

USE OF CITRULLINE AND COMBINATION COMPOUND FOR IMPROVING MALE
FERTILITY

- 5 The invention relates to a combination compound for improving sperm quantity and quality comprising at least one antioxidant and at least one of the substances C vitamins, E vitamins, zinc, selenium, acetyl cysteine, L-carnitine, glutathione, lycopene, ubiquinone 10 components, and the use thereof as well as citrulline for improving sperm quality.
- 10 An ever increasing number of couples are finding it more difficult to conceive the child they desire. In industrialized nations such as Germany and the USA, one in ten couples these days is already childless but does not want to be so and this tendency is on the increase. Reduced fertility can be caused by many factors. The increasing age of the couples wishing to conceive may be just as important a factor as environmental pollution, reduced sperm quality, defective
- 15 egg cells, unhealthy living as well as others. So-called lifestyle factors also play a decisive role. One of the crucial factors of fertility for both male and female is an adequate supply to the body of specific micro-nutrients, energy substrates and vitamins. These days, it is unfortunately increasingly difficult to ensure an adequate supply of vitamins and certain nutrients. Given the toll of increased stress in day to day life, a lower quality of foodstuffs and un-
- 20 healthy diet, the human organism is often inadequately supplied. As a result, the body is subjected to permanent stress and this is particularly the case where cells are at their most sensitive – in the region of the egg and semen cells. The male sperm becomes inert, egg cells “miss” their ovulation and fertility can therefore suffer due to poor diet. Numerous studies have already demonstrated how very important correct diet is to those wishing to conceive.
- 25 Whilst the female is already born with egg cells, the male creates sperm during his entire life. In the case of every second couple wishing to but unable to conceive, it is the male who is partly the cause and in one in three cases, it is even the male who is solely the cause. The quality of male fertility has decreased continuously in recent decades. One of the most common reasons for male infertility is a reduced sperm quality in the sense of oligozoospermia
- 30 (too low a sperm count), asthenozoospermia (too low a sperm motility) or teratozoospermia (too many malformed sperm). All too commonly, all three deficiencies may even be manifested by one and the same patient (OAT syndrome). In addition to a reduced sperm count, how-

ever, the integrity of the DNA transported in the sperm plays an important role in fulfilling couples' desire to start a family. A major cause of DNA damage in the sperm is oxidative stress. In the last ten years, attention has therefore been increasingly focused on oxidative stress as a cause of infertility (Agarwal, 2004). By oxidative stress is meant damage to cells, tissues or even organs due to increased quantities of so-called reactive oxygen species (ROS) (Moller et al, 1996; Sharma and Agarwal, 1996; Saleh et al, 2003). If the quantity of reactive oxygen species exceeds the capacities of the body's own antioxidative defense mechanisms, the result will be oxidative stress (OS) as outlined above. 30 – 80 % of all infertile males have an increased quantity of ROS in the seminal plasma (Agarwal, 2004). In 2009, Varghese et al. also demonstrated a strong correlation between asthenospermia and reduced antioxidants in the seminal fluid. Particularly in the case of males who produce excessive quantities of reactive oxygen species, the normal sperm may be damaged (Aitken et al., 1998, Alvarez et al., 2002, Saleh et al., 2002, Agarwal et al., 2003). Sperm are particularly susceptible to attacks by ROS because they do not have intrinsic cytoplasmic defense and repair mechanisms (Donnelly et al, 1999; Saleh and Agarwal, 2002). In addition, they have a plasma membrane with a particularly large amount of polyunsaturated fatty acids. These constitute good points of attack for ROS. (Agarwal et al, 1994; Kobayashi et al, 2001; Zalata et al, 2004). Antioxidants which are absorbed with food represent an important part of the human anti-oxidative protection system – in particular also during the phase of spermiogenesis. Fruit and vegetables are a major source of the different antioxidants but given the increasing amount of stress common these days and the resulting increase in oxidative stress, they can barely produce the requisite amount, even in the case of a well-balanced diet. Another exacerbating factor is that males in particular often pay little attention to ensuring a healthy diet. According to a survey conducted amongst male patients undergoing medical treatment for conditions related to reproduction, the majority of males consider that they have a well-balanced diet even though, by their own admission, they do not eat more than one or at most two portions of fruit and vegetables per day. However, barely a single male eats the five portions of fruit and vegetables recommended by the health authorities of many states (Wogatzky et al, presentation to the 4th International Congress of the Jordanische Gesellschaft für Fruchtbarkeit und Genetik, 20 – 22 April 2011). In one Spanish study conducted in 2009, it was demonstrated that males who consumed few antioxidants with their food on average had a poorer semen quality (Mendiola et al, 2009).

