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# Non-hormonal treatment for male infertility: the potential role of *Serenoa repens*, selenium and lycopene

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**Abstract. – OBJECTIVE: Male infertility is a wide spread disease among couple of childbearing age. Spermatozoa are highly susceptible to oxidative stress. Reactive oxygen species (ROS) are capable of damaging the sperm membrane and DNA, inducing lipid peroxidation and sperm DNA fragmentation (SDF). Antioxidant supplementation is currently suggested after a complete diagnostic work-up, as recognized by the Italian Society of Andrology and Sexual Medicine (SIAMS). Indeed, it has been showed to improve sperm quality, DNA fragmentation and pregnancy rate. The administration of *Serenoa repens* extracts (SrE), including free fatty acids (FFA), methyl and ethyl esters, glycerides, flavonoids and sterols, has never been investigated for male infertility. However, their antioxidant and anti-inflammatory properties provide the rational for their possible effectiveness. The aim of this review was to collect all the evidence supporting the potential usefulness of SrE, alone or in combination with other molecules with proven antioxidant effects, like selenium and lycopene (along with which they are often commercialized), to improve sperm parameters.**

**MATERIALS AND METHODS: A systematic search was performed using Pubmed, MEDLINE, Cochrane, Academic One Files, Google Scholar and Scopus databases. The search strategy included the following key words: Serenoa repens, selenium, lycopene, oligozoospermia, oxidative stress, DNA fragmentation, male infertility, pregnancy rate.**

**CONCLUSIONS: By triggering multiple inflammatory and oxidative pathways, the combined administration of SrE, selenium and lycopene might likely improve the sperm quality. Proper studies are needed to test this hypothesis. Finally, since prostatitis can affect the sperm quality and considering the anti-estrogenic properties of SrE, we speculate about a possible specific indication in those patients with male infertility and "metabolic" prostatitis (where obesity and abnormal androgen/estrogen ratio concomitantly occur).**

*Key Words:*
Serenoa repens, Lycopene, Selenium, Oxidative stress, Male infertility, Sperm parameters.

### Abbreviations

BPH, benign prostate hyperplasia; CCL2, C-C motif ligand 2; COX-2, cyclooxygenase-2; CXCL10, C-X-C motif chemokine 10; ER, estrogen receptors; FFA, free fatty acids; FGFβ, Fibroblast growth factor β; GPx, glutathione peroxidase; iNOS, inducible nitric oxide synthase; IL, interleukin; IP, induced protein; LPS, lipopolysaccharide; LUTS, low urinary tract symptoms; MCP-1, monocyte chemo-attractant protein-1; MIF, macrophage migration inhibitory factor; NO, nitric oxide; PGE2, prostaglandin E2; $Q_{max}$, maximum urinary flow rate; ROS, reactive oxygen species; SDF, sperm DNA fragmentation; Se, selenium; SIAMS, Italian Society of Andrology and Sexual Medicine; SOD, superoxide dismutase; SrE, *Serenoa repens* extracts; TNFα, Tumor necrosis factor α; VEGF, vascular endothelial growth factor.

## Introduction

Infertility is defined as the failure to conceive after 1-2 years of unprotected sexual intercourse[1]. It concerns about the 15% of couples of reproductive age in industrialized countries[2]. Half of the cases recognize a male factor of infertility[3]. Medical treatment of male infertility includes hormonal[3] and non-hormonal strategies. Among non-hormonal options, antioxidants play a relevant role in idiopathic cases (especially when sperm oxidative damage is ascertained and microbial infection has been excluded)[4]. The benefits of the antioxidant therapy have been recognized by the Italian Society of Andrology and Sexual Medicine (SIAMS), which suggests their use in case of altered sperm parameters and abnormal sperm DNA fragmentation (SDF) after a complete diagnostic workup[4]. In agreement, despite the low quality evidence



