

**Supplementary Table S1:** In vitro models investigating antioxidants, micronutrients or phytonutrients including both testosterone and oxidative stress outcomes

| Antioxidant                | Animal Model   | Reported Outcomes  | Reference |
|----------------------------|--|--|-----------|
| Cerium oxide nanoparticles | Radiofrequency radiation induced oxidative stress in primary mouse Leydig cells      | <ul style="list-style-type: none"> <li>• ↑ testosterone</li> <li>• ↑ StAR and 3β-HSD</li> <li>• ↑ TAC</li> <li>• ↑ CAT</li> <li>• ↓ MDA</li> </ul>   | [159]     |
| Taurine                    | di(2-ethylhexyl)phthalate induced oxidative stress and apoptosis in TM3 Leydig cells | <ul style="list-style-type: none"> <li>• ↑ cellular viability</li> <li>• ↑ testosterone</li> <li>• ↓ MDA</li> <li>• ↓ Bax/Bcl2 ratio</li> <li>• ↓ caspase-3 and -9</li> </ul>  | [160]     |
| Astaxanthin                | Hydrogen peroxide induced oxidative stress in TM3 Leydig cells                       | <ul style="list-style-type: none"> <li>• ↑ testosterone and progesterone</li> <li>• ↓ intracellular ROS</li> <li>• ↑ StAR expression</li> </ul>  | [161]     |
| Melatonin                  | LPS induced inflammation in primary sheep Leydig cells and macrophages co-culture    | <ul style="list-style-type: none"> <li>• ↑ testosterone in Leydig cells</li> <li>• ↑ StAR, 3β-HSD and SF-1 in Leydig cells</li> <li>• ↓ TNF-α, IL-1β, and IL-6</li> <li>• ↑ IL-10</li> <li>• ↓ macrophages secreting inflammatory cytokines and ↑ phagocytic macrophages</li> <li>• ↓ p38/MAPK in macrophages</li> <li>• ↓ TLR4-mediated inflammatory genes in macrophages</li> <li>• ↓ iNOS and NADPH in macrophages</li> </ul> | [162]     |
| Resveratrol                | Hydrogen peroxide induced oxidative stress in TM3 Leydig cells                       | <ul style="list-style-type: none"> <li>• ↑ testosterone and progesterone</li> <li>• ↑ metabolic activity and cell membrane integrity</li> <li>• ↓ intracellular ROS</li> </ul>   | [163]     |
|                            | Primary Leydig cells of energy restricted sheep                                      | <ul style="list-style-type: none"> <li>• ↑ testosterone</li> <li>• ↑ cell proliferation</li> <li>• ↑ steroidogenesis enzymes</li> </ul>  | [164]     |
|                            | Benzo(a)Pyrene induced steroidogenic dysfunction in TM3 Leydig cells                 | <ul style="list-style-type: none"> <li>• ↑ cellular viability</li> <li>• ↑ testosterone</li> <li>• ↑ expression of StAR, CYP11A1, 3β-HSD and 17β-HSD</li> <li>• ↑ p38 MAPK</li> <li>• ↑ SF1</li> <li>• ↑ SOD1, SOD2, GPx and CAT</li> </ul>  | [165]     |
| Rutin                      | Hydrogen peroxide induced oxidative stress in TM3 Leydig cells                       | <ul style="list-style-type: none"> <li>• ↑ cell survival rate</li> <li>• ↑ testosterone</li> <li>• ↓ intracellular ROS and LPO</li> <li>• ↓ GPx</li> </ul>   | [166]     |

|                            |  |   |       |
|----------------------------|--|---|-------|
|                            |  | <ul style="list-style-type: none"> <li>• ↑ CAT, SOD, peroxidase</li> <li>• ↑ Bcl-2, PI3K and p-AKT</li> <li>• ↓ Bax and caspase-3</li> </ul>  |       |
| Quercetin                  | Triptolide induced oxidative stress in rat Leydig cells        | <ul style="list-style-type: none"> <li>• ↑ testosterone</li> <li>• ↓ intracellular ROS</li> <li>• ↑ GPx and SOD</li> <li>• ↓ Apoptosis</li> <li>• ↑ MMP</li> <li>• ↓ BAX/Bcl-2 ratio</li> <li>• ↓ caspase-3 and -9</li> </ul> | [167] |
| <i>Morinda officinalis</i> | Hydrogen peroxide induced oxidative stress in TM3 Leydig cells | <ul style="list-style-type: none"> <li>• ↑ cellular viability</li> <li>• ↑ testosterone</li> <li>• ↓ LPO</li> <li>• ↑ SOD</li> </ul>  | [168] |
| <i>Moringa oleifera</i>    | TM3 Leydig cells   | <ul style="list-style-type: none"> <li>• No change in cell viability</li> <li>• ↑ testosterone</li> <li>• ↑ GSH</li> <li>• No change for CAT, SOD and TAC</li> <li>• No change for lipid peroxidation</li> </ul>              | [169] |
| <i>Salvia officinalis</i>  | TM3 Leydig cells   | <ul style="list-style-type: none"> <li>• ↑ testosterone and progesterone</li> <li>• No induction of oxidative stress except at highest concentrations exposed</li> </ul>  | [170] |