The compound Fertilovit[®] M manufactured by the applicant is known in this connection. Fertilovit[®] M contains a combination of vitamins and other vital substances which help to mature sperm in addition to antioxidants in depot form, affording round the clock protection against oxidative stress. Due to its specific composition incorporating natural body substances, Fertilovit[®] M for the male improves semen quality.

Accordingly, the objective of this invention is to propose a substance or a combination compound which further improves male sperm quality and increases sperm quantity.

The objective of the invention is achieved, independently in each case, by a combination compound comprising at least one antioxidant as well as citrulline and/or omega 3 fatty acids or comprising at least one of the substances C-vitamins, E-vitamins, zinc, selenium, acetyl cysteine, L-carnitine, glutathione, lycopene, ubiquinone 10 components, and which contains/contain at least citrulline and/or omega 3 fatty acids, and, independently by citrulline for the treatment of a poor spermiogram. Citrulline has a very good bio-availability, as a result of which the organism is able to produce a sufficient quantity of the polyamines spermine and spermidine, which occur in the sperm fluid in a high concentration, as well as the protamines necessary for packaging sperm-DNA and which stabilize the DNA. Omega 3 fatty acids demonstrate a positive effect on the fusion of egg and semen cells and the prostaglandin and steroid hormone metabolism. In many patients (approximately 70 %), the routine intake of additional antioxidants through the combination compound significantly improves sperm quality. Patients who do not take advantage of such a measure, on the other hand need, not fear any negative side effects. C-vitamins in the combination compound interrupt the radical chain reaction and thus neutralize hydroxyl, superoxide, and hydrogen peroxide radicals. C vitamins act as the main antioxidant in the seminal plasma of fertile males; here, the concentration is even ten times higher than in the blood plasma. The seminal fluid of infertile males usually contains only a small quantity.

E-vitamins are located locally in the cell membrane, where they are very effective at interrupting the radical chain reaction and thus neutralize primarily H₂O₂, OH and O₂⁻. As a result, they protect the cell membrane from lipid oxidation. The particular advantage of this is that sperm motility is improved in 60 % of patients with asthenozoospermia.

Due to the selenium in the combination compound, the sperm motility, life and morphology of the sperm can be improved in OAT patients. In addition, the sperm-DNA is protected against oxidative stress by promoting the protamine packaging of the DNA and selenium also has an anti-oxidative effect, being a constituent part of glutathione peroxidase. Selenium also works in a synergetic relationship with vitamin E.

Zinc is an essential constituent of spermatocytes. If there is not enough zinc available in the body for sperm production, the latter will decrease significantly. The motility of the semen cells will also decrease because zinc plays a part in binding the semen head to the semen tail. The additional zinc provided by the combination compound results in an improved spermogram in infertile males. The combination of zinc with folic acid results in a 74 % increase in sperm count. Furthermore, treatment for a period of 3 months leads to a significant improvement in cases of asthenozoospermia. Zinc, which takes part in almost all biochemical processes in the body, assists the effect of the combination compound proposed by the invention.

L-carnitine in the combination compound acts as a receptor molecule for activated fatty acids in the cytosol and in the mitochondria (in the interchange with acetyl-CoA) and is an important energy substrate for the spermatozoa. However, carnitines are also antioxidants, which reduce the quantity of reactive oxygen species because they remove excessive intracellular acetyl-CoA. Otherwise, the latter increases ROS production by the mitochondria. L-carnitine also improves sperm motility. Carnitine, more specifically L-carnitine, plays an essential role in the energy metabolism of animal cells.