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due to the small number of trials and of their sample size, according to the last Cochrane systematic review, antioxidant supplementation may increase the clinical pregnancy rate[5]. Spermatozoa are highly susceptible to reactive oxygen species (ROS). Indeed, polyunsaturated fatty acids, the main components of the plasma membrane, make the spermatozoa particularly vulnerable to lipid peroxidation[6]. Also, high amounts of ROS are capable of inducing SDF due to the low levels of cytoplasmic antioxidant enzymes and inefficient DNA repair mechanisms[7]. Hence, the oxidative damage impairs sperm quality, thus negatively impacting on the pregnancy rate. These premises represent the rational basis supporting the use of antioxidants in idiopathic male infertility. Concerning the therapeutic regimen, no specific indication has been provided due to the lack of comparative studies between the different antioxidants and/or combinations[4]. We recently reviewed the effects on sperm parameters and pregnancy rate of the main commercially available antioxidant and prokinetic molecules, such as carnitine, coenzyme Q10, myoinositol, vitamin C, vitamin E, lycopene, selenium (Se), zinc and others[8]. *Serenoa repens* extracts (SrE) are compounds with proven antioxidant and anti-inflammatory activity[9-11], whose effects on sperm quality have rarely been investigated. SrE are frequently combined with other compounds known to positively impact on sperm quality and pregnancy rate such as selenium (Se) and lycopene[8]. The evidence mainly suggests their use for prostatic disease[12]. The aim of this paper was to comprehensively review the literature in the attempt to provide the rational, if any, supporting the indication of the administration of SrE, alone or in combination with Se and lycopene for male infertility.

## Materials and Methods

Data were independently extracted by R.C. and S.L.V. A systematic search was performed through the Pubmed, MEDLINE, Cochrane, Academic One Files, Google Scholar and Scopus databases, from each database inception to November 30, 2018, using Medical Subjects Headings (MeSH) indexes and key words searches. The search strategy used combined MeSH terms and key words and was based on the following key words: *Serenoa repens*, selenium, lycopene, oligozoospermia, oxidative stress, DNA fragmentation, male infertility, pregnancy rate. Additional manual searches were made using the reference lists of relevant studies. No language restriction was used for any literature search.

### *Serenoa Repens*

*Serenoa repens* (alternatively known as saw palmetto or American dwarf palm) is a plant whose extracts have been used for the treatment of benign prostate hyperplasia (BPH)[12]. SrE mainly include free fatty acids (FFA), methyl and ethyl esters, glycerides, flavonoids and sterols[13]. The specific composition of SrE is influenced by the extraction procedures[14]. In great detail, quantitative composition depends on the solubility of the solvent used in the extraction procedure. The use of non-polar solvents ensures the extraction of lipophilic bioactive compounds. A higher FFA concentration is expected to associate with a greater efficacy[14]. Furthermore, due to the thermo-lability of active biomolecules, temperature and other parameters may also influence qualitative composition of SrE. These parameters need to be standardized[14]. Differences in the extraction procedures justify the variable content in SrE among brands, thus influencing the efficacy[13]. SrE target multiple molecular mechanisms. *In vitro* evidence has shown their role as non-competitive inhibitors of 5α-reductase[15]. This is a well-known effect providing the rational for the clinical indication in BPH. The evidence for the effectiveness of SrE in BPH is contradictory. In detail, the last Cochrane meta-analysis investigating a wide range of brands did not find the SrE efficacy on low urinary tract symptoms (LUTS) and maximum urinary flow rate ($Q_{max}$) compared to placebo in BPH patients[16]. However, previous Cochrane meta-analysis of the same group focusing on a specific brand adopting non-polar solvents in the extraction procedures[17,18,12], as well as trials using oily SrE[19,20] showed the effectiveness of SrE in BPH patients. The contradictory data support the different efficacy of brands in the clinical practice, in agreement with the previous statements. This highlights the importance of the adoption of phytotherapic agents obtained with the same validated extraction techniques[21], as clearly stated in the last 2017 European Academy of Urology guidelines[22]. Normal intra-testicular testosterone levels are required for human spermatogenesis[23]. Despite the evidence suggests a slight reversible negative effect on conventional sperm parameters after pharmacological treatment with 5α-reductase inhibitors (e.g. finasteride, dutasteride)[24], the mild 5α-reductase inhibition of SrE might not