**Abbreviations:** 3 $\beta$ -HSD: 3 $\beta$ -Hydroxysteroid dehydrogenase; 17 $\beta$ -HSD: 17 $\beta$ -Hydroxysteroid dehydrogenase; Akt: Protein kinase B; Bax: Bcl-2-associated X protein; CAT: catalase; CYP11A1: cytochrome P450 family 11 subfamily A member 1; GPx: glutathione peroxidase; GSH: glutathione; IL: interleukin; iNOS: inducible nitric oxide synthase; LPO: lipid peroxidation; MDA: malondialdehyde; MMP: mitochondrial membrane potential; PI3K: phosphatidylinositol 3-kinases; ROS: reactive oxygen species; SF1: splicing factor 1; SOD: superoxide dismutase; TAC: total antioxidant capacity; StAR: steroidogenic acute regulatory; TLR4: toll-like receptor 4; TNF $\alpha$ : tumor necrosis factor alpha.

**Supplementary Table S2:** Animal models investigating antioxidants, micronutrients or phytonutrients including both testosterone and oxidative stress outcomes

| Antioxidant                         | Animal Model   | Reported Outcomes   | Reference |
|-------------------------------------|--|---|-----------|
| Vitamin A and Vitamin C Combination | Aroclor induced testicular toxicity in adult rats                  | <ul style="list-style-type: none"> <li>• ↑ serum testosterone, LH and FSH</li> <li>• ↓ serum prolactin and oestrogen</li> <li>• ↑ LH receptor expression on Leydig cells</li> <li>• ↑ P450<sub>scc</sub>, 3β-HSD and 17β-HSD in Leydig cells</li> <li>• ↑ SOD, CAT, GPx, GR, γ-GT and GST in Leydig cells</li> <li>• ↓ ROS and LPO in Leydig cells</li> </ul> | [171]     |
| Zinc                                | Cadmium induced testicular toxicity in adult rats                  | <ul style="list-style-type: none"> <li>• ↑ serum testosterone and LH</li> <li>• ↑ sperm concentration and motility</li> <li>• ↓ testicular MDA</li> <li>• ↓ testicular TNFα</li> <li>• ↓ testicular NO and iNOS</li> <li>• Improvement in testicular histological damage</li> </ul>   | [172]     |
| N-acetylcysteine (NAC)              | Aroclor induced testicular toxicity in adult rats                  | <ul style="list-style-type: none"> <li>• ↑ serum testosterone</li> <li>• ↑ Leydig cell intracellular cAMP</li> <li>• ↓ Leydig cell LPO</li> <li>• ↓ Leydig cell apoptosis</li> <li>• ↓ Leydig cell caspase-3, -8 and -9, Bax, Fas, FasL and JNK/pJNK</li> <li>• ↑ Bcl-2, pAkt/Akt and NF-κβ</li> </ul>  | [173]     |
|                                     | BMI1 null mice   | <ul style="list-style-type: none"> <li>• ↑ steroidogenesis</li> <li>• ↓ DNA damage</li> <li>• ↓ cellular senescence</li> </ul>  | [174]     |
| Gallic acid                         | Cisplatin induced reproductive toxicity in adult rats              | <ul style="list-style-type: none"> <li>• ↑ serum testosterone</li> <li>• ↑ spermatogonia, Leydig and Sertoli cell numbers</li> <li>• ↑ testicular volume</li> <li>• ↑ testicular CAT, SOD and GSH enzymes</li> </ul>  | [175]     |
| Lycopene                            | Polychlorinated biphenyl induced testicular toxicity in adult rats | <ul style="list-style-type: none"> <li>• ↑ serum testosterone</li> <li>• ↑ Leydig cell StAR, P450<sub>scc</sub> and 3β-HSD expression</li> </ul>  | [176]     |
| Forskolin                           | Mancozeb-induced reproductive toxicity in adult rats               | <ul style="list-style-type: none"> <li>• ↑ serum testosterone</li> <li>• ↑ spermatogenesis</li> <li>• ↑ epididymal sperm count</li> <li>• ↑ testicular GSH, SOD and CAT activity</li> </ul>   | [177]     |

