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## Article

# Organotherapy with Placenta: Past and Present

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**Abstract:** For several millennia, doctors and healers used therapeutic ingredients extracted from minerals, plants, and animals. Among the active remedies derived from animals, the placenta was among the most popular ones. The use of placenta-based remedies has retained its significance in our time. The placenta-based therapeutics are indicated for stimulating immunity, wound healing, reduction of skin pigmentation, treatment of various patients suffering from gynecological disorders, etc. By the beginning of the 21st century, the majority of specific functions and chemical ingredients of the placenta were identified and described. However, only now active proteins and peptides with molecular weight of about ten kDa were revealed. Presumably, they play an essential role during the therapeutic application of placental extract. Hopefully, this discovery will start a new era in the research and clinical application of organotherapeutic remedies, including placenta.

**Keywords:** organotherapy; placenta; peptides; nano-peptides; integrative medicine

## 1. Introduction

During ancient times, doctors and healers used plants, minerals, and animal or human origin products for therapy, prevention of diseases, and to increase life expectancy. Raw or prepared materials and extracts derived from animal organs were applied singly or as part of complex remedies. In the 19th century, this type of therapeutics got the name 'Opothrapy' in French or 'Organotherapy' in English (1894). [1]

Placenta, as a part of Organotherapy, played an essential role during the history of folk and state healthcare. In the *History of Medicine*, Le Clerk mentioned that the human placenta had been used at least since Hippocrates. In particular, he provided a list of simple ingredients written in French, including *Aristoloché*, *Armoise*, *Aromates en général*, *Arrière-fais d'une femme*, *Arroches*, *Asne*, etc. [2] '*Arrière-fais*' in French means '*After-birth*' in English. [3] Unfortunately, there are no references to the book of Hippocrates, where the therapeutic application of the placenta was mentioned.

## 2. Terminology

### 2.1. Initially, the term "Placenta" meant a "Pie" or "Cake"

In ancient writings, the well-known term "Placenta" meant a "flat cake" made of wheat flour mixed with additional ingredients. In the *Illustrated Companion to the Latin Dictionary and Greek Lexicon*, Placenta (πλακοῦς) is "A thin flat cake made of wheat flour, mixed with cheese and honey, but of considerable size, so that it would cut up into a number of separate pieces, for each of the guests present" (1849). [4]

### 2.2. In anatomy or medicine, the term "Secundina" was used instead of "Placenta"

In the old days, when they mentioned the placenta in the modern anatomical or physiological sense, they used the term – '*Secundine*,' '*Secundæ*' (pl), for example, in the book *Aristotle's compleat and experienc'd midwife*, edited by William Salmon, it is written: "Setting aside the name given to this by the Greeks and Latins, it is called in English by the name of Secundine, After-Birth, and After-Burden; which are held to be four in number. 1. The first is called Placentia, because it resembles the form of

Cake ... 2. The second is Chorion: this skin, and that called the Amnion, involve the Child round both above and underneath ... 3. The third thing which makes up the Secundine is the Alantois, of which is a great dispute amongst Anatomists ... 4. The fourth and last covering of the Child is called Amnios ... (1700). [5] In a *New English-Latin Dictionary*, the 'after-birth' was translated as '*Secundinæ*,' '*Secundæ*' (pl), (1783). [6]

### 2.3. Anatomical and medical application of the term "Placenta" began in the 16th century

They began to use the term "Placenta" in books on anatomy or physiology in the 16th century. In the *Lessons on Antiques* (1516), an Italian philologist Luigi Richieri Rhodiginus, analyzed and explained various old terms. He gave examples when the term 'placenta' was used dealing with the various cakes, like *Sesamo Placenta est* {p. 240}; *pacto a Placenta* {241}; *Nam placenta crepidam* {710}. But in the chapter dealing with the terms relevant to the navel and umbilical cord, he used the word 'placentæ' as an anatomical term: "*Nā Epomphalium est quod Vmbilico incumbit, Mesophali uero sunt Placentæ quædā*" {413}. [7]