necessarily impact on sperm conventional parameters. Furthermore, no available data investigated the effects of the 5α-reductase inhibition on SDF as well as pregnancy rate as far. SrE anti-inflammatory, anti-oxidant and anti-estrogenic properties have been reported[25-27]. Concerning the anti-inflammatory effects, a wide spectrum of enzymes and inflammation mediators like cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), prostaglandins and leukotrienes seem to be targeted by the bioactive compounds included in SrE. Indeed, flavonoids are capable of modulating nitric oxide (NO) production through the inhibition of iNOS in a dose-dependent manner[28]. In addition, they inhibit the lipopolysaccharide (LPS)-induced prostaglandin E2 (PGE2) release and COX-2 expression[28]. SrE have also been showed to significantly reduce the production of leukotrienes and other 5-lipoxygenase metabolites in human polymorphonuclear neutrophils[29]. The effectiveness of SrE administration in the down-regulation of prostate pro-inflammatory cytokines (CCR7, CXCL6, IL-6 and IL-17) has been shown also in mice prostatic tissue[30]. Furthermore, a randomized, double-blind, tamsulosin-controlled clinical trial carried out in 206 men with BPH and LUTS found a significant reduction of inflammatory markers in seminal fluid after digital rectal examination in the group receiving SrE 320 mg compared to that taking tamsulosin 0.4 mg after a 3-month long daily administration[31]. The main outcomes were the macrophage migration inhibitory factor (MIF), the monocyte chemo-attractant protein-1 (MCP-1), also known as Chemokine (C-C motif) ligand 2 (CCL2) and the induced protein (IP)10, also known as C-X-C motif chemokine 10 (CXCL10)[31]. MIF is a T cell-derived cytokine playing a role in innate immunity[32]. It promotes and amplifies inflammatory reactions such as monocytes/macrophage survival of cytokine release[32]. MCP-1/CCL2 and IP-10/CXCL10 are fibroblast-derived cytokines primarily involved in $CD4^+$T cells activation[33,34]. These findings support the *in vivo* anti-inflammatory properties of SrE. Studies on animals largely confirm the anti-inflammatory properties of SrE, but also suggest anti-oxidant effects. In mice models with testosterone-induced BPH, SrE administration reduced total nitrates, malondialdehyde (a marker of lipid peroxidation), pro-inflammatory cytokines [Tumor necrosis factor α (TNFα), interleukin (IL)-1β and IL-6], growth factors [Vascular endothelial growth factor (VEGF) and Fibroblast growth factor β (FGFβ)] and improved total glutathione and the activity of anti-oxidant enzymes like SOD and catalase at the prostatic level[35]. A great amount of literature addressed to glutathione, catalase and SOD a pivotal role in the tricky balance between pro-oxidant and anti-oxidant factors and are currently the main targets of many anti-oxidant therapeutic regimens[8, 36,37]. SrE anti-inflammatory and anti-oxidant effects are listed in Table I. The impact of SrE on the amount of seminal cytokines[31], pro-inflammatory molecules and/or enzymes like leukotrienes [29, PGE2, COX-2[28], as well as on anti-oxidant enzymes (superoxide dismutase [SOD], catalase[35]) and molecules (glutathione[35]) may potentially improve the sperm quality and metabolism. In agreement, the incubation with SrE (9.0 mg/ml) results in the increase of sperm curvilinear velocity and beat cross frequency[20], thus suggesting an improvement of sperm function. Noteworthy, no study evaluated the effects of SrE on SDF or

**Table I.** Anti-inflammatory and anti-oxidant effects con Serenoa repens extracts.

| | Mechanism | References |
|---|---|---|
| Anti-inflammatory | ↓iNOS | |
| | ↓PGE2 | |
| | ↓COX-2 | |
| | ↓Leukotrienes | |
| | ↓Pro-inflammatory cytokines | 19,20,22,25 |
| Anti-oxidant | ↓NO | |
| | ↓Malondialdehyde | |
| | ↑Glutathione | |
| | ↑SOD | |
| | ↑Catalase | 21 |
| Anti-estrogenic | Down-regulation of nuclear ER in mice prostatic tissue | 38 |

Abbreviations: COX-2, cyclooxygenase-2; ER, estrogen receptor; iNOS, inducible nitric oxide synthase; NO, nitric oxide; PGE2, prostaglandin E2; SOD, superoxide dismutase.

pregnancy rate. This represents a black hole and requires further investigation. SrE anti-estrogenic properties have been reported[38]. In a double-blind placebo-controlled study on BPH patients, after a 3-month long SrE administration, the analysis of cytosolic and nuclear estrogen receptors (ER) revealed a significant reduction in nuclear ER in the treated group compared to controls, while the cytosolic ER was mildly affected[38], thus possibly suggesting a role for SrE in ER down-regulation. The possible involvement of ER in the pathogenesis of prostatitis and BPH has been questioned. The evidence suggests a role for the Erα in the promotion of prostatic inflammation[39]. On the contrary, studies indicate the immune-protective effects of Erβ[40,41]. Furthermore, an abnormal Erα/Erβ ratio has been observed in mice models of chronic prostatitis and BPH[42]. Which ER type is specifically down-regulated by SrE is not known. However, the effectiveness on LUTS and BPH may suggest a specific influence on the Erα. Obese patients as well as those with metabolic syndrome or insulin-resistance show a greater risk for prostatitis[43], probably due to the higher aromatase levels and the consequent abnormal androgen/estrogen ratio and relative hyperestrogenism[44]. Meta-analytic data show a negative impact of chronic prostatitis on sperm parameters[45]. Therefore, treatment of prostatitis is an important topic in the management of male infertile patients[8]. In this perspective, SrE supplementation may find elective indication in those cases with "metabolic" prostatitis, due to the anti-estrogenic action of SrE on the prostate tissue[46].

