage placental extracts as a treatment variety of diseases. Pubmed (from inception to 2020),Web of science (from 1975 to 2020) and Cochrane library were searched to identify relevant studies. All citations were downloaded and combined into EndNote version X6 (Thomson Reuters, New York, NY, USA), duplicates were removed by EndNote and manually.We also used the Rayyan online screening tool for screening the articles[17]. No limits were used concerning the year of publication.

Search strategies were performed by using a combination of freetext and MeSH terms.: "Placental Extracts/therapeutic use"[Mesh]) OR "Placental Extracts"[Mesh];“placenta* AND extract*”; “placental suspension*”; “human placental extract*”; “animal placental extract*”

The articles were selected in two stages. First, the titles and abstracts identified by the above searches were screened for relevant studies. Second, the full texts of these shortlisted articles were downloaded and assessed for eligibility based on the inclusion criteria.

Data Extraction procedure

Two members of reviewindependently extracted the data on participant characteristics, intervention details and outcomes measures. Disagreements were resolved by oral discussion or resolved by a third author. Data were collected using a data extraction spreadsheet developed specifically for this study.

Criteria for considering studies for this review

Types of studieswere eligible for inclusion in this review: written in English**;** reported original data**;** utilized a clinical trial or randomized controlled trail**;** research conducted with human participants**;** animal studies**;**

Types of participants Anyonewho receivedtreatment y with placental extracts in any forms depends on disease. Studies with human participation, also with animal model of experiment were included in this investigation.

Types of intervention Active agents: any intervention for the treatment with placental extracts. Control: may be placebo, no treatment, or another traditional intervention.

Exclusion criterions: case reports, case series, observational studies (case–control, cross-sectional, and cohort studies), systematic reviews and meta-analyses, letters to the editor, reviews, editorials, commentaries, basic science studies and abstracts from conference proceedings were excluded.

Characteristics of included studies

-Methods (Study design; duration of study);

-Participants (Number of participants allocated to each treatment group; mean age/age range; gender distribution; severity of disease, inclusion and exclusion criteria.);

-Interventions (Total number of intervention groups with number of participants in each group; type of intervention);

-Outcomes (Primary and secondary outcomes assessed in the study);

Results

Study selection and study characteristics

Figure 1 shows the procedure of literature search and selection. Our initial query yielded 1091 potentially relevant records, of which 118 were excluded for duplicate records and Inspection of the abstracts and titles led to 899 of these studies to be discarded. A total of 74 studies were assessed for eligibility after which 59 studies were included in qualitative synthesis.

In 59 selectedarticle regarding therapeutic properties of placental extract, 23 studies were carried out in Korea, 17 studies were carried out in India. 13 and 2 studies were conducted in Japan and China, respectively. In Taiwan 2 investigations were conducted, also one study was performed in Iran and Yugoslavia.

Preclinical studies

There were 35 preclinical studies identified in this systematic review. In 30 preclinical studies rats and micemodel was used, in 3 preclinical studies a rabbit model was used and 2 study pigs model was used. All preclinical studies reported a beneficial therapeutic effect of PE. However 1 out of 35 investigation described therapeutic efficiency on co-administration with other methodology.

Clinical studies

In this systematic review overall 24 clinical studies mentioned. 14 of them displayed positive effect of PE administration. However in 3 studies no beneficial effect was found, also an identical therapeutic efficiency with control or placebo group was observed in 2 trials. Moreover 2 studies described efficiency of PE in combination with other drug, also in 1 trial two form of

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PE administration (gel or cream) was discussed with almost an identical therapeutic effect. However in 2 investigations full curable effect were not achieved.

Placental extracts in climacteric syndrome

8 articles were devoted to the use of PE in the treatment of menopausal symptoms[11, 12, 18-23]. Human PE were administrated in two studies (Kong et al., 2008, Choi and Kim, 2019),whereas in remaining studiesa porcinePE were used[12, 18-20, 22, 23].

As for clinical studies, Kong et al. [11] examine the effects of HPE on menopausal symptoms, fatigue, and risk factors for cardiovascular disease in middle-aged Korean women in a single-blind randomized controlled trial. After 8 week treatment with human placental hydrollysate (Laennec) in HPE group the score from The Menopause Rating Scale (MRS) ($p=0.033$), Fatigue Severity Scale($p= 0.002$) , Visual Analog Scale (VAS) scores ($p=0.001$) significantly decreased and 17ß-estradiol level significantly increased compared to placebo group ($p=0.031$).However there were no changes in risk factors for cardiovascular disease in both group during the study period.Regarding limitations of this study, he results could notrepresent a longer effect because of the 8-week duration of the study, also sample size were small.Choi et al. [21]published a preliminar protocol of randomized placebo-controlled single-blind multi-center parallel-design clinical trial, where in the pharmacopuncture group 0.5 cc of PLC will injected twice weekly at four acupoints. Primary (number of hot flashes) and secondary outcomes(mean changes in MRS, follicle-stimulating hormone and estradiol levels) will be assessed after 8 weeks, however outcomes of this study are still unknown.

To assess whether porcine placental extracts (PPE) has an impact on climacteric symptoms in perimenopausal and postmenopausal women [20]PPE group received three capsules of 350 mg PPE/day orally for the initial 12 weeks and six capsules/day for the next 12 weeks in comparison with control group who intook an oral herbal remedy Toki-shakuyaku-san (TJ23).Treatment with PPE was significantly ($p<0.01$) more effective in reducing the Simplified Menopausal index (SMI)score, Zung's Self Rating Depression Scale (ZSDS) and Spielberger State-Trait Anxiety Inventory (STAI) measures at 12 and 24 weeks than treatmentwithTJ23. Treatment with PPE was also significantly ($p<0.01$) alleviated the subscale scores of the SMI for symptoms such as hot flashes, insomnia, irritability, depression, fatigue and joint pain. PPE treatment had no significant side effects. Limitations of this study were small sample size and study was not a double-blind and duration was short.