The glutathione in the combination compound significantly increases the motility of sperm. In addition, glutathione reduces DNA damage by ROS. Tripeptide glutathione (cysteine, glutamate, glycine) is the most common antioxidant in the human body. It protects lipids, proteins and nucleic acids against oxidative stress. Almost all cells contain a high concentration of glutathione which is one of the most important substances acting as an antioxidant in the human body. At the same time, it is a reserve for cysteine. In combination with vitamin E and selenium, it produces glutathione peroxidase. However, the intake of glutathione as a food supplement is not always enough on its own to obtain the desired success because oral administration results in only a moderate increase in the glutathione circulating through the body. However, oral administration of N-acetyl cysteine in the combination compound, an im-

portant precursor molecule of glutathione, effectively increases the glutathione content of cells. Acetyl cysteine administered orally for a period of 3 months leads to a significant increase in the overall anti-oxidative capacity in plasma. This is accompanied by a low viscosity and hence improved motility of the semen.

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Lycopene, as well as leukopine, is an antioxidant and acts as a radical scavenger, i.e. it can render specific reactive molecules in the human body harmless. Lycopene is a carotinoid with very good anti-oxidative and anti-inflammatory properties. Due to these anti-inflammatory properties, incorporating it in the combination compound reduces seminal reproduction of ROS by leukocytes.

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Adding ubiquinone 10 components (coenzyme Q10) to the combination compound leads to an increase in sperm quantity and improves motility. Coenzyme Q10 (CoQ10) is needed by the body, amongst other things to capture energy in the mitochondria. It is therefore to be found in sperm, primarily in the middle section. However, it also has anti-oxidative properties because it recycles vitamin E and suppresses its pro-oxidative activity. The tissue concentration of coenzyme Q10 decreases with age, and this decrease can be compensated by the combination compound. Administering the combination compound with oral CoQ-10 to infertile male subjects significantly increases the fertilization rate. CoQ-10 also prevents the production of H_2O_2 in seminal fluid.

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Folic acid assists the protamine packaging of the sperm-DNA. In a male, a diet low in folic acid increases the number of sperm with chromosomal aberrations.

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Males who take in sufficient folic acid through their diet or through vitamin tablets have sperm exhibiting disomy of the X chromosome (Klinefelter's syndrome) or chromosome 21 (Down's syndrome) or nullosomy of the X chromosome (Turner) significantly less often. After taking account of other factors, such as age, alcohol consumption and comorbidity, males with the highest intake of folic acid (722-1150 $\mu\text{g}/\text{d}$) have up to 20-30 percent less sperm with aneuploidies in the ejaculate than males with the lowest intake of folic acid. For every 100 μg of folic acid, the risk is reduced by 3.6 percent. Folic acid also promotes the homocysteine metabolism, which counteracts hyperhomocysteinaemia and advantageously also has an effect on spermiogenesis.

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Through high-value omega 3 fatty acids, the combination compound improves the membrane structure of the sperm, which is important in terms of fusing semen cells and egg cells during the actual fertilization because a balanced membrane structure of the cells plays an important role in healthy sperm function. Compared with fertile males, infertile males have a lower proportion of polyunsaturated fatty acids, and in particular a lower proportion of omega 3 fatty acids. This goes hand in hand with a reduced sperm count, motility and structure of the sperm. An intake of omega 3 fatty acids can counteract these problems. A positive side-effect is the protective effect of omega 3 fatty acids for the prostate and heart-circulation system. The membrane is made up of fats for the most part. Due to changing dietary conditions, the relative proportions of different fatty acids in cell membranes have been shown to have changed in recent years. In particular, the essential polyunsaturated omega 3 fatty acids are present in too low amounts, relatively speaking. This has an effect on processes such as the fusion of egg and semen cells, for example, as well as the prostaglandin and steroid hormone metabolism. Whilst it has been shown that saturated and also single unsaturated fats have a damaging effect on sperm quality, both omega 6 and omega 3 fatty acids are very good for sperm quality. Also of importance is the ratio of omega 3 fatty acids to omega 6 fatty acids.