In the *Anatomy of Humane Bodies Epitomized* (1697), Thomas Gibson used several terms for placenta: "Upon the cutting open the Womb of a Woman with Child, the first thing that offers itself is the *Placenta uterina*, or Womb-cake, otherwise called *Hepar uterinum*, or Womb-liver, from the likeness of substance, and also use, according to those that imposed the name... It was an old tradition continued for many hundred years, that the Placenta adheres to the Womb by certain parts called *Cotyledones* or *Acetabula*. [8]

In the *Dictionary of Medical Science* (1874), there are examples of the terms used in the literature to mention Placenta or Secundine, in English: "Secundines, *Hystera*, *Deuter'ion*, *Metra*, *Secundæ*, *Secundinæ*, *Afterbirth*, *Afterburden*. It means all that remains in the uterus after the birth of the child – viz., the placenta, a portion of the umbilical cord, and the membrane of the ovum. These are commonly not expelled till some time after the birth of the foetus; hence their name". [3]

In Chinese language there are several terms that correspond to the placenta, including *Zǐ hé chē* (紫河车 / 紫河車), *Zǐ hé zhī* (紫河肢), *Hòu rén* (後人), *Tāi yī* (胎衣), *Bāo yī* (胞衣).[9] However, in some regions of China, the term *Zǐ hé chē* (紫河车 / 紫河車) may mean a herb *Paris Polyphylla* Fr. [10]

Thus, the terms used to refer to the placenta in an anatomical or physiological sense include, *in Chinese*: *Zǐ hé chē* (紫河车 / 紫河車), *Zǐ hé zhī* (紫河肢), *Hòu rén* (後人), *Tāi yī* (胎衣), *Bāo yī* (胞衣); *in English*: placenta, secundine, after-birth, after-burden, sugar-cake, placenta uteri, womb-cake; *hepar uteri*, womb-liver; *in French*: l'arrière-faix, carpelle, cotylédon, délivre, secundijne, secundyne; *in German*: die Nach-geburt, Wisorax, Mutterkuchen, Nachgeburt; *in Greek*: πλακούντας, ύστερο; *in Latin*: secundas, secundinas, secundinæ, secundinarum, secundines, membrana partus (membrane delivery), placenta uteri, epar uterinum, etc. [5-11] In old books a long 's' letter [f] could be used instead of a standard 's', for example, *secundine*, *secundas*. [12]

### 2.4. The term "Placenta" in botany

The term "Placenta" (Placentas, or Placentae, pl) in botany means the surface of the carpel (highly modified leaf) to which the ovules (potential seeds) are attached. For better understanding this term in the Botany one can read the following excerpt: "When tomatoes were first cultivated in our gardens there was but one variety; this had a large, red, much wrinkled, and often irregular and misshapen fruit, with a thick outer wall, and a central placenta bearing the seeds surrounded by their pulp, and a considerable cavity or empty space between the two". [13]

## 3. Historical review of the medical application of the placenta

### 3.1. Medical application of the placenta in the first centuries of the first millennium AD

In the Ancient Encyclopedia known as the *Natural History* compiled by Pliny, the elder (*Caius Plinius Secundus*, AD 23-79) in the first century, several books were devoted to therapeutic remedies made from ingredients obtained from minerals, plants, animals, and human. [14] There are also

recommendations on how to use she-ass placenta to prevent and treat epileptic seizures, plus sheep and goat placenta for treatment of female complaints and diseases. For example, "the membrane in which the kid (of goat) is enclosed in the uterus, dried and taken in wine, acts as an expellent upon the after-birth"; [15] "for diseases incident to females, a ewe's placenta is very useful, as already mentioned by us, when speaking of goats" [16]. Presumably, the oldest copy of the *Natural History* by Pliny available nowadays on the Internet, where the cited text could be found, was published in 1459. [17]

About three centuries after Pliny, the elder, Dr. Sextus Placitus wrote a book *Drugs derived from the animal kingdom*. In chapter 5 on Goats at the 29th note, Dr. Sextus Placitus recommended the usage of goat placenta with wine to expel the placenta. [18]

