HUMAN PLACENTA: POTENTIAL SOURCE OF BIOACTIVE COMPOUNDS

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Introduction:

Placenta is the organ that connects as well as separates the mother from fetus. Since antiquity, placenta has attracted attention of mankind. There is wealth of information about the placenta available in the printed literature and online via internet. Numbers of formulations containing human placental extract are in market at the same time, various studies on cosmetic applicability of placenta, pharmacological actions exhibited by placenta and placental drug transfer have been carried out. At the same there are some concerns addressing safety, blood borned diseases such as hepatitis and HIV, have been found and also the concern about the use of substances with estrogenic or other biological activity in cosmetic formulations (1, 2). Lot of work has been done on human placenta but major work is focused on transport of various drugs through placenta, still some aspects needed much investigation. It is, therefore, interesting to look at different kinds of studies reported on placenta. Taking into account the importance of placenta, in this review we have consolidated different aspects of human placenta.

Importance of placenta:

The term 'placenta' originates from the Latin word for '*flat cake*'. Functions of placenta can be roughly classified in to three such as production, exchange and protection. Human placenta functions as an important transport organ that mediates the exchange of nutrients and metabolites between maternal and fetal circulations. This function is made possible because of the expression of a multitude of transport proteins in the placental syncytiotrophoblast with differential localization in the maternal-facing brush border membrane versus the fetal-facing basal membrane (3). Placenta serves as the sole link between the mother and fetus. At the same time it has obligatory role in the growth and development of the fetus. Elimination of various metabolic waste products such as bilirubin from the fetus (4). Placenta secrets different important hormones like Human chorionic gonadotrophin (HCG), human placental lactogen, estrogens, the

anterior-pituitary-like hormone of the human placenta without these hormones pregnancy would not be possible (5). It exchanges water, nutrients, oxygen, water-soluble vitamins, free fatty acids, maternal steroid hormones, glucose, amino acids, fatty acids, minerals and carbon-di-oxide. Never the less, placental observation at the time of birth can give much indication relating to status of baby as well as mother.

Placenta is also responsible for transfer of various compounds and now a day's research is being focused on placental transfer of drugs to avoid adverse effects of various drugs. Pregnant mothers are exposed to a wide variety of foreign chemicals. This exposure is most commonly due to maternal medication, lifestyle factors, such as smoking, drug abuse, and alcohol consumption, or occupational and environmental sources. Foreign compounds may interfere with placental functions at many levels e.g. signaling, production and release of hormones and enzymes, transport of nutrients and waste products, implantation, cellular growth and maturation, and finally, at the terminal phase of placental life, i.e. delivery. Placental responses may also be due to pharmaco-/toxicodynamic responses to foreign chemicals, e.g. hypoxia. On the other hand, placental xenobiotic-metabolizing enzymes can detoxify or activate foreign chemicals, and transporters either enhance or prevent cellular accumulation and transfer across the placenta. The understanding of what xenobiotics do to the placenta and what the placenta does to the xenobiotics should provide the basis for the use of placenta as a tool to investigate and predict some aspects of developmental toxicity (6). On this background it is not surprise placenta has attracted attention of researchers worldwide to check various claims.

Composition of placenta:

Various reports investigate the nutrients and hormone levels in dry heated-human placenta and found that it composed of high protein content and minerals. It contains nutrients like fiber, protein, fat, ash, amino acids like aspartic acid, threonine, serine, glutamic acid, praline, glycine, alanine, cystine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, histidine, lysine, arginine, tryptophan. It also contains hormones like estradiol, progesterone, testosterone, growth hormone and minerals & vitamins like sodium, potassium, phosphorus, calcium, iron, magnesium, zinc, copper, manganese, vitamin (7, 8).

Uses of placenta:

Human placenta can be used for medical treatment, research and teaching. Now days, considerable research is being focused on placental as well as cord blood. Umbilical cord blood is used for transfusion and transplantation (9-11) but placental cotyledons are still being disposed which cost a lot of money and affect the environment. Since animals eat their own placentas for health, human placentas may be used as the nutritional resource for animals instead of being disposed as waste product (12-13). Amnion is useful in plastics and eye surgery. Umbilical cord blood and stem cell can be used for transfusion and transplantation in paediatrics and hematologic diseases. Umbilical vessels can also be used as a model to practice microsurgery.