In another work of Koike et al.[19] efficiency of PPE oral treatment regarding shoulder stiffness, which is the most common type of muscle-tendon stiffness, in (a) climacteric women and in (b) postmenopausal women with hormone therapy (HT) was studied.The terapeutic dozes of PPE and TJ23 in both randomized groups were an identical with previous investigaion [20].Changes in the degree of shoulder stiffness were evaluated by VASat baseline, during the treatment period (every 4 weeks) and 4 weeks after treatment.The trial consisted on two separate steps of investigation: (a) in the study among climacteric women and (b) among postmenopausal women with hormone therapy where PPE or TJ23 administrated as adjunctive therapy combined with HT, in both groups compared to control group receiving PPE were significantly effective in reducing the VAS score for shoulder stiffness 4 weeks after treatment began and during the remaining study period.The VAS score at the end of treatment was significantly reduced ($p< 0.01$ vs. baseline) by 76.4% for (a) climacteric women and 64.8% for (B) postmenopausal women with HT compared with baseline. Limitations of this study were small sample size and study was not a double-blind and duration was short.

As for knee pain treatment amid postmenopausal women,Koike et al.[18] investigated an effectiveness of PPE as an adjunctive oral supplement in the case ofresistancy for hormone replasement therapy(HRT), longlasting knee pain. Combination of PPE (9capsules/day) + HRT was significantly effective in reducing the VAS score for knee pain at 4 weeks ($p < 0.05$), at 8 weeks ($p< 0.01$) and at 12 weeks ($p<0.01$), compared with control group where patients received 3 months open treatment with calcium (260 mg/day)+ HRT. Side effects of PPE was not observed.Limitations of this study were small sample size and study was not a double-blind and duration was short, results should not apply to everyone with painful knee osteoarthritis.

Yoshikawa et al. [22] after measuring wrinkle widths of 185 healthy women via skin analyzer, compared wrinkle widths below the eyealso by skin analyser on climacteric womenin the study were 22 women received three 350-mg capsules of PPE per day with 22 women in none treatment control group. Therapy with PPE was significantly ($p < 0.05$) usefull in reducing wrinkle widths at 24 weeks compared with control groups. Moreover retrospective analysis which was conducted during this investigation revealed that receiving three ($p<0.05$) or six ($p<0.01$) 350-mg capsules of PPE per dayhad an equall significant effectivenes regarding reduction in wrinkle widths below the eye compared to control subjects. Limitations of this study were small sample size and study was not a double-blind and duration was short.

To assess therapeutic features of PPE for amelioration the mild menopausal symptoms compared to placebo group Kitanohara et al. [12] administrated oral PPE (300mg/day) on treatment group during 12 weeks, where SMI score, serum estradiol (E2) and follicle stimulating hormone (FSH) levels were estimated. As a result the total SMI score of the PPE group was significantly more improved after 12 weeks than that of the placebo group ($p=0.031$). Also three subscores (vasomotor, psychological, and somatic symptoms) were significantly improved at 8 and/or 12 weeks compared with the baseline values in the PPE group ($p<0.05$).However after oral intake PPE levels of E2 and FSH in the blood were not improved, thus despite the fact of improvement the subjective feelings of climacteric women, hormonal balans was not ameliorated. None adverse effects were registered.

As regards preclinical study, Han et al.[23] in a menopause model of mice after ovariectomy (OVX), human breast cancer cell line (MCT-7) cells and human osteoblast cell line (MC-63) investigated efficiency PPE and arginine(Arg), which is a main

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PPE amino acidfor treatment menopausal symptoms including osteoporosis.. Among all 8 groups (n=5 per group) there weresham-operated mice; sham-operated mice treated with10 mg/kg PP;OVX mice; OVX mice treated with 10 mg/kgArg(arginine); OVX mice treated with 100 nM E2 and OVX mice treatedwith several doses of 0.1mg/kg; 1mg/kg ;10 mg/kg PPE. In terms of obtained results, PPE or Arg would have estrogenic and osteoblastic activity, thus improved the vaginal atrophy, bone mineral density and porosity, level of 17ß-estradioland alkaline phosphatase activity in the OVX mice($p < 0.05$). In addition, PPE or Arg in the MCF-7 and MG-63 cells significantly increased the cell proliferation($p < 0.05$).However, not everything is known about the side effects

Placental extracts on wound healing process

Among overall 9 investigations contrary to the animal studies[13, 24-29], number of human studies[30, 31]where we can find an assessment of wound healing efficiency of PE were limited.

In one of them, Shukla et al.[30] found that during 8 weeks topical use of Placentrex can help to achieve 50% healing of wound compared to 23.3% in untreated group ($p<0.001$), with improvement of neoangiogenesis according microscopic angiogenesis grading system (MAGS) score. However were not assessed comorbidities of patients could be a limitation of this study.

Tiwary et al.[31] during comparison of therapeutic effect between placentalextract gel and placental cream on non-healing wounds indicated not statistically significant difference ($p=0.92$). Hence, 50% healing of wounds was registered after 8 weeks in 72% on group with administration placental gel compared to 75% placental cream group. However symptoms of pain and discomfort during dressing changes were less in placental extract cream group ($p<0.03$), which more preferable for topical use.

Among preclinical studies, Biswas et al.[25]in wound model on rats indicated that wound size ($p<0.05$), wound index ($p<0.05$), number of days for complete healing ($p<0.01$), gain in tensile strength ($p<0.01$) were significant decreased and tissue DNA, total protein, collagenesis were raised in HPE groups. Moreover, compared to topical use intramuscular injection (2.5 ml/kg) provided with high collagenous growth of wound.

