



159159

Composition of estrogen and other hormones with ascorbate, lysine, proline and other substances

This invention concerns compositions of estrogen and related hormones in combination with ascorbate, lysine, proline and other substances effecting connective tissues, their ability and their use in contraception, hormonal replacement therapy during menopause, and for other use in medicine, physiology, pharmacology, pharmaceuticals and cosmetic application.

Estrogens and related hormones are widely used in medicine. Their primary applications are contraception and hormone replacement therapy during menopause and others.

Long-term use of estrogen and related hormones, however, has significant and frequent side-effects including cancer, particularly cancer of the breast, uterus and other malignancies in organs of the reproductive system, heart diseases and others which are related to extracellular matrix degeneration. According to some sources (Pschyrembel, Klinisches Wörterbuch, 259 edition) the treatment with estrogens is considered to be contraindicated in cases of estrogen depending tumors, acute or chronic diseases of the liver, thrombo-embolie and hypertension. In case of thrombo-embolitic and ischemic diseases, increased hypertension estrogen treatment should be stopped immediately.

Estrogens and related hormones promote the spread of cancer and the exacerbation of other diseases by weakening the extracellular matrix. This effect of estrogen is mediated by the activation of connective tissue degrading enzymes including plasmin, collagenases and by other direct and indirect mechanism destabilising the connective tissue.

It is known from European Patent Application 00115643.9 published January 17, 2001 that pharmaceutical compositions comprising ascorbate or compositions comprising ascorbate and fibrinolizes inhibitors like lysine and proline combined with other substances like tocopherol, coratine, silenium, pro-vitamins and trace elements are suitable pharmaceutical compositions for the prevention and treatment of diseases of pathological states related to the degradation of the extracellular matrix including degenerative diseases particularly artheroscleroses, cancers an other related diseases.



G00002

There is an obvious need to develop therapeutical strategies to minimize the side-effects of treatments with estrogen of otherwise beneficial hormone therapies.

It was supposed that when administering estrogen in combination with ascorbate, lysine, proline and other substances actions of each of these compositions would cancel each other. Estrogen treatment leads to a degradation of the extracellular matrix while known compositions of ascorbic acids, particularly in combination with lysine and proline, reduce or inhibit such degradations whereby estrogen treatment would become useless. However, surprisingly this is at least partly not the case because of the synergistic effect of such ascorbic acid compositions, particularly when combined with lysine and proline which on the one hand prevent or inhibit extracellular matrix degeneration, on the other hand however enhance collagen synthesis, particularly with ascorbic acid which creates and supports the extracellular matrix.

The compounds used in this invention for a combined use or therapeutic application with estrogens and related hormones are chosen to counteract the weakening of the connective tissue by those hormones. Ascorbate is known to stimulate the synthesis of collagen, elastin and other connective tissue macromolecules from fibroblast and related cells. The amino acids lysine and proline are the predominant amino acids required for the synthesis of connective tissue molecules. Iron and copper are trace elements that catalyze the production of these macromolecules.

During physiological conditions such as ovulation and pregnancy the degradation of connective tissue by estrogen is counteracted by a regulated system of natural mechanisms to prevent the degradation of collagen. Under pathological conditions caused by side-effects of beneficial hormone therapies the natural mechanism which are no more active during and after menopause can be replaced by the therapeutic use of the combinations according to this invention. They are useful to minimize or prevent side-effects of long-term hormone therapies including cancer and other severe health conditions while allowing the desired medical or therapeutic effect of estrogen and related hormones.

The different compounds claimed in this application can be used together in form of covalently bound compounds or as physical mixture or in any other combination.

Claims

1. A pharmaceutical composition of estrogen and related hormones in combination with pharmaceutical compositions for the prevention and treatment of pathological conditions related to extra cellular matrix degeneration.
2. A pharmaceutical composition according to claim 1 comprising ascorbic acid or ascorbate salts.
3. A pharmaceutical composition according to claim 1, comprising estrogen, estradiol, ethinylestradiol, estriol, norethisterone, lynestrenol and related hormones comprising lysine or lysine salts or hydroxylysine or hydroxylysine salts.
4. A pharmaceutical compositions according to the preceding claims comprising proline or proline salts or hydroxyproline or hydroxyproline salts.
5. A pharmaceutical composition according to the preceding claims comprising selenium, or selenium salts, copper or copper salts, iron or iron salts and other minerals or trace elements.
6. A pharmaceutical composition according to the preceding claims comprising chondroitin sulfate, glycosaminoglycanes or other proteoglycanes or glycoproteins known to be part of the extra cellular matrix.
7. The use of pharmaceutical compositions according to the preceding claims for fertility control, hormonal replacement therapy to alleviate typical symptoms related to menopause.
8. The use of the pharmaceutical composition according to claim 1 to 6 to prevent osteoporosis, cardiovascular diseases and other ailments during menopause.
9. The use of pharmaceutical compositions according to the proceeding claims in oral forms, tablets, capsules or in any other form suited for digestion, for sublingual, intravenous, subcutaneous, intra-muscular, transdermal and any other parenteral application.