The combination compound may also contain citrulline. The body uses citrulline for the synthesis of arginine. An important property of arginine is that it is in turn a precursor of the neurotransmitter nitrogen monoxide (NO). The enzyme nitrogen monoxide synthase catalyzes conversion of the amino acid arginine into endothelium derived relaxing factor (EDRF) – another name for nitrogen monoxide. This diffuses through the muscle layers of the vessels and Corpus cavernosum. Here, by activating the enzyme guanylate cyclase, it leads to increased diffusion of cyclic guanosine monophosphate (cGMP). The increase in cGMP causes a relaxation of the smooth musculature and hence a decrease in vascular tone. Consequently, gaseous NO spreads through the cardiac muscle and causes a relaxation of vascular smooth muscles.

By releasing nitrogen monoxide, the amino acid L-arginine improves the blood flow and oxygen supply to the coronary and peripheral blood vessels, inhibits the formation of lumps in thrombocytes and reduces blood pressure. These mechanisms also enable the ability to maintain an erection of the member to be increased.

Arginine is also necessary for normal spermatogenesis. From arginine, the body specifically forms the polyamines spermine and spermidine, which occur in a high concentration in the seminal fluid, as well as the protamines which are necessary for packaging the sperm-DNA and which stabilize the DNA.

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The combination compound already leads to an increase in sperm quantity and motility after 6 to 8 weeks in infertile males. However, the disadvantage of arginine, administered orally, is that it does not offer optimum bio-availability. The amino acid L-citrulline is an important precursor for producing arginine in the body but, by contrast with arginine, it is very much better enterally resorbed. It therefore has a very good bio-availability. Taken orally, L-citrulline is absorbed into the blood stream via the intestines and converted to L-arginine in the body. Studies have shown that taking a supplement incorporating citrulline can increase the arginine level more effectively than if the same dose of arginine were taken directly. Since the body converts citrulline into arginine with a time delay, citrulline has the effect of extending dwell time based on the retard function and increases the arginine level in the blood for a longer period of time. The organism therefore has the positive effect of a perceptively longer arginine effect. The use of citrulline to produce a combination compound containing at least antioxidants for improving sperm quality has therefore also been shown to be of advantage.

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It has also been found to be of advantage to use a ratio of eicosapentaenoic acid to docosahexaenoic acid of 3 to 2, because the sperm count can be increased and the motility and structure of the sperm improved.

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The positive effects of the individual substances combined with one another in an optimum ratio, thereby increasing sperm quality and their number as effectively as possible, can be obtained by opting for quantities of the substances C vitamins in quantities of 1 to 20 % by weight, in particular 5 to 15 % by weight, preferably 6 to 10 % by weight, E vitamins in quantities of 1 to 20 % by weight, in particular 5 to 15 % by weight, preferably 6 to 10 % by weight, B9 vitamins in quantities of 0.005 to 2 % by weight, in particular 0.009 to 1 % by weight, preferably 0.01 to 0.1 % by weight, zinc in quantities of 0.5 to 5 % by weight, in particular 0.8 to 3.5 % by weight, preferably 1.2 to 2.5 % by weight, selenium in quantities of 0.001 to 1 % by weight, in particular 0.004 to 0.5 % by weight, preferably 0.006 to 0.1 % by weight, acetyl cysteine in quantities of 0.5 to 10 % by weight, in particular 1 to 6 % by

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weight, preferably 2.5 to 4.5 % by weight, carnitine in quantities of 3 to 30 % by weight, in particular 5 to 25 % by weight, preferably 10 to 23 % by weight, glutathione in quantities of 0.5 to 15 % by weight, in particular 1 to 10 % by weight, preferably 3 to 6 % by weight, lycopene in quantities of 0.05 to 3 % by weight, in particular 0.08 to 1 % by weight, preferably 0.2 to 0.1 % by weight, and ubiquinone 10 components in quantities of 0.05 to 10 % by weight, in particular 0.1 to 5 % by weight, preferably 0.8 to 3 % by weight, and omega 3 fatty acids in quantities of 5 to 50 % by weight, in particular 10 to 40 % by weight, preferably 20 to 35 % by weight, and/or citrulline in quantities of 5 to 40 % by weight, in particular 8 to 30 % by weight, preferably 12 to 20 % by weight, relative to the total weight of the therapeutically active substances of the combination compound. Incorporating B6 vitamins and B12 vitamins in the combination compound enables the vascular function to be assisted by reducing homocysteine values, thereby assisting an adequate production of sperm and spermatogenesis.