### 3.2. Therapeutic application of placenta in the XVI-XVIII centuries

Animal or human placentas were common remedies in medical practice during the Middle Ages and later. Dr. Varignana Guilielmo recommended using a prepared human placenta to expel stones from the kidney and urine bladder (1522). [19] Dr. Joseph Du Chesne applied extracts from the womb of a hare and human placenta to treat female infertility (1615). [20] In the book *Harvest of Innovative Medicine*, by Dr. Jean-Jacques Manget, it is written about application of cat and deer placentas, and also human placenta and umbilical cord (1683). [21]

During the 16th to 18th centuries, hundreds of books on internal medicine and pharmacology were published where the placenta was mentioned as a therapeutic remedy. One of the most comprehensive descriptions of the medical application of the placenta was found in the *Opera Omnia* or *The works of Johann Schröder, Pierre Morell, and Daniel Ludwig* (1728). An author, Michael Ettmüller, collected information about therapeutic remedies from books of various famous predecessors. [22] The main symptoms requiring the use of placenta from various origins were female complaints and diseases, kidney and urine bladder stones, general weakness, epilepsy and melancholy, and also to stimulate libido and fertility, as anthelmintic medicine, and other diseases. Generally, the placenta was used after special preparation – it was soaked in wine, dried, and pulverized.

### 3.3. Therapeutic application of placenta in Traditional Chinese Medicine (TCM)

Presumably, the first mention of the use of the placenta for therapeutic purposes in Chinese medicine was in the book *Precious Prescriptions for Emergencies* (Bèi jí qiānjīn yào fāng) by Dr. Sun Simiao (孫思邈, 581-682). In the 15th volume devoted to eye diseases, Dr. Sun Simiao described the preparation of the eye wash medicine from a dried human placenta. [23]

The following famous book which included human placenta as a therapeutic remedy was *Gleanings from the Materia Medica* (Běncǎo Shíyí) by Dr. Chén Cáng-Qi (陳藏器, 687-757). He recommended a complex prescription that included powder of dried human placenta (紫河车) and various plants like *Phellodendron*, *Eucommia*, *Rehmannia*, *angelica sinensis*, etc. The main effect of this prescription is to invigorate Qi and nourish the blood. [24]

In the 16th century, various aspects of different medical remedies, including the human placenta, were described in *Compendium of Materia Medica* (Běncǎo gāngmù) by Dr. Li Shi Zhen (李時珍, 1518-1593). [25]

In the mid-19th century, several articles in European journals reported on TCM medicines, including information about human placenta application. One of the examples was a particular remedy that strengthened kidneys and testes: a mixture of extracts from stag horns, dog flesh, a species of fern, walnuts, and dried human placenta, etc. [26]

In 1902, a book on TCM published in Europe wrote: "If a woman who delivered a baby had chlorose (anemia) she was prescribed a remedy from the dried placenta." [27]

According to TCM view, the placenta has sweet and salty tastes and warm properties and enters channels of the Liver, Lung, and Kidney. The main effects of the placenta are to warm the Kidney yang, stimulate the Lung and Kidney qi, and nourish the blood and essence. [28]

### 3.4. Therapeutic application of placenta in the Middle East

In the book on Persian Pharmacology published in the Latin language in Europe, three complex prescriptions included camel placenta (1681). [29]

# 932. The prescription 'Lebovb Kebir' was designed by a Persian physician. This medicine included pistachios, acorns, walnuts, asparagus seeds, peppermint herb, . . . and camel placenta. There were around fifty various ingredients in total. The effect of this medicine is to warm and strengthen the Kidneys and Stomach, increase fertility, strengthen muscles, etc.

# 994. The prescription 'Magi-Oun Foulad' was designed by an Indian physician and adapted to Persian medicine. Besides various herbal ingredients, it included camel placenta.

# 999. The prescription 'Magi-Oun Chovb Chini' was designed in China and adapted to Persian medicine by the local doctor. This medicine increased male power, supported the stomach, heart, and brain, and strengthened muscles. One of the ingredients was camel placenta.