According Hong et al.[26]diluted solution of HPE which was injected at 8 points along the boundary of the wound model of mice compared to control subjects accelerated decrease of wound size, also rise of transforming growth factor beta (TGF-ß) on the 6^{th} day and vascular endothelial growth factor (VEGF) on the 14^{th} day were statistically significant ($p<0.05$). Meanwhile increase of CD31+ level was statistically insignificant. Thus growth ofTGF-ß and VEGF during early and late period of healing process provided efficiency of HPE.

Singh et al.[28] after making in vitro and in vivo study found that administration of corticotropin releasing factor (CRF) which purified from human placental extract during the wound healing process can decrease level of TNF-α and IFN-ɤ. As a result, purified placental CRF had benefits on cell proliferation, apoptosis, wound healing.

Akela et al.[24] indicated enhanced effect of PE ointment with bone marrow cells in the autologous plasma compared to control and group which administrated buffy coat in the autologous plasmawith PE ointmenton rabbit wound model. This result was obtained during 30 days of macroscopically observed data were granulation, earlierdisappearanceofinflammatoryreaction,betterepithelialisation,significantlymaximum neovascularisation,fibroplasiasandcollagenationingroup which treated with combination of bone marrow cells+ autologous plasmawith PE ointment.

If several previous studies revealed administration of PE on cutaneous wounds, Nagata et al.[13] exhibited effectiveness of JBP485 (cyclo-trans-4-L-hydroxyprolyl-L-serine) is a dipeptide that was first isolated from Laennec (a purified hydrolysate from human placenta) on rabbit's corneal epithelial wound healing, hence JBP485promotes proliferation and migration of corneal epithelial cells (CECs) during 5 days treatment.

In another study, Nakamura et al.[32] also on rabbit model indicated efficiency of JBP485 in dry eye syndrome by acceleration of mucin and aqueous tear secretion in ocular surface epithelium compared to control .

Wu et al.[33] indicated wound healing effects of PPE on rats thermal injury model. Application of 30 mg ml PPE provided with growth of fibroblast growth factors (FGF) and transforming growth factors (TGF) compared to control group, which decrease a wound healing time by about 50%.

Kwon et al.[27] investigated dose-related positive effect of HPE on skin flap survival on rats model and comparison with control. Groups treated by HPE showed growth of vascularendothelial growth factor-positivecells, high level of glutathione peroxidase, lower level of lipid peroxidation and inhibition of apoptosis via lowering caspase-3 activity. Furthermore in group which received thehigher dosage(0.3 mL/d) of PE the flap areasurvivalratesweresignificantlyhigher, more VEGF-positivemicrovesselsoccurred compared to control, localized PE injection group and low dose of PE received group ($p<0.0083$).

PE in fatigue syndrome.

Totally four preclinical [34, 35] and clinical [14, 36] investigated an opportunity to use PE in fatigue syndrome.

Han et al.[34] on the mice model of protein-energy malnutrition compared effect of PPE and its amino acids (glutamic acid (GA), glycine, arginine and proline) to ameliorate fatigue symptoms after a forced swimming test (FST). Results has depicted that anti-fatigue activty of PPE related to inhibition the production of fatigue- related inflammaory cytokines,growth of the

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mRNA and protein expression of Ki-17 and by proliferation of splenocytes.Thus, here anti –fatigue activity of PPE and its constituents performed by enhancing immune responses through regulating T cells.

Moon at al.[35] also supported a main idea of previous investigation[34] and described anti- fatigue effects of PPE and its several amino acids on animal model (mice).During using FST teston mice its indicated that PE regulated the effects of interferon (IFN)-ɤand tumor necrosis factor (TNF)-α; GA regulated the effects of IFN--ɤ ; Gly and Arg regulated the effects of interleukin (IL)-6; and all of the amino acids present in PE regulated the effects of TNF-α.As determined from the serum after the TST: PE and Gly regulated the effects of TNF-α; Gly and Arg regulated the effects of IL-1ß; Gly, Pro, and Arg regulated the effects of IL-6; PE and all of the amino acids present in PE regulated the effects of TNF-α.

Efficiency of HPE was indicated in placebo- controlled study by Lee at al.[36]. Authors by using checklist of individual strength (CIS) found that administration Unicenta solution(HPE solution) (p=0.0002) or HPE(p=0.0001) showed statistically significant fatigue recovery compared to placebo group. By received results oral HPE was more preferable to improvement of fatigue. There were not differences of adverse effects between experimental and placebo groups.

On manifestation of chronic fatigue syndrome (CFS) in the investigation of Park et al[14] the positive effect of subcutaneous injection of HPE hydrolysiate (Laennec) was demonstrated by measuring fatigue severity scale (FSS), visual VAS scale and multidimensional fatigue inventory (MFI) between CFS group treted by HPE and placebo group. After 6 week treatment scores of FSS (p=0.0242), VAS (p=0.0009) and MFI (p=0.0159) significantly decreased in CFS compared to placebo group, which proved benefical effect from these injections.

Administration of PE on liver diseases

One study [37] out of six selected investigations related to liver pathology was clinical, whereas others were preclinical subjects[1, 4, 38-40].

Three investigation were devoted to non-alcoholic steatohepatitis (NASH) [37, 38, 40].

Choi et al.[37] during comparison the curative effect of HPE (Laennec) and the treatment with an active drug, liver extract and flavin adenine dinucleotide (LE–FAD) did not find any statistically significant difference between two treatment schemes for the management alcoholic steatogepatitis (ASH) and NASH due to an equal efficiency and a similar side effects (p>0.05).Thus, both HPE and LE–FAD decreased the levels of AST, ALT, TB, ALP, and γ-GTP during this study.

Yamauchi et al.[40] on NASH mice model with evaluation of liver fibrosis made an assessment of intramuscular administration 0.1 ml of Laennec(3.6 mg/kg) in comparison with control group. According to the results, HPE ameliorates NASH-associated pathologies by suppressing inflammation, oxidative stress and fibrosis. Another investigation of Yamauchi et al.[38] regarding mice model fibrosis in NASH showed dose- dependent efficiency of PE compared to control. The lowest dose of hPE (50.4 mg/kg) did not decrease fibrosis. The two high hPE doses (201.6 and 806.4 mg/ kg) displayed a tendency to reduce the fibrotic area, but it was statisticallyinsignificant.