Copper is an element of many enzymes (metalloenzymes) and hence an essential trace element for life, which therefore also assists optimum sperm production.

Sperm quality is also improved by the high antioxidative potential of the other carotinoids.

It has also proved to be of advantage to add copper in quantities of 0.001 to 1 % by weight, in particular 0.003 to 0.5 % by weight, preferably 0.05 to 0.1 % by weight, B6 vitamins in quantities of 0.05 to 3 % by weight, in particular 0.08 to 1 % by weight, preferably 0.2 to 0.1 % by weight, B12 vitamins in quantities of 0.001 to 1 % by weight, in particular 0.003 to 0.5 % by weight, preferably 0.05 to 0.1 % by weight, other carotinoids, such as β -carotin, α -carotin, β -cryptoxanthin, lutein and zeaxanthin in quantities of 0.05 to 3 % by weight, in particular 0.08 to 1 % by weight, preferably 0.2 to 0.1 % by weight, relative to the total weight of the therapeutically active substances of the combination compound, because the advantageous effects described above have a cumulative effect on development of the sperm. As a result of the composition of the combination compound described above, cooperation of the individual substances with one another is optimized and the synergetic effects enhanced. In addition, a balanced interaction with the other substances can be achieved.

The combination compound may be used both as a medicament with a balanced diet or as a food supplement and, if authorized as a medicament with a balanced diet, the user can be as-

sured that the compound has been through at least one clinical study, whereas if authorized as a food supplement, the compound will be more easily and optionally more discreetly available.

5 It has also been found to be of advantage to use citrulline for the treatment of oligozoospermia, asthenozoospermia and/or teratozoospermia. Citrulline has been found to be effective in daily doses of 100 mg to 1000 mg, in particular 150 mg to 500 mg, preferably 200 mg to 300 mg, which guarantees an adequate level of citrulline in the organism, thereby enabling normal spermatogenesis. This results in a high sperm quantity and good sperm motility.

10 Citrulline is incorporated in the combination compound in quantities of 2 to 50 % by weight, in particular 5 to 35 % by weight, preferably 10 to 20 % by weight, relative to the total weight of the therapeutically active substances of the combination compound, which on the one hand results in an effective level of citrulline but without the risk of an excessive dose. The selected
15 proportion by weight also results in good processability during manufacture of the combination compound.

The invention describes citrulline for use in a therapeutic process for treating poor spermiogram results. The combination with antioxidants has proved to be particularly beneficial. An
20 antioxidant within the meaning of the invention is a chemical compound which selectively prevents undesirable oxidation of other substances. Antioxidants are of major physiological important due to their action as radical scavengers. They inactivate reactive oxygen species (ROS) in the organism, the excessive occurrence of which leads to oxidative stress. Oxidative stress is one of the contributing factors to the aging process and to the impairment of fertility
25 and is also a factor in connection with the occurrence of a whole series of illnesses.

The invention also describes citrulline for use in a method of producing a combination compound for treating poor spermiogram results. The effects of the different substances in the combination compound were described above. Based on the specific selection of substances
30 in the corresponding quantities, the combination compound has proved to be of particular advantage in the treatment of poor spermiogram results in cases of oligozoospermia, asthenozoospermia and/or teratozoospermia. Of particular advantage is a combination of C vitamins,

E vitamins, zinc, selenium, acetyl cysteine, L-carnitine, glutathione, lycopene, ubiquinone 10 components with citrulline and/or Omega-3-fatty acids.