### Selenium

Se is a trace element displaying an essential role for many antioxidant systems in mammals (mainly the glutathione and the thioredoxin-dependent ones)[47]. It is a component of several redox-active selenoenzymes, including five glutathione peroxidases (GPx), three thioredoxin reductase and methionine sulfoxide reductase 2, containing Se in the active site[48]. GPx enzymes reduce hydrogen peroxide, organic hydroperoxides and phospholipid hydroperoxides using reduced glutathione as co-substrate[48,49]. Furthermore, circulating Se protein 1, a serum Se transported protein, displays antioxidant activities, acting as a phospholipid hydroperoxide-GPx and as a peroxynitrite reductase[50,51]. Se influences testicular development, spermatogenesis, sperm motility and function. Indeed, its deficiency has be related to spermatogenic failure, testicular hypotrophy, atrophy of seminiferous epithelium, abnormal sperm motility and morphology[37].The intra-peritoneal administration of Se nanoparticles resulted, after a complete spermatogenic cycle, in more powerful antioxidant properties of testicular and blood tissues coming from treated animals compared to those of controls[52]. In this study, catalase, SOD and glutathione peroxidase activities and malondialdehyde levels were used as indicators of tissue antioxidant capacity. Furthermore, treated mice also showed greater sperm quality and *in vitro* fertilization outcomes compared to controls[52]. These results are in favor of the antioxidant role of Se. Different trials investigated the effects of Se supplementation in sperm parameters. A recent meta-analysis of randomized clinical trials found the efficacy of Se supplementation in raising sperm concentration, motility and morphology[53]. Furthermore, Se *in vitro* incubation improves human sperm motility, reduces malondialdehyde levels and SDF in asthenozoospermic samples[54]. Also, it's administration has been suggested to positively impact on sperm parameters[55]. No study evaluated the effects of Se single supplementation on pregnancy rate. The 100-day long combined administration of Se (200μg daily) plus vitamin E (400 units daily) resulted in a higher spontaneous pregnancy rate in treated patients compared to controls[56]. The role of Se administration in the management of male infertility has been recognized by the SIAMS, which included this micronutrient among the list of the available nutraceuticals with antioxidant properties detailed in the 2017 Guidelines on this topic[4].

### Lycopene

Lycopene, which can be found in ripe tomato fruit, watermelon or pink grapefruit, belongs to the family of carotenoids, that include also α-tochoferol, α-carotene, β-cryptoxanthin, β-carotene and lutein. It is able to quench single oxygen, being the most effective antioxidant among carotenoids[57]. It has also been suggested to indirectly increase antioxidant enzymes levels and to decrease transcription of pro-inflammatory factors[58]. Studies on bovine spermatozoa confirm the *in vitro* ROS-scavenging properties. Indeed, the incubation with lycopene at the dose of 1 and 2 mmol/l prevented the decline of sperm motility, preserved mitochondrial activity and antioxidant charac-