During the study of regeneration process in carbon tetrachloride (CCL_4)- injured rat model Jung et al.[4] administrated 1 mg/ml N-hP (HPE, fresh without heatihg) or 1 mg/ml P-hP (HPE, with heating). Obtained results revealed N-hP and P-hP could improve CCL_4-injured liver compared to control group in vivo studies. In vitro study treatment with N-hP was more effective to promote proliferation CCL_4-injured rat hepatic cells compared to P-hP group (p<0.05).

Another work [1] which described mice liver injury (concanavalin A (Con A)-induced) model showed oral administration sheep placental extract (SPE) in different doses (0,5,10and50mg/kg)oramixtureofaminoacidsfor3daysbefore liver injury. Regarding the histological assay receiving SPE in different doses (0,5,10and50mg/kg) significantly ameliorated liver injury (p<0.05), however usage of amino acids +50 mg/kg SPE did not give significant curative result (p>0.05). Adminisration of SPE promoted antioxidative activity, reduced aminotransaminase activity and secretion of pro-inflammatory cytocines,also prevented growth level of nitric oxide, which will be beneficial in immune-mediated hepatitis.

In one study conducted by Kim et al. [39]enzymatic porcine placental extract (EPPE) was used to ameliorate acute alcohol toxicity on rats model. According to results EPPE in single different doses (0.5, 1.0, and 2,5 g/kg) could show a significant inhibitory effect on absorption of orally administered alcohol and prevented alcjhol poisoning compared to control subjects. Limitation of this study related to obtained results of administration single doses of EPPE acute alcohol toxicity which not suited in chronic alcohol toxicity and it requires further investigations.

Anti-inflammatory properties of PE

Sur et al.[41] made an investigation of anti-inflammatory (in rats model) and anti-platelet aggregation activity (clinical trial) of HPE. According to obtained results in study of anti-inflammatory activity intramuscular administration of HPE (300mg/kg) showed better results against edema compared to diclofenac received group (p<0.01). As for anti-plateletaggregationactivity HPE at all different doses (2.5,5,10,and20μL/mL) demonstrated highlysignificant efficiency (p<0.01).

Oral mucositis

5 selected articles regarding oral submucous fibrosis were clinical studies[42-46].

In investigation performed by Gupta et al.[42] curative effect of PE injections on oral submucous fibrosis (OSF) was not confirmed. Beneficial therapeutic result was obtained with a combination of dexamethasone+ chymotrypsin, +hyaluronidase,

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whereas single administration of PE did not have significant efficiency. Comparatively slightly effect from PE was when it was used in combination with dexamethasone.

Similarly, Kakar et al.[43]among four therapeutic regimens which were presented in study claimed a positive effect of single hyaluronidase administration for quicker improvement in OSFsymptoms or its combination with dexamethasone for achieving better longer-term results. However topical use of PE did not show significant efficiency.

Thakur et al.[44] prospectively compared therapeutic potency of topical application of PE gel with control group among patients who suffered from OSFon the postoperative fibrotomy wound with mouth opening less than 20mm. After topical application of PE during 4 weeks in this group were observed beneficial wound healing, better results in postoperative mouth opening ($p=0.0027$) in comparison with control group with statistical significance.

Interestingly, despite considerations of previous authors [42, 43], in the retrospective investigation of Shah et al.[45] administration of combination of PE + dexamethasone vs hyaluronic acid + dexamethasone during 8 weeks were equally effective among OSF patients regarding improvement of mouth opening and reduction ($p=0.0735$) of burning sensation ($p=0.759$).

Kondaveeti et al.[46] retrospectively investigated therapeutic benefit of Placentrex amid oral cancer patients suffered from acute chemo radiation induced mucositis. According obtained results oral cancer patients treated by combination concurrent chemoradiation with weekly Cisplatin+ received 2ml of Placentrex injection compared to control group who had received treatment prior to the study period without PE combination had beneficial curative effect ($p<0.05$).

Rhinitis

Two studies presented a data of therapeutic properties of PE against rhinitis wih different genesis[47, 48]. In one of preclinical study Kim et al.[47] on murine allergic rhinitis model investigated HPE efficiency which administrated in the periods before (pre-S) and after sensitization (post-C) with allergen (Derf) compared to control group received phosphate buffered saline (PBS). Prophylactic and therapeutic treatments adminisrtation of HPE significantlly decreased inflammation due to a rise of CD4+CD25+ Foxp3+T cells, level of Foxp3 mRNA ($p<0.05$) , also thanks to reduction eosinophil counts, GATA-3 and IL4 expression.

Jaswal et al.[21] in the clinical study compared therapeutic benefits of HPE (Placentrex) compared to control and rifampicin received groups. According to results rifampicin group had significant improvement in histological characteristics of mucosa , amelioration of fibrosis, vascularization recovery compared to submucosal injection of HPE. Moreover patients of HPE group had more rapid recurrence of rhinitis symptoms compared to group with rifampicin intake.

Osteoarthritis

During preclinical in vitro and in vivo study Kim et al.[49] found curable effect of HPE injection regarding cartilage degradation rat model compared to control group, hence 2 week administration of HPE showed significant inhibition of pro and active forms of Matrix metalloproteinase (MMP)-2, degradation in articular cartilage explants. Also reduced knee joint deformity.

Neuroinflammation

Parida et al. [6]observed suppressive effect against neuroinflammationin hippocampus toxic injury caused byBenzo[alpha]Pyrene (B[a]P) in rat model. According to results HPE +0.25μM B[a]P injection showed a decrease in theCytochrome P450 1A1 (CYP1A1) activity in the hippocampus compared to the 0.25μM B[a]P group. HPE in a role of anti-inflammatory agent in the hippocampus t can be used for therapy due to a modulation of the cytokine signaling.