### 3.5. Common recommendations from the Old Books

There were many medical books that recommended recipes that included the placenta of humans or various animals. Here are some of them, published in English:

The book "*Pharmacopœia Bateana*" (1694) by Doctor William Salmon included a section "XCIV. *Secundinæ Preparatæ*, the Secundines or After-birth prepared" where it is written:

Bate.] R: The Secundine of Woman, or of a Sow, at its time of bringing forth; wash it in White-wine; dry it as speedily as may be, and reduce it into a fine Pouder, S.A. Dose is ad ʒj. against the Falling-sickness and Suffocation of the Womb: it also facilitates the Birth in time of Travel, &c."

Salmon.] § 1. After it is washt in White Wine, it will be best to cut it into small pieces, for by that means it will the more easily dry, and be made fit to reduce into Pouder.

§ 2. But that it might the more speedily be reduced, it will be best after the washing it with Wine, and drying it with Cloths, to wash it in the best rectified S.V. and then let it dry of its own accord, and being dried to dip it in again, and let it dry again, and this work to reiterate four or five times; for by this means the Fire, or Sulphur of the S.V. will more effectively dry it in one Day, than by the other it will be dried in a Week; and so it will be much more easily reduced to a Pouder.

§ 3. The Author has shown you its Vertues, for which it is excellent, but the Dose is too small upon some occasions. It may be given à ʒij ad ʒij, in some proper Vehicle: But Note, the Afterburden of a Woman much exceeds, and is more Specific than that of a Beast (1694). [30]

"*The Receipts of the famous John Moncrief of Tippermalloch*" (1716) had the following prescription in the case of female infertility: "*Of Barrenness*. The After-Birth of a Woman is believed to be of great Efficacy, being dried and powdered, and taken to the quantity of a Dram". [31]

In 1762, Dr. Nicholas Culpeper recommended the human placenta in case of difficult childbirth: " ... some prepare the Secundine thus: take the Navel-string and dry it in an Oven. Take two Drams of the Powder, Cinnamon, a Dram, Saffron, half a Scruple, with the juice of Savin, make Troches, give two Drams, or wash the Secundine in Wine, and bake it in a Pot, then wash in Endive-water and Wine, take half a Dram of it, Long-pepper, Galangal, each half a Dram, Plantain, and Endive-seed, each a Dram and half, Lavender-seed, four Ounces". [32]

### 3.6. Folk traditions regarding the placenta after childbirth

To this day, stories about the local traditions of various tribes have survived, according to which the human placenta had a symbolic or healing effect. For example, German traveler and naturalist Johann G. Gmelin visited the Siberian lands of the Russian Empire in 1733-1743 and reported that Jakut and Tungus people had a fascinating tradition. After the birth of a child, the placenta was given to the child's father, who, after cooking the placenta, invited friends and relatives to eat it together as a celebration of the new birth. [33]

There is also a folk prescription from the Caribbean nations: "Take the sun-dried placenta and soak it in water. Then, use the water to wash the eyes in the case of ophthalmic problems in children". [34]



#### 4. Revival of therapeutic application of placenta in the early 20th century

As mentioned above, animal or human-origin placenta was quite popular among physicians before the end of the 18th century. However, in the 19th century, doctors suddenly fell silent and stopped discussing animal-origin medications, including human or animal placenta.

In 1889, Dr. C.-É. Brown-Séquard reported his trial on subcutaneous injections of a liquid obtained from the testicles of young dogs. [35] After this successful trial, animal-origin medications, called Organotherapy, were revived and used widely by classic medicine again. [36]

In April 1898, at the 4th French Congress on Internal Medicine (Montpellier), Dr. Henry Iscovesco reported on the successful use of the fresh ewe's placenta in the cases of chronic metritis. [37] In 1902, British Medical Journal published an article about a trial of Dr. Leon Bouchacourt, who used sheep placenta pills in treating 10 cases of metritis, uterine subinvolution, and as a galactagogue. The same article described placentophagia among animals and humans and the history of placenta application in classic medicine. [38] Shortly after these reports, various forms of therapeutics containing the placenta became popular among physicians again. [39]

#### 5. Discovery of the endocrine function of the placenta

In ancient times, Aristotle (384-322 BC) and Hippocrates (460-357 BC) assumed that a foetus breathed and was nourished through the umbilical cord and placenta. Therefore, the placenta performed the functions both of the lung and intestine. [40]