However, placental cotyledons are still to be disposed. In most countries, including Thailand, burying and incinerating placenta is the common practice in disposal of this tissue waste. However, incineration causes air pollution and costs a lot of money (14). In literature different activities of human placental extracts were reported. Placental extract has a beneficial role to play as a topical agent in the management of chronic non-healing wounds (15). A purified peptide from the aqueous extract of human placenta can be used as wound healer (16). Human placental extract may be useful in suppressing inflammation and platelet aggregation (17). This extract also shows immuno-modulating potential in rabbit and human also (18). Hydro-alcoholic extract of human placenta have shown skin pigmenting activity (19). Internationally China, US have carried out much work in this area. Placenta is mainly reported for monoamine oxidase inhibitor (20), hypogalactia, urticarias, asthmatic bronchitis and oral mucositis (21-23). It also shows in vitro HIV inhibitory activity (24). Proteins isolated from placenta named as Calphobidin I, II & III has anticoagulant action (25).

Traditional Chinese Medicine and human placenta:

In traditional Chinese system of medicine, placenta has been given respectable position. It is observed that some animals including cows eat their own placentas after giving birth in order to be healthy. However, there is no record whether the human placentas can be eaten. We have heard that people in the northeastern part of Thailand eat cows' placenta with the belief that it is a good medicine. Traditional Chinese Medicine (TCM) experts claim the Chinese has eaten the human placenta for 2,500 years. There are many benefits to eating placenta and although it is not well documented in western society it is has been used as a medicine in China for many years. Ample of research papers in scientific journals validate traditional claims. Chinese believe it contains "Qi"(Chinese for life force) and use it as a remedy for a whole range of problems such as lethargy, rejuvenating ageing skin, hair tonic and promoting breast milk production, placenta facial, blood circulation and to make the body more resistant to disease. In fact, the placenta is quite sort after, being included in pharmacological preparations to treat infertility, chronic fatigue syndrome and a variety of other diseases. Placenta is bought from young, healthy women then tested and treated accordingly. It augments Qi (energy) and Xue (Blood) and therefore tonifies Yang, Yin and Jing (Vital Essence). Placenta (*Placenta Hominis)* is often included in traditional medicinal combinations with restorative functions. Mainly used after childbirth but also can be used after high stress or an extremely draining experience. In combination with other herbs placentas have been used to treat infertility and cancer. When consumed directly after childbirth it helps to contract the uterus. Amniotic membrane can be used for treatment of burns (26). In Singapore, human placenta from China is readily available in a dried form from Chinese medical halls. Demand for remedies such as human placentas, used to combat baldness, prescribed for epilepsy. Most of these claims are now scientifically evaluated and found effective. It improves wrinkles, restore hair growth and boost the immune system Traditional medicine is a holistic approach designed to maintain and restore health. However, the Food Drug Administration (FDA) in the United States classifies animal extract from organs such as placenta as potentially dangerous. Assays have not been carried out to determine the presence of viruses in animal materials from China. Concern

was raised about the possibility of human viruses in placental material from China. The processing of human placenta before it is shipped to the west includes boiling followed by baking, and the material that arrives is very dry, making it highly unlikely to contain any organisms that might have been originally present. The materials are further heated and dried by the grinding process used for making powders (for pills); alternatively, it is sterilized by boiling when the material is used in making a decoction. Small amounts of any residual viable virus would be very unlikely to cause disease when consumed orally. Nonetheless, the FDA has recently restricted use of human placenta because of their general rules-regarding potential contamination-for use of human substances in medicine.

Also blood from umbilical cord vessels and placenta following delivery has been found to be a rich source of haemopoietic stem cells, which can be collected and stored, in appropriate conditions for future use. Human placenta contributes to normal and abnormal pregnancy development. Human placenta serves as convenient source of homologous material, for diagnosis and therapy of inborn errors of metabolism. Other findings represent a novel source of human mast cells and, since placentas are readily available in quantity, such tissue is proposed as an ideal source of mast cells for biochemical and pharmacological use. The presence of moderate amounts of histamine in the human placenta was confirmed Light microscope studies of placental tissue stained with HRP-conjugated anti-human IgE demonstrated cells with a typical 'halo' effect indicating cell-bound IgE, and electron microscopy revealed cells containing membrane-bound electron dense granules. A single mast cell was calculated to contain approximately 1 pg of histamine. Enzymatic digestion of placental tissue with collagenase (1.5 mg/ml) yielded viable cell suspension containing mast cells in a purity of 0.6%, which exhibited a low spontaneous output of histamine (12%) (27).

Infants of pregnant women exposed to environmental lead and cadmium may experience adverse perinatal effects, such as decreased fetal growth and birth weight, congenital malformations, and preterm birth. A biological indicator that could monitor fetal exposures to these metals would be useful for identifying newborn children at risk for developing adverse health effects. The placenta cannot totally prevent the fetus from exposure to lead and cadmium; both metals, especially cadmium, accumulate in human placenta. Some authors have suggested that metal accumulation may interfere with the regulatory and nutritional functions of the placenta. This suggestion could be one of the reasons for adverse effects of heavy metals on the fetus. A reliable biological indicator for longer-term exposure is needed. Maria Falcon et al. examined the feasibility of using placenta to assess chronic metal exposure, because of that organ's accessibility and because it accumulates metals from the first three months of gestation (28).