5 As omega 3 fatty acids, it is preferable to use eicosapentaenoic acid (EPA) and docosahex-
aenoic acid (DHA). However, α -linolenic acid (ALA) may also be used as an omega 3 fatty
acid in the combination compound. From the point of view of producing the combination
compound, it is preferable to use fish oil, in which case DHA accounts for 18 % and EPA
12%. It is possible to use omega 3 fatty acids both of animal and vegetable origin.

10 The combination compound proposed by the invention is particularly beneficial in terms of
the requirements of the male organism if wishing to conceive. It may be used both as a food
supplement, a dietary foodstuff for specific medical purposes (supplementing a balanced diet)
and as a medicament.

15 The combination compound proposed by the invention contains a specially adapted mixture
of antioxidants, some in depot form, and other nutrients and minerals which are important for
the reproductive cells. For example, vitamin C may be incorporated as a retard form. Prepara-
tions enabling a delayed release of active substances are described in the prior art. For exam-
ple, vitamin C may be coated with hydroxypropylmethyl cellulose. This provides the male
20 with an optimum supply. Naturally, it would also be possible to use other methods known
from the prior art which enable the delayed release of vitamin C.

The active mechanisms of the individual substances in the combination compound proposed
by the invention are complex. In addition to providing nutrients and inducing enzymes, an
25 essential active mechanism is the selective reduction of oxygen radicals.

The combination of mutually adapted active ingredients in the combination compound pro-
posed by the invention has demonstrated in trials that it leads to a significant improvement in
the fertility of males.

30 The mechanisms described above preferably work in combination with the active substances
and by assisting other antioxidants.

The synergistic effect of the individual substances in the selected ranges of quantities improves effectiveness in terms of sperm quality and quantity as a result of the combination compound proposed by the invention.

- 5 The use of citrulline, optionally in conjunction with at least one antioxidant or omega 3 fatty acids with at least one antioxidant together with the combination compound proposed by the invention is preferably recommended for oral administration. The compound may be used as both a human and veterinary product.
- 10 The table below sets out the quantity ranges for the recommended daily dose of the individual active ingredients relevant to the invention. The combination compound proposed by the invention may be taken in the form of two capsules per day. However, the quantities of substances may be selected so that only one capsule is necessary per day in order to obtain the recommended daily dose.

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Ingredient	Recommended quantity in mg per day
Vitamin C	50 -200
Vitamin E	10 – 120
Folic acid	0.1 – 0.7
Zinc	5 – 50
Selenium	0.02 – 0.2
Acetyl cysteine	10 – 100
Carnitine	10 – 500
Glutathione	10 – 100
Lycopene	1 – 15
Ubiquinone	1 – 50
10 components	
Omega 3 fatty acids	100 – 1000
Citrulline	1 – 600

Copper	0.05 – 10
Vitamin B12	0.01 – 1
Vitamin B6	1 – 10
Carotinoids	0.1 - 10

Excipients, such as auxiliary substances, fillers, carrier substances, binding agents, etc., which are necessary for the technical processing of the combination compound proposed by the invention are also used. However, these excipients have no therapeutic effect and no positive effects on the sperm and therefore do not constitute therapeutically active substances within the meaning of the invention.

Examples of embodiments of the composition of the therapeutically active substances in mg per daily dose of the combination compound proposed by the invention which produce the advantageous effects are set out below.

Ingredients	1	2	3	4	5	6	7	8	9	10
Vitamin C	-	50	120	150	100	180	200	100	80	100
Vitamin E	-	10	20	50	100	100	120	100	60	80
Folic acid	-	0.1	0.3	0.3	0.5	0.6	0.7	0.5	0.4	0.5
Zinc	-	5	10	15	25	40	50	25	30	10
Selenium	-	0.02	0.05	0.07	0.1	0.1	0.2	0.1	0.09	0.15
Acetyl cysteine	-	10	40	30	50	90	100	50	80	80
Carnitine	-	10	100	200	300	400	500	300	250	350
Glutathione	-	10	20	25	50	80	100	50	90	70
Lycopene	-	1	2	3	4	2.5	15	4	13	10
Ubiquinone 10 components	-	1	3	10	15	15	50	15	30	40
Omega 3 fatty acids	-	100	200	400	500	350	1000	500	700	900
Citrulline	500	100	300	800	300	600	600	200	60	10