Giovanni Battista Ercolani (1819-1883) was the first among 'modern doctors' who supposed that the placenta had an endocrine function. In his book, published in 1869, he described glandular structures of the placenta belonging to various animals. [41] A similar idea about the endocrine function of the placenta was later suggested by Dr. L. Nattan-Larrier (1900) [42] and Dr. Josef von Halban (1904). [43]

In 1913 the endocrine function of the placenta was proven with experiments conducted by Dr. B. Aschner. He injected ovarian and placental extracts into guinea pigs subcutaneously and observed stimulation of milk secretion, hyperemia of the genitalia, and haemorrhagia from the uterus of the guinea pigs. Placental extract generated a more impactful response in the guinea pig's body than extract prepared from the ovary. [44]

#### 6. Therapeutic application of Placenta as a part of Organotherapy

Organotherapy is a treatment of disease using medicines prepared from the organs of the lower animals, chiefly the ox and the sheep. [45] Placenta was one of the ingredients used in Organotherapy. [39] Usually, the placenta of sheep or cows was used in a form of powder, tablets, or liquid extracts.

##### 6.1. Main indications for placental Organotherapy in the 20th century

The main therapeutic indications of placental Organotherapy were agalactia, pernicious vomiting during pregnancy, weakness after labor, and prevention of atrophy of the uterine walls after ovariectomy. Combining the placenta with mammary and pituitary glands was a common strategy. [46]

In the book *Treatise on Organotherapy and Pluriglandular therapy* (1921), there is a brief description of the placental product:

"*Source and Parts Used.* The placenta of sheep and cows is chiefly used. One part of the desiccated parenchyma of the placenta represents about six parts of the fresh gland.

*Therapeutic Indication.* Extract of the parenchyma of the placenta is used to cause an increase in the production of milk. This product has given satisfaction in the treatment of fibroma and carcinoma of the uterus, menorrhagia, dysmenorrhea, enlarged and sensitive uterus. It is recommended to prevent atrophy of the generative organs after ovariectomy, chronic metritis and infections after labor. *Synergistics.* Mammary gland, pituitary total. *Dose.* Three to nine grains, four times per day, between meals. Tablets of three grains". [47]

A book on internal secretion *The Endocrines* (1921), contains many cases of successful application of animal-origin therapeutics, including extract of placenta. [48] The author of the book, Dr. Samuel W. Bandler, explained the application of organ-specific extracts based on the physiological relation between the uterus, ovary, placenta, and pituitary gland. In the case of premenstrual syndrome and small fibroid in the uterus, he used extracts of placenta and thyroid [49], and in the case of fibroids of the uteri, he used extracts of placenta, thyroid, and ovary. [50]

Subsequently, the placental extract was used in cases of various diseases, such as psoriasis, [51] rheumatoid arthritis, [52] multiple sclerosis, [53] chronic fatigue syndrome, [54] etc.

From the modern analysis of more than 3,500 publications dealing with the therapeutic application of placental extracts, all works could be divided into six groups:

- 36 % - stimulating or balancing immunity;
- 33 % - application for wound healing;
- 10 % - neurotrophic effect;
- 8 % - normalization of the skin pigmentation;
- 8 % - hepatoprotective effect;
- 5 % - using placental extracts in gynecological patients and obstetrics groups. [54]

## 6.2. Immuno-stimulating and anti-tumor effects of placenta

The immuno-stimulating effect has been reported in most studies (36%). The initial experiments in this field were carried out at the beginning of the 20th century.