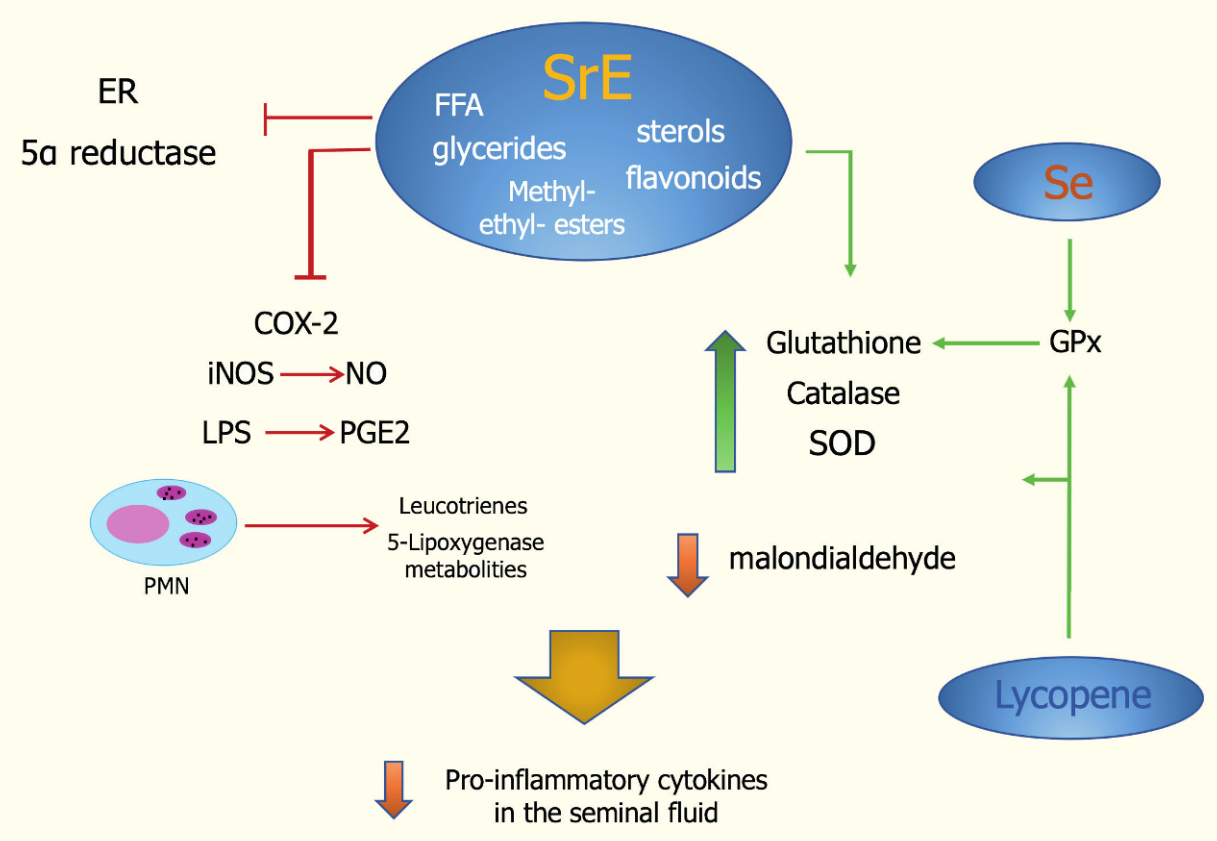


**Figure 1.** Effects of combined administration of *Serenoa repens* extracts, selenium and lycopene on markers of inflammation and oxidative stress. Serenoa repens extracts (SrE), including free-fat acids (FFA), glycerides, methyl- and ethyl-esters, sterols and flavonoids, show anti-estrogenic properties, inhibits the 5α-reductase and display anti-inflammatory and anti-oxidant effects. The anti-inflammatory function is due to the inhibition of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) expression, lipopolysaccharide (LPS)-derived prostaglandin E2 (PGE2) synthesis, secretion of leucotrienes and 5-lipoxygenase metabolites from polymorphonucleate cells (PMN). The anti-oxidant effects are displayed by the raise in glutathione, catalase and superoxide dismutase (SOD) levels and the decrease of malondialdehyde. All together, these mechanisms result in a reduction of pro-inflammatory cytokines in the seminal fluid. Selenium (Se) and lycopene may synergize with SrE raising glutathione, catalase and SOD levels and reducing malondialdehyde ones.

teristics (e.g. glutathione and malondialdehyde concentrations, SOD, catalase, GPx intracellular activity) despite the addition of a pro-oxidative substance[59]. In healthy young men, lycopene intake has been positively correlated to sperm morphology[60]. Accordingly, evidence from a randomized clinical trial suggested that tomato juice consumption, by increasing plasma lycopene levels, significantly reduce white blood cells and increases sperm motility[61]. Furthermore, sperm incubation with lycopene seems effective in reducing the oxidative damage to sperm mitochondria and plasma membrane in the freezing-thawing process. In addition, it improves sperm anti-apoptosis ability[62] and SDF[63]. Finally, lycopene administration has been shown to facilitate spontaneous and assisted conception[64]. These data support lycopene anti-oxidant properties as well as its effectiveness in preventing sperm from oxidative stress-induced damage, as recognized from the SIAMS[4].