Copper	-	-	-	-	-	0.5	-	1	-	-
Vitamin B12	-	-	0.05	-	-	0.01	-	0.09	-	-
Vitamin B6	-	-	-	-	-	1	-	3	2	-
Carotinoids		-	-	5	-	5	-	3	-	3
Fillers and carrier substances	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Tests showed that example 5 was particularly effective. A composition based on example 5 was found to improve the spermiogram and lead to an increase of ca. 20 % increase in fertilization rate. Generally speaking, it was found that the compound proposed by the invention significantly improved sperm quantity and quality in more than 70 % of males.

The table below sets out examples for the composition of the substances in absolute figures for two combination compounds proposed by the invention which produce advantageous effects.

Ingredients	Quantity in mg per daily dose	% by weight	Quantity in mg per daily dose	% by weight
Vitamin C	100	7.43715603	100	7.39814602
Vitamin E	100	7.43715603	100	7.39814602
Folic acid (vitamin B9)	0.5	0.03718578	0.5	0.03699073
Zinc	25	1.85928901	25	1.84953651
Selenium	0.1	0.00743716	0.1	0.00739815
Acetyl cysteine	50	3.71857802	50	3.69907301
Carnitine	300	22.3114681	300	22.1944381
Glutathione	50	3.71857802	50	3.69907301
Lycopene	4	0.29748624	4	0.29592584
Ubiquinone 10 components	15	1.1155734	15	1.1097219
Omega 3 fatty acids	500	37.1857802	500	36.9907301

Citrulline	300	14.8743121	300	14.796292
Copper	-	0	3	0.22194438
Vitamin B12	-	0	0.09	0.00665833
Vitamin B6	-	0	1	0.07398146
Carotinoids	-	0	3	0.22194438

Based on one embodiment, the combination compound proposed by the invention comprises L-carnitine, L-ascorbic acid, D-alpha-tocopheryl acetate, folic acid, silicon dioxide, calcium carbonate, N-acetyl-L-cysteine, glutathione, corn starch, zinc oxide, coenzyme Q10, lycopene, vegetable oils, pteroyl-L-glutamate, sodium selenite, fish oil and citrulline. The capsule shell is preferably made from cellulose, but may be of any other type. Vegetable oils are an option because the raw material lycopene is soluble in oil and dissolves in them. Instead of sodium selenite, the organic variant of L-selenomethionine may also be used. Corn starch is a carrier substance for the otherwise oily vitamin E.

The positive effect of citrulline and the combination compound proposed by the invention may be used both in preparation for a natural pregnancy as well as in preparation for insemination, in vitro fertilization and intracytoplasmic sperm injection.

The combination compound proposed by the invention should be taken twice a day orally in the form of a capsule. The recommended minimum period of treatment is 3 months.

All the figures relating to ranges of values in the description should be construed as meaning that they include any and all part-ranges, in which case, for example, the range of 1 to 10 should be understood as including all part-ranges starting from the lower limit of 1 to the upper limit of 10, i.e. all part-ranges starting with a lower limit of 1 or more and ending with an upper limit of 10 or less, e.g. 1 to 1.7, or 3.2 to 8.1 or 5.5 to 10.

The embodiments illustrated as examples represent possible variants of the combination compound, and it should be pointed out at this stage that the invention is not specifically limited to the variants specifically illustrated, and instead the individual variants may be used in different combinations with one another and these possible variations lie within the reach of the person skilled in this technical field given the disclosed technical teaching. Accordingly, all

conceivable variants which can be obtained by combining individual details of the variants described and illustrated are possible and fall within the scope of the invention.

The objective underlying the independent inventive solutions may be found in the description.

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Claims

1. Combination compound for improving sperm quantity and quality, comprising at least one antioxidant, wherein it contains citrulline and/or omega 3 fatty acids.