In 1908-1909, Dr. G. Fichera used a product obtained by hydrolysis of the human placenta and foetus and reported the disappearance or reduction in the size of malignant tumors in the patient. [56] Dr. S. Higuchi demonstrated in experiments on animals a high degree of immunity induced by treatment with mouse placenta, a lower degree of immunity with mouse blood, and an absence of immunity after treatment with other rat tissues (1913). [57] Drs. J. O. W. Barratt and A. J. Gelairé discovered in the experiments regression of implanted carcinoma after injection of pulped mouse foetus and placenta (1913). [58] Dr. S. Itami reported the results of his research dealing with mesodermal derivatives to immunize mice against transplantable tumors. He proved that a whole embryo of a mouse, mouse fetal skin, liver, mamma, spleen (containing blood), blood, testis, kidney, lymph nodes, and mouse placenta (washed free of blood) had immunization against transplantable carcinoma; at the same time the lens, brain, cartilage, bone or muscle had no effects of immunization (1919). [59]

In the 1930s to 1940s, Dr. Emanuel Revici revealed the relation of pain and other symptoms to the pH (acid or alkaline) in the diseased area and urine. [60] He also explained that the application of placental extract in a group of patients with the same diagnoses, the effect of therapy could be positive or negative. So, in the group of patients with incurable cancer, Dr. Revici recommended using placental extract only in the case of acid urine. [61]

From the 1970s to the 1990s, Dr. Valentin Govallo used immuno-therapy with placental extract to treat cancer. [62] In 1974, a clinical trial group of 45 patients with various advanced cancers received immuno-therapy with placenta extract. In 1997, 29 out of 45 patients were still alive. Therefore, the 20-year survival rate was 64.4%. [63]

According to the patent granted in Taiwan in 2009, a fraction of mammal placental extract that includes a peptide with a molecular weight of less than three kDa had antitumor activity. [64]

In 2012, a report stated that placental extracts added to tumor cells would induce tumor cell differentiation *in vitro*. This effect was not dependent on the species of mammals used as the source of the placenta. Administration of placental extracts inhibited tumor growth and metastasis *in vitro* and *in vivo*. So, the concept of non-toxic biological therapy of cancer through the induction of tumor cell differentiation has obtained a scientific basis. [65]

## 6.3. Discovery of wound healing and regeneration effects by Dr. V. P. Filatov

Revival of therapeutic application of placenta for wound healing occurred in the 1940s to 1950s following the clinical trials of Vladimir P. Filatov, a surgeon, and ophthalmologist from Odessa (the

Soviet Union). At the beginning of the 1930s, Dr. V. P. Filatov performed transplantation of cornea tissue taken from the human cadaver and received optimistic results. [66] In order to accelerate the process of regeneration and stimulate wound healing, Dr. Filatov used various types of preserved tissue and pieces of placenta, or placental extract. A new method of stimulation and rejuvenation gained the name '*Tissue Therapy*.' [67]

#### 6.4. Efficacy of Placenta as a Galactagogue

Stimulation of lactation using the placenta has been reported by many doctors. [68-70] On the 6th of October 1915, at the meeting of the Tri-State Medical Society, Bertha Van Hoosen, from Chicago, shared her results of the application of dried placenta by women just after labor. Her presentation included the following story: "... The first report of our results came as a complaint from the nurses. They requested that the dosage (of the placenta) be cut down because the patient had so much milk that it was a burden to keep the breasts empty". [71]

In another research carried out in Los Angeles County Hospital, a group of healthy women ingested 0.6 g of desiccated placenta three times daily, commencing from the day of delivery. The diet was the same throughout the study for all the women in the trial and control groups. Quantitatively, the production level for lactose and protein had been raised while that for fat had been decreased slightly. [72]

The maternal ingestion of desiccated placenta also increased the growth and growth capacity of the breastfed infants above the usual occurrence. This effect was assumed to be due to the presence of unidentified growth-promoting substances in the placenta. [73]

Functional uterine bleeding was another gynecological disorder treated successfully using placenta extract. [74]

### 7. Development of a scientific basis for modern Organotherapy with the placenta

Throughout the centuries, doctors used the concept of "organ-specific remedies" to treat various diseased organs. It was widely known amongst physicians that the "brain helps the brain, and lungs heal the lungs," and so on. [75] This empiric idea was practical but quite far off from the scientific approach.

With the development of new laboratory diagnostic methods, finding a scientific explanation and objective confirmation of the previously used empiric Organotherapy became possible.