PEusage on aging, memory loss and other neurological disorders

Antiaging properties of PE were described in two clinical studies[50, 51].

Lin et al. [50] found beneficial properties of 20070721GX (pig placental extract, royal jelly, avocado oil, and wheat germ oil) as a food supplement compared to placebo group in terms of rejuvenation and antiaging. Receiving 3 capsules of 20070721GX per day during the month provided with nearly 6-fold higher number of CD34 progenitor cells in peripheral blood ($p<0.001$), also telomerase activity was bigger to 30%($p=0.016$). However reduction level of IGF1 was not show statistical significance ($p=0.40$).

Kong et al.[51]investigated improvement of health status elderly people ≥65 years of age with administration subcutaneous injections of HPE (Laennec) for 8 weeks in comparison with placebo group. Regarding obtained results of Korean Health Status Measure for the Elderly questionnaire (KoHSME V1.0) in HPE group was observed statistically significant improvement on scales such as physical function ($p=0.007$), sexual life ($p=0.020$) and general heath perception($p=0.005$) after 8 weeks. Limitations of this study were small sample size and short duration of investigation.

Park et al.[53] on the model ofhypoxic-ischemic brain injury in neonatal rats investigated the neuroprotective properties of HPE (Laennec) regarding recovery of cognitive and behavioral function on injured brain. Pre-treatmentwith intraperitoneal administrationof 0.5 ml/10g/dose HPE demonstrated statistically significant neuroprotection compared to other groups (control, 0.1 ml/10g/dose HPE, 0.25 ml/10g/dose HPE), however post-treatment use of HPE did not show significant neuroprotective ability. Locomotor or exploratory activity which asssessed by open field test did not find significant difference between

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groups, however by morris water maze test HPE and sham group demonstrated shorter escape latencies thaan the no-treatment group ($p<0.05$).

Takuma et al. [54] investigated neuroprotective and cognition-enhancing effects oforally adminisrated PPE (120 and 2160 mg/kg) in the mice overectomized (OVX) model under chronic restraint stress (CS). In terms of results, compared to sham- operated and vehicle-treated groups treatment with PPE (120 and 2160 mg/kg)can attenuate neuronal loss of the hippocampal CA3 region and significantly ameliorated theOVX/CS-induced impairment of conditioned fear memory in mice.Also, both doses of PPE did not affect the decreases in uterine weightand bone mineral density.

Yamauchi et al. [55] found curable effect of new modified PPE (SD-F) regarding age-associated decrease in memory function in mice in a dose-dependent manner (500, 1,000, and 5,000mg/kg) compared to control. SD-F treated mice did not have significant changes in body weightin comparison to control group. SD-F significantly improved memory ability in the object recognition and object location tasks, also Nissl-positive cells in the hippocampal cornuammonis 3 (CA3) and dentate gyrus (DG) regions were raised. The efficacy of SD-F was slightly reduced in administration 5,000 mg/ kg compared to 1,000 mg/kg, also any adverseeffects were not observed

PE and pain syndrome

Kim et al. [56]showed the current protocol of probable efficiency HPE pharmacopuncture for chronic temporomandibular disorder in planned randomized controlled clinical trial. According to future trial scheme injection of 0.1ml of JHG002 to eight pain locations during 25 weeks will be compared to effect in physical therapy group.

In the preclinical study Gurgel et al.[57] investigated therapeutic effect of HPE in chemical and thermal nociception in mice by acetic acid and hot- plate test. In chemical nociception model using of HPE (200 and 400 mg/kg) led to decrease of abdominal writhes, also on dose 200 mg/kg HPE reinforced significantly antinociception produced by 1.25 mg/kg morphine. However in thermal nociception model an intraperitoneal administration of HPE did not show any significant analgesia, although co-administration of morphine and HPE (400 mg/kg) enhanced duration of morphine analgesia.

Radioprotective properties of PE

Mićić et al.[58] described clinical outcomes after instillations of early PE on patients with chronic cystitis due to irradiation therapy (cervical cancer). Compared to control group instillation of PE during the month demonstrated a significant improvement on the treatment of cystitis.

Kawakatsu et al. [59] in mice ɤ-ray radiation model used oral administration of PPE to study effect against radiation injury. Oral receiving PPE compared to placebo group significantly increased the number and colony-forming capacity, also reduced the DNA damage of bone marrow stem/progenitor cells and the levels of the inflammatory cytokines IL-6 and TNF-α in the plasmadue to anti-inflammatory activity.

Antitumorogenic characteristics of PE

Yamaguchi et al.[60] investigated efficiency of aspartic acid and glutamic acid (compounds of PE) for cell death of hepatocellular carcinoma (HCC) in vivo and in vitro study. In rabbit tumor model administration of high-dose of aspartic acid and glutamic acid (1.4 mg/kg Asp and 1.5 mg/kg Glu) showed a significant tumor inhibition effect only in combination with Lipiodol.

Melanocytes disorders

Therapeutic benefits of PE in Idiopathic GuttateHypomelanosis (IGH) were assessed by Gupta et al.[61]. Spot peeling with PE in combination with 88% phenol demonstrated non-significant difference in re-pigmentation of lesions ($p=0.8203$) compared to control group, treated with only 88% phenol and both group showed a similar better results, but is quite encouraging to use placental extracts as an adjuvant.

Allergic skin diseases

Kim et al.[62] in a mouse model of contact hypersensitivity (CHS) assessed of PE inhibition properties regarding CHS. Placental extract implantation after sensitization of allergic antigen (Ag)had positive therapeutic effect due to decreased numbers of $CD4^+$ T cells, tissue-infiltrating lymphocytes and preferential production of TH2-type cytokines. In addition cyclo-trans-4-L-hydroxyprolyl-L-serin dipeptide derived from PE was an important factor which ameliorated the severity of allergic CHS.