In traditional Chinese and other medicinal systems placenta plays crucial role. In Indian medicinal system Ayurveda, *Susruta* have used placenta as criteria to classify animal kingdom e.g., man and other animals, who have placenta at the time of birth in one group and those do not having placenta in other group. Also some Ayurvedic physician recommends massage of newly born child with placenta in order to minimize unwanted hairs on hands and feet.

Different pharmacological activity of placental components:

Placenta as cosmetics on skin problems:

Human Placenta is a therapeutic agent with potent regenerating activities on skin. It rebuilds deteriorating cells and restores their youth. It pulls water out of dry desert air. This skin formula contains both, and ingredients to improve skin firmness and elasticity. It intensely moisturizes and revives skin and helps prevent the breakdown of Elastin, for firmer younger looking skin. Vitiligo is an acquired idiopathic depigmentary disorder, which, though worldwide in distribution, is very common in India, Egypt and other tropical countries (29). The authenticity of various prototype human placental extracts with biological activity, such as that inducing vitiligo repigmentation, is under serious criticism, mainly due to a lack of demonstration at the cellular level. Considering the present worldwide scenario with regard to the occurrence and treatment of vitiligo, a thorough scientific exploration of such extracts should be undertaken (30). Because of its enigmatic character, vitiligo is tricky to treat especially when the disease is in the active progressive stage (31, 32). The extract was found to be a potent mitogen in the *in vitro* condition and a potent melanogen in both the *in vitro* and *in vivo* situations. This strongly suggests its therapeutic potential for the repigmentation of vitiligo patch. There are several reports in which placenta plays pivotal role. Placenta due to its activity widely used in cosmetics and on skin problems (33) like psoriasis (34), urticariasis (35), and skin withering (36) placental extract also has proved melanocyte growth promoting activity (37). Some studies also reports that endothelins can be responsible for melanocyte growth promoting activity. The presence of keratinocyte growth-promoting activity in the placenta with distinctive properties suggests that this is a previously undescribed material with growth-promoting properties for epithelium (38). Placental extract injections had been used with success in case of loss of hair in women (39). These all reports suggest human placental extract has potential cosmetic applicability.

Placenta as wound healer:

Wound healing activity is another important facet of placenta. Amniotic membranes are used as biological dressing in treatment of thermal burns (40-45) and corneal ulcer (46, 47). Human placental extract that is used as a wound healer, acts as a stimulating agent for tissue repair. It has an effective inhibitory role on the growth of different microbes like bacteria, e.g. *Escherichia coli*, *Staphylococcus aureus* and fungi, e.g. *Saccharomyces cerevisiae*, *Kluyveromyces fragilis* and *Candida albicans*. It also prevents growth of clinically isolated bacteria, e.g. *E. coli* from urine and blood culture and *S. aureus* from pus. Various drug resistant strains of *E. coli* and *Pseudomonus aeruginosa* were also significantly inhibited by the extract. The extract has both bacteriostatic and fungistatic activities. Dose-dependent response of the extract was observed. Antimicrobial activity was retained after heating but was lost after dialysis. The MIC of the extract varies between 200 and 8000 mg/l. No antimicrobial activity was observed with human serum and aqueous extract of mouse muscle serving as control. According to some reports, mixture of polydeoxyribonucleotides (PDRN) appears to be

responsible for antimicrobial activity. Partial protection of the wound from secondary microbial infection is thus indicated (48).

In another study, a peptide of around 7.4 kDa has been purified from the aqueous extract of human placenta used as wound healer. Derived partial amino acid sequence from mass spectrometric analysis showed its homology with human fibronectin type III. Under nondenaturing condition, it formed aggregate, the elution pattern of which from reverse-phase HPLC was identical with that of fibronectin type III. Immuno-blot of the peptide with reference fibronectin type III-C showed strong cross reactivity. Since fibronectin type III plays important roles in wound healing, similar peptide in the extract is likely to take part in curing process (49).

Clinical studies were carried out, mainly in Switzerland and Italy, in order to show the healing activity of placenta. These studies included more than 250 patients with surgical wounds, varicose ulcers, fistulae or abscess. All the investigators emphasize the good results obtained, particularly in these cases where, in addition to local application of placental extract, the product was administered parentally. Wound healing activity may be due to antimicrobial activity of human placenta as well as cell growth promoting and pigment-inducing activities.