In the research published by Belonovsky and Miller (1928), extracts prepared from the various animal organs being injected into the experimental animals were accumulated mainly in the similar organs of the animals. This selective accumulation of the organ-specific substance called "organotaxis" was confirmed by adding dyes to organ-specific extracts. [76]

In 1955, it was proven by isotopes that after injections of extract prepared from a specific animal organ, its ingredients would mainly be spread in the target organ. [77]

In 1957, it was revealed that affinity between similar types of cells originating from various species was better than between different types of cells originating from the same species. For example, it was reported that "in the course of tissue reconstruction, the dissociated embryonic cells became grouped preferentially, according to their original type identities, regardless of their generic origin." [78]

In 2009, a new membrane-protective peptide was isolated from tissue of pigmented epithelium of bovine eyes. This peptide had a molecular weight of 4.372 kilo Dalton (kDa). The membrane-protective effect was observed at a concentration of 10-17 mg/mL. [79] In 2018, small biologically active peptides were isolated from the testicle tissue of cattle. These peptides increased the motility of human spermatozoa *in vitro* by 50-70%, and this effect persisted for several hours. A mixture of peptides included molecules with a molecular weight from 1 to 10 kDa and around 66 kDa; the concentration of active peptides varied from 10-8 to 10-15 mg/ml. [80] Biologically active peptides were isolated from the bovine ovarian tissue in another study. They improved the viability and maturation of follicles in ovarian tissue *in vitro*. A mixture of peptides included molecules with a molecular weight from 0.8 to 6 kDa and around 67 kDa; the concentration of peptides was 10-9 mg/ml. [81]



In 2019, a series of studies was carried out in the LC-MS/MS laboratory of the Jeffrey Cheah School of Medicine & Health Sciences, Monash University, Kuala Lumpur, Malaysia. The following results were obtained: the peptide content in the extracts of "rabbit placenta 1" and "rabbit placenta 2" were 89.42 and 96.08 mμ/1 mL, respectively; the peptide content in the extract of rabbit kidney was 114.53 mμ/1 mL; the peptide content in the extract of rabbit brain was 130.93 mμ/1 mL; the peptide content in the mixture of the extracts obtained from rabbit placenta and mesenchyme (called 'APR') was 102.25 mμ/1 mL; the peptide content in the mixture of the extracts obtained from rabbit kidney, placenta, liver, pancreas, spleen, stomach and intestinal mucosa, mesenchyme, smooth muscle, and nerves was 119.71 mμ/1 mL, and so on. [82-83]

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was applied to determine the molecular weight of peptides contained in the extracts of rabbit skin, mesenchyme, and the mixture of extracts of rabbit placenta and rabbit mesenchyme. The performed analysis has confirmed that all peptides had molecular weights of around ten kDa and less. [84]

Identifying proteins from a sample called 'APR' was performed using Liquid chromatography-mass spectrometry (LCMS-MS) [PEAKS Studio 7.0, Bioinformatics Solution Inc., Waterloo, ON, Canada]. LCMS-MS test revealed the following proteins and peptides: *Profilin* (10607 Da), *Acyl-CoA-binding protein* (9915 Da), *Small Muscle Protein X-linked Protein* (9397 Da), *Ubiquitin* (9397 Da), and *Thymosin beta-4* (5037 Da), etc. [85]

## 8. Practical application of Organotherapy with the placenta

Since ancient times, doctors have used the classic approach to selecting and prescribing various therapeutics. It had a foundation on the knowledge, experience, and clinical trials that lasted decades or hundreds of years. In each case, the doctor determined the etiology and pathogenesis of the disease and selected the most appropriate treatment. So, the classic treatment scheme meant that each protocol was tailored to one patient. With the accumulation of knowledge and experience of the particular doctor, his treatment's effectiveness increased, which depended on his hard work and talent. Nowadays, this medical practice sometimes falls into the "off-label" treatment category. The weakest points of this approach are the knowledge and experience of each practice doctor.