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Alopecia

According Kwon et al.[63]alopecia or human baldness on mice model can be treated with co administration HPE and minoxidil (MXD). Results revealed that due to hair growth-promoting activity combination of HP+ MXD during 21 days enhanced hair growth, formation of hair follicles ($P < 0.05$) compared to other comparison groups.

Immune-modulation characteristics of PE

Lee et al.[9] in a piglet model investigated immune modulation effect of PE-PBS80 (porcine placental extracts using PBS at 80°C) during an administration as a food supplement in doses 0.1%, 0.3%, and 0.5%for 3 week after weaning. In terms of results after usage of PE-PBS80 as a food supplement number of WBC and monocytes , T- and B-cell activation were increased ($P < 0.01$). Also administration of PE-PBS80 showed efficiency regardless viral infection increased ($P < 0.01$).Moreover, in the PE-PBS80 treatment the rate of granulocytes, interferon-γ, IL-1β, and IgGwere increased, especially in 0.3% concentration of PE-PBS80 compared to control and the other treatment groups, which showed immune modulation activity in early piglet period.

Anti-oxidative activities of PEduring toxic injury

Park et al.[3] indicated anti-oxidative and anti-inflammatory activities of PE in benzo[a] pyrene (BaP) exposed rat model. Pre- treatment with PE for 2 weeks before BaP exposure led to a significant decrease in the Olive Tailmoments compared to group without administration of PE. Moreover, pre-treatment with PE showed a significant reduction of pro-inflammatory cytokines such as TNF-α, IL-1ß and IL-6. By doing this pre-treatment with PE significantly ameliorates oxidative injury and immunotoxicity caused by BaP.

Zhang et al. [64] indicated curable effect of HPE in cyclophosphamide (CTX) –induced ovarian toxicity in the mice experimental model. Injection of HPE at different doses (2.4 ml/kg; 1.2 ml/kg 0.6 ml/kg during 28 days compared to control group animals (received 1.2 ml/kg phosphate buffered saline) ameliorated ovarian injury by protecting follicular granulosa cells from undergoing apoptosis and decrease atresia follicle formation(in a medium and high doses) ($p< 0.05$).

Samiei et al.[65] described a protective property of HPE in amiodarone- induced structural changes in the lung tissue. Results revealed that group treated by amiodarone in combination HPE compared to other studied groups could suppress changes in thickness and total volume of the alveolar septum increased after amiodarone administration and HPE.

Regeneration

Chang et al.[66] in rat model of study displayed that co-administration ofmineral trioxide aggregate (MTA) with HPE enhanced cell growth, differentiation and angiogenesis in human dental pulp cells (HDPCs). Pulp capping with HPE plus MTA showed superior results when compared to single administration of MTA. Hence, the combination of MTA+ HPE may be useful for regenerative endodontics.

Vitiligo

Majid [67] in the clinical study indicated a modest, however statistically insignificant effect of topical PE in a combination with narrowband UVB (NB-UVB) therapy of repigmentation in vitiligo. Hence, results of combination PE+ NB-UVB vs only NB-UVB were repigmentation 63% vs 62% respectively ($p>0.05$).

Pal et al.[68]in guinea pig vitiligo model demonstrated curable effect of hydroalcoholicHPE compared to control group due to ear pigmentation and hypertrophy of the experimental nipples to varying degrees. In another work Pal et al.[69] in vivo (mice model) found that application of HPE during 4 weeks led to development of new melanogenic centers and hair follicles, also in vitro experiment melanogenesis was induced.

Conclusion

Analysis of theselected studies in many cases prove the effectiveness of placental extract for various therapeutic purposes, however, many of them refer to non-clinical studies, which requires more in-depth studies for their introduction into clinical practice.

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References

[1] Liu, J., et al., The Protective Effect of Sheep Placental Extract on Concanavalin A-induced Liver Injury in Mice. Molecules, 2018. 24(1).

[2] Pogozhykh, O., et al., Placenta and Placental Derivatives in Regenerative Therapies: Experimental Studies, History, and Prospects. Stem Cells International, 2018. 2018.

[3] Park, S.Y., et al., Anti-oxidative and anti-inflammatory activities of placental extracts in benzo[a]pyrene-exposed rats. Placenta, 2010. 31(10): p. 873-9.

[4] Jung, J., et al., Placenta extract promote liver regeneration in CCl4-injured liver rat model. Int Immunopharmacol, 2011. 11(8): p. 976-84.

[5] Chakraborty, P.D., et al., Human aqueous placental extract as a wound healer. J Wound Care, 2009. 18(11): p. 462, 464-7.

[6] Parida, R., et al., Human placental extract ameliorates cytokine and cytokine receptor signaling in the rat hippocampus upon Benzo a Pyrene exposure. Journal of Chemical Neuroanatomy, 2019. 98: p. 8-16.

[7] Yamasaki, M., et al., Placental extracts induce the expression of antioxidant enzyme genes and suppress melanogenesis in B16 melanoma cells. Nat Prod Res, 2015. 29(22): p. 2103-6.

[8] Park, H.J., et al., Immune Modulation Effect of Pig Placenta Extracts in a Mouse Model: Putative Use as a Functional Food Supplement. Korean Journal for Food Science of Animal Resources, 2011. 31(5): p. 701-709.

[9] Lee, K.H., et al., Immune modulation effect of porcine placenta extracts in weaned the pig. J Anim Sci, 2013. 91(5): p. 2405-13.

[10] Nair, B. and A.R. Elmore, Final report on the safety assessment of human placental protein, hydrolyzed human placental protein, human placental enzymes, human placental lipids, human umbilical extract, placental protein, hydrolyzed placental protein, placental enzymes, placental lipids, and umbilical extract. Int J Toxicol, 2002. 21 Suppl 1: p. 81-91.

[11] Kong, M.H., et al., Effect of human placental extract on menopausal symptoms, fatigue, and risk factors for cardiovascular disease in middle-aged Korean women. Menopause, 2008. 15(2): p. 296-303.