## Conclusions

Despite few evidence has investigated the effects of SrE supplementation on sperm quality and oxidative damage so far, their anti-inflammatory and anti-oxidant properties suggest a

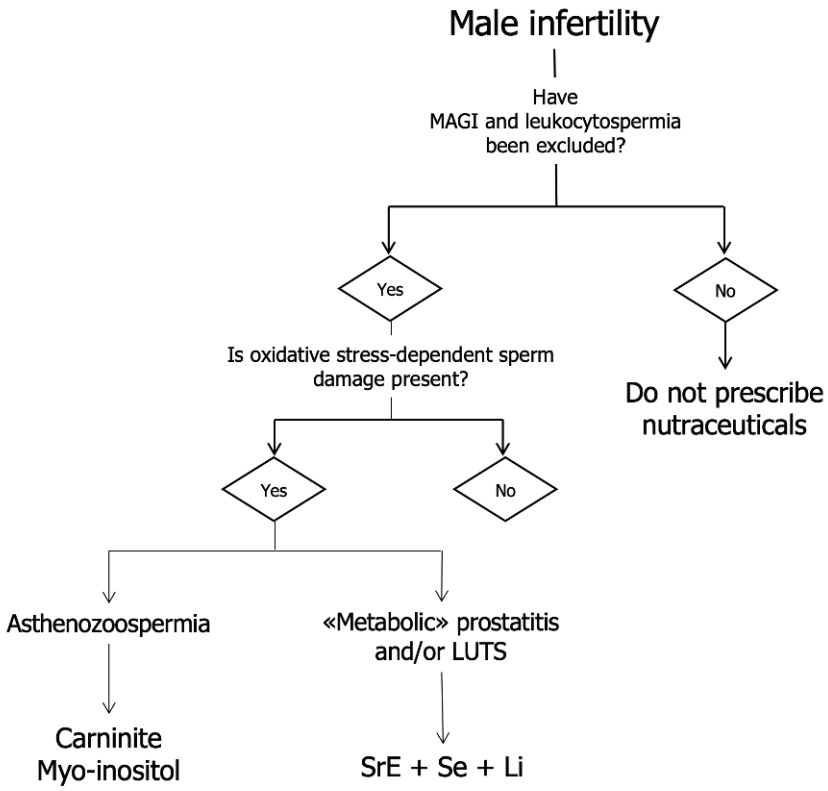


**Figure 2.** Flow-chart of the choice of the nutraceutical supplement to be considered in patients with idiopathic male infertility. In patients with male infertility, whose idiopathic form has been ascertained and no sign of male accessory gland infection/inflammation (MAGI) as well as leukocytospermia has be found, antioxidant administration has to be considered in case of demonstrated sperm oxidative stress-dependent damage. In particular, carnitine or myo-inositol might be suggested in case of asthenozoospermia, whereas *Serenoa repens* extracts (SrE) combined with Selenium (Se) and Licopene (Li) may be considered when "metabolic" prostatitis and/or low urinary tract symptoms (LUTS) occur.

possible role of SrE in the treatment of male infertility. SrE are available alone or often in combination with Se and lycopene. Some evidence suggest a greater efficacy of the combined therapy compared to SrE alone on prostatic inflammation[19,20]. This may be attributed to a synergic action of such nutraceuticals. In fact, combined therapy may amplify the raise of glutathione, catalase and SOD levels and reduce malondialdehyde ones (Figure 1), thus likely improving the sperm quality. Since prostatitis negatively influence the sperm parameters[45,65], SrE anti-estrogenic properties might let to hypothesize a specific therapeutic indication for the subgroup of infertile patients with "metabolic" prostatitis (those cases of prostatitis in which obesity and abnormal androgen/estrogen ratio concomitantly occur). We suggest a possible flow-chart to be applied for those patients with idiopathic male infertility, which might help the clinician to personalize the choice of the nutraceutical supplement in a case-specific manner. In great detail, after the exclusion of male accessory gland infections, a highly frequent disease negatively impacting on quality of life and sexual performance[66] as well as leucocytospermia, patients with asthenozoospermia may benefit from carnitine or myo-inositol administration. Indeed, both carnitine (by the transport of long-chain fatty acids into the mitochondrial matrix) and myo-inositol (acting on the mitochondrial membrane potential) can improve the mitochondrial function and sperm motility[67,68]. On the contrary, patients with idiopathic infertility and "metabolic" prostatitis and/or LUTS might be addressed to SrE supplementation (Figure 2). In summary, this review provides the rational for the administration of SrE combined with Se and lycopene in male infertility. Proper studies investigating

the effects of SrE combined supplementation on sperm quality are warranted.

### Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

### Conflict of Interest

The Authors declare that they have no conflict of interest.

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