2. Combination compound according to claim 1, wherein it contains at least one of the substances C vitamins, E vitamins, zinc, selenium, acetyl cysteine, L-carnitine, glutathione, lycopene, ubiquinone 10 components.

3. Combination compound according to claim 1 or 2, wherein it contains the omega 3 fatty acids, eicosapentaenoic acid to docosahexaenoic acid, in a ratio of 3 to 2.

4. Combination compound according to one of claims 1 to 3, wherein it contains C vitamins in quantities of 1 to 20 % by weight, in particular 5 to 15 % by weight, preferably 6 to 10 % by weight, E vitamins in quantities of 1 to 20 % by weight, in particular 5 to 15 % by weight, preferably 6 to 10 % by weight, B9 vitamins in quantities of 0.005 to 2 % by weight, in particular 0.009 to 1 % by weight, preferably 0.01 to 0.1 % by weight, zinc in quantities of 0.5 to 5 % by weight, in particular 0.8 to 3.5 % by weight, preferably 1.2 to 2.5 % by weight, selenium in quantities of 0.001 to 1 % by weight, in particular 0.004 to 0.5 % by weight, preferably 0.006 to 0.1 % by weight, acetyl cysteine in quantities of 0.5 to 10 % by weight, in particular 1 to 6 % by weight, preferably 2.5 to 4.5 % by weight, carnitine in quantities of 3 to 30 % by weight, in particular 5 to 25 % by weight, preferably 10 to 23 % by weight, glutathione in quantities of 0.5 to 15 % by weight, in particular 1 to 10 % by weight, preferably 3 to 6 % by weight, lycopene in quantities of 0.05 to 3 % by weight, in particular 0.08 to 1 % by weight, preferably 0.2 to 0.1 % by weight, and a ubiquinone 10 component in quantities of 0.05 to 10 % by weight, in particular 0.1 to 5 % by weight, preferably 0.8 to 3 % by weight, and omega 3 fatty acids in quantities of 5 to 50 % by weight, in particular 10 to 40 % by weight, preferably 20 to 35 % by weight, and/or citrulline in quantities of 0.5 to 40 % by weight, in particular 1 to 30 % by weight, preferably 12 to 20 % by weight, relative to the total weight of the therapeutically active substances of the combination compound.

5. Combination compound according to one of claims 1 to 4, wherein it contains copper, other carotinoids, B6 vitamins, B12 vitamins.

6. Combination compound according to claim 5, wherein it contains copper in quantities of 0.001 to 1 % by weight, in particular 0.003 to 0.5 % by weight, preferably 0.05 to 0.1 % by weight, B6-vitamins in quantities of 0.05 to 3 % by weight, in particular 0.08 to 1 % by weight, preferably 0.2 to 0.1 % by weight, B12-vitamins in quantities of 0.001 to 1 % by weight, in particular 0.003 to 0.5 % by weight, preferably 0.05 to 0.1 % by weight, other carotinoids, such as β -carotin, α -carotin, β -cryptoxanthin, lutein and zeaxanthin in quantities of 0.05 to 5 % by weight, in particular 0.08 to 1 % by weight, preferably 0.2 to 0.1 % by weight, relative to the total weight of the therapeutically active substances of the combination compound.

7. Use of the combination compound according to one of claims 1 to 6 as a medicament, balanced diet and/or food supplement.

8. Citrulline for the treatment of oligozoospermia, asthenozoospermia and/or teratozoospermia.

9. Citrulline according to claim 8, wherein it is contained in a combination compound comprising therapeutically active substances, such as at least one antioxidant.

10. Citrulline according to claim 8 or 9, wherein it is administered in daily doses of 1 mg to 600 mg, in particular 10 mg to 500 mg, preferably 200 mg to 400 mg.

11. Citrulline according to claim 8 to 10, wherein it is incorporated in quantities of 0.5 to 40 % by weight, in particular 5 to 35 % by weight, preferably 10 to 20 % by weight, relative to the total weight of the therapeutically active substances of the combination compound.