[12] Kitanohara, M., et al., Effect of porcine placental extract on the mild menopausal symptoms of climacteric women. Climacteric, 2017. 20(2): p. 144-150.

[13] Nagata, M., et al., JBP485 promotes corneal epithelial wound healing. Scientific Reports, 2015. 5.

[14] Park, S.B., et al., Human Placental Extract as a Subcutaneous Injection Is Effective in Chronic Fatigue Syndrome: A Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study. Biol Pharm Bull, 2016. 39(5): p. 674-9.

[15] Higgins J, Green S. Cochrane Handbook for

[16] Systematic Reviews of Interventions Version 5.1.0. [updated March 2011]: The

[17] Cochrane Collaboration; 2011.

[18] Moher, D., et al., Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med, 2009. 151(4): p. 264-9, w64.

[19] Ouzzani, M., et al., Rayyan-a web and mobile app for systematic reviews. Syst Rev, 2016. 5(1): p. 210.

[20] Koike, K., et al., Efficacy of porcine placental extracts with hormone therapy for postmenopausal women with knee pain. Climacteric, 2012. 15(1): p. 30-5.

[21] Koike, K., et al., Efficacy of porcine placental extract on shoulder stiffness in climacteric women. Climacteric, 2013. 16(4): p. 447-52.

[22] Koike, K., et al., Efficacy of porcine placental extract on climacteric symptoms in peri- and postmenopausal women. Climacteric, 2013. 16(1): p. 28-35.

[23] Choi, S.J. and D.I. Kim, To evaluate the efficacy and safety of PLC in perimenopausal or postmenopausal women with Hot Flashes: study protocol for a randomized controlled trial. Trials, 2019. 20(1): p. 415.

[24] Yoshikawa, C., et al., Efficacy of porcine placental extract on wrinkle widths below the eye in climacteric women. Climacteric, 2014. 17(4): p. 370-6.

[25] Han, N.R., et al., Protective effect of porcine placenta in a menopausal ovariectomized mouse. Reproduction, 2015. 150(3): p. 173-81.

[26] Akela, A., et al., Autologous bone marrow-derived cells with placental extract for healing excisional cutaneous wounds in animal model. Int Wound J, 2013. 10(2): p. 167-76.

[27] Biswas, T.K., et al., Wound healing activity of human placental extracts in rats. Acta Pharmacol Sin, 2001. 22(12): p. 1113-6.

[28] Hong, J.W., et al., The effect of human placenta extract in a wound healing model. Ann Plast Surg, 2010. 65(1): p. 96-100.

[29] Kwon, J.W., et al., Effect of Human Placental Extract Treatment on Random-Pattern Skin Flap Survival in Rats. J Invest Surg, 2019. 32(4): p. 304-313.

[30] Singh, N. and D. Bhattacharyya, Biochemical and functional analysis of corticotropin releasing factor purified from an aqueous extract of human placenta used as wound healer. Journal of Pharmaceutical and Biomedical Analysis, 2017. 145: p. 298-306.

[31] Wu, C.H.J., et al., Effects of porcine placental extracts for wound healing of thermally-injured rats. Faseb Journal, 2001. 15(4): p. A79-A79.

[32] Shukla, V.K., et al., A trial to determine the role of placental extract in the treatment of chronic non-healing wounds. J Wound Care, 2004. 13(5): p. 177-9.

[33] Tiwary, S.K., et al., Effect of placental-extract gel and cream on non-healing wounds. J Wound Care, 2006. 15(7): p. 325-8.