About 200 years ago, homeopathic physicians designed a new approach to clinical trials to test their remedies. They conducted multicenter trials where large groups of volunteers were involved. According to a historical document, Dr. Rudolf Virchow, the father of modern Pathology, criticized this new approach to the clinical trial. He insisted that despite certain similarities in pathology discovered in different patients with a similar disease, each patient has his disease, so instead of using statistics collected from large groups of patients, doctors should pay more attention to detailed analysis of each case. [86]

Nevertheless, a new standard was introduced into modern pharmacological research and became a foundation for "evidence-based medicine." They use relatively short clinical trials where large groups of patients with the same nosological diagnosis (or syndrome) are formed. All patients in these groups receive treatment with the study remedy according to the standard protocol. Based on the results obtained, the tested remedy is added to the list of drugs recommended for treating a particular disease or removed from this list. This approach has several weak points: first is the knowledge and experience of the doctor who designs the trial protocol; the second is the knowledge and experience of the doctor who forms the study and control groups because the results of the study are very sensitive to the homogeneity of the groups in the sense of the similarity of the key pathogenesis of the disease which is targeted by the tested drug. The additional factor that can affect the results of these trials is the variability of the sensitivity of the patients to the standard dose of the tested drug.

When using Organotherapy, both approaches discussed above may be used.

It has already been proven by the previous generations of doctors that "the brain helps the brain, and lungs the lungs." [75] However, there are questions while prescribing extracts that affect the entire body, for example, placenta extracts, which were usually used based on the knowledge and experience of the previous generations.

A review published in 2012 listed the main indications when placenta extract is used nowadays. In particular, they use it to stimulate immunity, wound healing, reduce skin pigmentation, and treat various patients suffering from gynecological disorders and other pathological conditions. [55] This list of indications may be helpful for a doctor starting using placenta-origin therapeutics.

According to Dr. Emanuel Revici's research, the placenta extract's beneficial effect was observed if the patient's urine pH was acidic only. Therefore, measurement of urinary pH may be an essential sign for patient selection while prescribing placenta extract. [60,61]

If a doctor is familiar with the theory of traditional Chinese medicine, he can use placenta extract to treat "blood deficiency or/and liver, lung or kidney Yang deficiency." [28] Besides, it was noticed that when the blood uric acid concentration increases, the patient has signs of "heat" [87], which presumably means a predominance of exothermic chemical reactions over endothermic. Thus a blood test on uric acid may be an additional criterion for selecting patients who can be prescribed the placenta extract and for whom its use is not recommended.

As research into organotherapy continues, more data will be available to physicians who use biological remedies. The recent isolation of the specific nano-peptides from the rabbit placenta extract, including *Profilin*, *Acyl-CoA-binding protein*, *Ubiquitin*, *Thymosin beta-4*, etc. [85] starts a new era of organotherapy. It helps doctors to use the placenta extract based on the effects described for the isolated peptides.

## Conclusion.

For many centuries and even millennia, doctors and healers have used Organotherapy empirically, which is based on their knowledge, practical experience, and clinical trials. In some cases, they prescribed organ-specific remedies prepared from specific animal organs which were relevant to the diseased organs of the patient. In other cases, doctors used active remedies to impact the patient's entire body. Among the remedies of animal origin, having general stimulation or rejuvenation effects, the placenta was the most popular one.

With the development of 'modern' science, specific functions and chemical and biochemical components of the placenta were identified. However, some active components of the animal and human-origin placenta were not known to science due to the insufficient sensitivity threshold of the laboratory equipment. Recently a group of nano-peptides was isolated from the extract prepared from rabbit placenta, including *Profilin*, *Acyl-CoA-binding protein*, *Ubiquitin*, *Thymosin beta-4*, and others.

One may assume that revealed proteins and peptides can be essential to the therapeutic effects obtained using extracts from the animal placenta and other organs and tissues.

Hopefully, this discovery will start a new era in the research and clinical application of organo-therapeutic remedies in general and placental extracts in particular.

**Abbreviations:** TCM, Traditional Chinese Medicine; ATP, adenosine triphosphate; Da, Dalton; kDa, kilodalton; BCA Protein Assay, Bicinchoninic Acid Protein Assay; APR, AP revitalization; SDS-PAGE, Sodium dodecyl sulfate polyacrylamide gel electrophoresis; LCMS-MS, Liquid chromatography-mass spectrometry. S.A., Secundum Artem (According to Art, According to the Practice).

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