Placenta as immunomodulator:

A paradox about pregnancy is that the placenta, a semi-allograft of fetal tissue, avoids maternal immune rejection. Its importance is underscored by its location in the maternal-fetal interface, and it appears to act as a protection shield for the fetus. Fetal trophoblasts use several mechanisms to subvert normal maternal immune response. These include: a) selective expression of immune antigens critical to alloreactivity, such as expression of HLA-G by cytotrophoblasts, b) impaired responses to immune-activating cytokines present in placental tissue and c) secretion of factors which may suppress local immune responsiveness. Evidently, there is a bidirectional interaction between the maternal immune system and the feto-placental unit during pregnancy, with the placenta acting, not only as a sieve or a transport system, but also as an important source of immunomodulatory substances, such as Th2-cytokines, TGF and hormones (50). Placental immunomodulator ferritin, a novel immunoregulator, can be used for arthritis Human PLIF and C48 were shown to exert cross-species immunosuppressive activity *in vitro*. The *in vivo* suppression of articular inflammation in the experimental models of ZIA and AIA was the result of treatment with the anti-inflammatory human C48. These results suggest that treatment with C48 may offer an effective immunotherapeutic means of controlling inflammatory polyarthritis (51), and also affects cytokine-chemokine networks (52). According to some studies glycoshingolipids in placenta is responsible for modulation of T & B cell response. Leptin, the 16-kDa non-glycosylated protein product of the *ob* gene, is a hormone synthesized mainly in adipose cells to regulate weight control in a central manner, via its cognate receptor in the hypothalamus. Leptin can also be expressed at lower levels in other tissues, such as the placenta and stomach. In addition to the putative physiological role of leptin in the modulation of the immune

response, there is increasing evidence suggesting that leptin may have a role in some immunologically mediated pathophysiological conditions (53, 54).

Placenta as anti-inflammatory and anti platelet:

The HPE was studied for anti-inflammatory effect in Wistar rats on carrageenin, serotonin (5-HT), and prostaglandin E1 (PGE1) induced edema in acute model and cotton pellet induced granuloma on sub-acutemodel. Anti-platelet aggregation was studied against protection of adinosine diphosphate (ADP)-induced aggregation of human platelet through *in vitro* study. HPE showed positive results both in acute and sub-acute models of inflammation. Highly significant ($P<0.01$) results were obtained against 5-HT induced acute inflammation and cotton pellet induced sub-acute inflammation in comparison with standard (diclofenac sodium) and control (normal saline) drugs. The anti-inflammatory property of HPE in animal model was well supported with clinicalstudy of platelet aggregation. There was highly significant ($P<0.01$) inhibition of platelet aggregation with HPE atdifferent doses against ADP. Results from this study suggest that human placental extract may be useful in suppressing inflammation and platelet aggregation (55, 56).

Chart showing different constituents of human placenta and activities reported:

Sr. No	Activity	Ingredient	Reference
1	Melanogenesis inducing	Human placental lipid	58
2	Wound healer	Fibronectin Type III Like peptide, NADPH	59,60,61,62
3	Anti-inflammatory, anti-platelet aggregation	--	63,64
4	Antioxidant	L-tryptophan	65
5	Antinociceptive	--	66
6	Induction of nitric oxide	--	67
7	Treatment of oral mucositis	--	68
8	Vitiligo	--	69,70,71
9	Cell growth modulation	--	72,73,74
10	Increase in brain monoamines	--	75
11	Oral submucous fibrosis	--	76
12	periodontal disease	--	77
13	Rheumatic inflammation	--	78

Other diseases:

The parenteral administration of placenta for the treatment of gastric and duodenal ulcers was particularly investigated in Japan, where 14 studies were achieved. These studies were carried out on about 270 subjects. The efficiency of the treatment was found in 80% of the treated patients. These results were objective by 3 double blind studies and by numerous X-rays and endoscopic observations. The authors conclude that

placenta has proved to be one of the most effective drugs for the treatment of gastric and duodenal ulcers.

Twenty-five clinical investigations were done in Japan; among them, 5 were double blind studies. 825 patients suffering of gingivitis, pyorrhea alveolaris, aphtous stomatitis, periodontitis or arthritis of the jaw joint had been administered intramuscularly with placenta. In some cases of inflammatory diseases, the placental extract was successfully injected in the gum. The treatment was effective in more than 75% of the treated patients and it was concluded that placenta is a valuable drug clinically applicable in the odonto-stomatological field.

Human placental extract, an agent clinically used worldwide in a number of physiological anomalies, has been claimed to be effective in children of slow learners. The results showed that subchronic (5, 10, 15 or 20) administration of placental extract (2-4 ml/kg/day) had the effect of increasing all the monoamines and decreasing the MAO activity, which could be the possible mode of action of the extract in slow learners (57).

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