[34] Nakamura, T., et al., JBP485 promotes tear and mucin secretion in ocular surface epithelia. Scientific Reports, 2015. 5.
[35] Wu, C.H., et al., Wound healing effects of porcine placental extracts on rats with thermal injury. Br J Dermatol, 2003. 148(2): p. 236-45.
[36] Han, N.R., et al., Porcine placenta mitigates protein-energy malnutrition-induced fatigue. Nutrition, 2013. 29(11-12): p. 1381-7.
[37] Moon, P.D., et al., Anti-fatigue effects of porcine placenta and its amino acids in a behavioral test on mice. Can J Physiol Pharmacol, 2014. 92(11): p. 937-44.
[38] 36. Lee, K.K., et al., Efficacy and safety of human placental extract solution on fatigue: a double-blind, randomized, placebo-controlled study. Evid Based Complement Alternat Med, 2012. 2012: p. 130875.
[39] 37. Choi, J.Y., et al., Efficacy and safety of human placental extract for alcoholic and nonalcoholic steatohepatitis: an open-label, randomized, comparative study. Biol Pharm Bull, 2014. 37(12): p. 1853-9.
[40] 38. Yamauchi, A., et al., Placental extract ameliorates liver fibrosis in a methionine- and choline-deficient diet-induced mouse model of non-alcoholic steatohepatitis. Biomedical Research-Tokyo, 2020. 41(1): p. 1-12.
[41] 39. Kim, H.J., et al., Effect of Single-Dose, Oral Enzymatic Porcine Placental Extract on Pharmacokinetics of Alcohol and Liver Function in Rats. Alcoholism-Clinical and Experimental Research, 2020. 44(5): p. 1018-1024.
[42] 40. Yamauchi, A., et al., Placental extract ameliorates non-alcoholic steatohepatitis (NASH) by exerting protective effects on endothelial cells. Heliyon, 2017. 3(9).
[43] 41. Sur, T.K., et al., Anti-inflammatory and anti-platelet aggregation activity of human placental extract. Acta Pharmacol Sin, 2003. 24(2): p. 187-92.
[44] 42. Gupta, D. and S.C. Sharma, Oral submucous fibrosis--a new treatment regimen. J Oral Maxillofac Surg, 1988. 46(10): p. 830-3.
[45] 43. Kakar, P.K., R.K. Puri, and V.P. Venkatachalam, Oral submucous fibrosis--treatment with hyalase. J Laryngol Otol, 1985. 99(1): p. 57-9.
[46] 44. Thakur, G., et al., Does Topical Application of Placental Extract Gel on Postoperative Fibrotomy Wound Improve Mouth Opening and Wound Healing in Patients With Oral Submucous Fibrosis? J Oral Maxillofac Surg, 2015. 73(7): p. 1439.e1-10.
[47] 45. Shah, P.H., et al., Comparison of Therapeutic Efficacy of Placental Extract with Dexamethasone and Hyaluronic Acid with Dexamethasone for Oral Submucous Fibrosis - A Retrospective Analysis. Journal of Clinical and Diagnostic Research, 2016. 10(10): p. ZC63-ZC66.
[48] 46. Kondaveeti, S.S., et al., Therapeutic Benefit of Placentrex in the Management of Acute Chemo Radiation Induced Mucositis in Oral Cancer Patients. Asian Pac J Cancer Prev, 2018. 19(11): p. 3099-3103.
[49] 47. Kim, B.Y., et al., Human placental extract reduces allergic inflammation in a murine allergic rhinitis model. Laryngoscope, 2014. 124(10): p. E399-404.
[50] 48. Jaswal, A., et al., Novel treatment of atrophic rhinitis: early results. Eur Arch Otorhinolaryngol, 2008. 265(10): p. 1211-7.
[51] 49. Kim, J.K., et al., Protective effects of human placenta extract on cartilage degradation in experimental osteoarthritis. Biol Pharm Bull, 2010. 33(6): p. 1004-10.
[52] 50. Lin, P.C., et al., Food supplement 20070721-GX may increase CD34+ stem cells and telomerase activity. J Biomed Biotechnol, 2012. 2012: p. 498051.
[53] 51. Kong, M. and S.B. Park, Effect of human placental extract on health status in elderly koreans. Evid Based Complement Alternat Med, 2012. 2012: p. 732915.
[54] 52. Lee, K.W., et al., Effects of Hominis placenta on LPS-induced cell toxicity in BV2 microglial cells. J Ethnopharmacol, 2013. 147(2): p. 286-92.
[55] 53. Choi, W.S., et al., Neuroprotective effect of human placental extract on hypoxic-ischemic brain injury in neonatal rats. Annals of Neurology, 2007. 62: p. S107-S107.
[56] 54. Takuma, K., et al., Placental Extract Improves Hippocampal Neuronal Loss and Fear Memory Impairment Resulting From Chronic Restraint Stress in Ovariectomized Mice. Journal of Pharmacological Sciences, 2012. 120(2): p. 89-97.
[57] 55. Yamauchi, A., et al., Porcine placental extract facilitates memory and learning in aged mice. Food Science & Nutrition, 2019. 7(9): p. 2995-3005.
[58] 56. Kim, J., et al., Efficacy, safety, and economic assessment of hominis placental pharmacopuncture for chronic temporomandibular disorder: a protocol for a multicentre randomised controlled trial. Trials, 2020. 21(1).
[59] 57. Gurgel, L.A., F.A. Santos, and V.S. Rao, Effects of human placental extract on chemical and thermal nociception in mice. Eur J Pain, 2000. 4(4): p. 403-8.
[60] 58. Mićić, S. and O. Genbacev, Post-irradiation cystitis improved by instillation of early placental extract in saline. Eur Urol, 1988. 14(4): p. 291-3.
[61] 59. Kawakatsu, M., et al., Placental extract protects bone marrow-derived stem/progenitor cells against radiation injury through anti-inflammatory activity. J Radiat Res, 2013. 54(2): p. 268-76.
[62] 60. Yamaguchi, Y., et al., Combination of aspartic acid and glutamic acid inhibits tumor cell proliferation. Biomedical Research-Tokyo, 2016. 37(2): p. 153-159.
[63] 61. Gupta, K., S. Tripathi, and M. Kaur, Evaluation of Placental Extracts as an Adjuvant Therapy to Phenol in Treatment of Idiopathic Guttate Hypomelanolsis. J Clin Diagn Res, 2016. 10(8): p. Wc01-3.
[64] 62. Kim, Y.S., et al., Preventive and therapeutic potential of placental extract in contact hypersensitivity. International Immunopharmacology, 2010. 10(10): p. 1177-1184.

ISSN- 2394-5125VOL 7, ISSUE 15, 2020

[65] 63. Kwon, T.R., et al., Potential synergistic effects of human placental extract and minoxidil on hair growth-promoting activity in C57BL/6J mice. Clin Exp Dermatol, 2015. 40(6): p. 672-81.
[66] 64. Zhang, B.F., et al., The role of AKT and FOXO3 in preventing ovarian toxicity induced by cyclophosphamide. PLoS One, 2018. 13(8): p. e0201136.
[67] 65. Samiei, F., et al., Human Placental Extract Ameliorates Structural Lung Changes Iinduced by Amiodarone in Rats. Iranian Journal of Pharmaceutical Research, 2016. 15: p. 75-82.
[68] 66. Chang, S.W., et al., Combined effects of mineral trioxide aggregate and human placental extract on rat pulp tissue and growth, differentiation and angiogenesis in human dental pulp cells. Acta Odontol Scand, 2016. 74(4): p. 298-306.
[69] 67. Majid, I., Topical placental extract: does it increase the efficacy of narrowband UVB therapy in vitiligo? Indian J Dermatol Venereol Leprol, 2010. 76(3): p. 254-8.
[70] 68. Pal, P., et al., Hydroalcoholic human placental extract: skin pigmenting activity and gross chemical composition. Int J Dermatol, 1995. 34(1): p. 61-6.
[71] 69. Pal, P., et al., A human placental extract: in vivo and in vitro assessments of its melanocyte growth and pigment-inducing activities. Int J Dermatol, 2002. 41(11): p. 760-7.
[72]

Figure 1 PRISMA flow chart for study selection.

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