|  |  |  |       |
|--|--|--|-------|
| Resveratrol                                      | Diet induced obesity associated secondary hypogonadism in mice | <ul style="list-style-type: none"> <li>• ↑ serum testosterone and LH</li> <li>• ↑ testicular StAR and steroidogenic enzyme</li> <li>• ↑ testicular SOD and GPx</li> </ul>  | [178] |
|  | Benzo(a)Pyrene steroidogenic dysfunction in adult rats         | <ul style="list-style-type: none"> <li>• ↑ serum and intratesticular testosterone</li> <li>• ↓ intratesticular ROS</li> <li>• ↑ Leydig cell expression of StAR, CYP11A1, 3β-HSD and 17β-HSD</li> <li>• ↑ Leydig cell SF1 expression</li> <li>• ↓ Leydig cell DAX production</li> </ul>   | [165] |
| <i>Nigella sativa</i> seed oil                   | Chlorpyrifos-induced reproductive toxicity in adult rats       | <ul style="list-style-type: none"> <li>• ↑ serum testosterone</li> <li>• ↑ semen parameters</li> <li>• ↑ serum GSH and antioxidant enzymes</li> <li>• ↓ serum ROS</li> </ul>   | [179] |
| <i>Lycium chinense</i> Mill                      | Aged rat model of late-onset hypogonadism                      | <ul style="list-style-type: none"> <li>• ↑ serum testosterone</li> <li>• ↓ testicular oxidative stress</li> </ul>  | [180] |
| <i>Eruca sativa</i> seeds                        | Silver nanoparticles induced testicular toxicity in adult rats | <ul style="list-style-type: none"> <li>• ↑ serum testosterone, LH, FSH and prolactin</li> <li>• ↑ testicular GSH, GST, SOD</li> <li>• ↓ testicular serum TBARS</li> <li>• ↓ Leydig cell TNFα concentrations</li> <li>• ↓ testicular DNA fragmentation</li> </ul>   | [181] |
| <i>Moringa oleifera</i> leaves                   | Tramadol induced testicular toxicity in adult rats             | <ul style="list-style-type: none"> <li>• ↑ serum testosterone, LH and FSH</li> <li>• ↑ body weight and testes weight</li> <li>• ↑ sperm counts, vitality, total sperm motility and normal morphology</li> <li>• ↑ testicular CAT and SOD</li> <li>• ↓ testicular TBARS</li> <li>• ↑ spermatogenic cell and Leydig cell numbers</li> </ul>  | [182] |
| <i>Schisandra chinensis</i>                      | Varicocele induced testicular dysfunction                      | <ul style="list-style-type: none"> <li>• ↑ serum testosterone</li> <li>• ↓ serum LH and FSH</li> <li>• ↑ testicular weight, sperm count and sperm motility</li> <li>• ↑ testicular Johnsen score and spermatogenic cell density</li> <li>• ↑ testicular SOD, GPx and CAT</li> <li>• ↓ testicular MDA, ROS, RNS</li> <li>• ↓ apoptotic index</li> <li>• ↑ testicular StAR</li> <li>• ↓ Grp 78, p-JNK, p-IRE1α</li> <li>• ↓ cleaved caspase 3</li> <li>• ↓ Bax:Bcl2</li> </ul> | [183] |
| Ojayeonjonghwan (KH-204 - Korean herbal formula) | Aged rat model of late-onset hypogonadism                      | <ul style="list-style-type: none"> <li>• ↑ serum testosterone</li> <li>• ↑ serum SOD</li> <li>• ↓ serum 8-OHdG</li> </ul>  | [184] |

|   |  |  |       |
|---|--|--|-------|
|   | Leuprorelin induced androgen deprived rats                       | <ul style="list-style-type: none"> <li>• ↑ serum testosterone</li> <li>• ↑ serum SOD</li> <li>• ↓ serum 8-OHdG</li> <li>• ↑ Leydig cell expression of Nrf2/HO-1</li> <li>• ↓ expression of TGF-β 1/SMAD</li> </ul>             | [185] |
| Qilin pills (Traditional Chinese Medicine herbal formula) | Tripterygium glycoside induced oligoasthenospermia in adult rats | <ul style="list-style-type: none"> <li>• ↑ serum testosterone, LH, FSH, SHBG</li> <li>• ↑ semen parameters</li> <li>• ↑ testicular SOD</li> <li>• ↓ testicular ROS and MDA</li> <li>• Improved testicular histology</li> </ul> | [186] |

**Abbreviations:** 3β-HSD: 3β-Hydroxysteroid dehydrogenase; 8-OHdG: 8-hydroxy-20-deoxyguanosine; 17β-HSD: 17β-Hydroxysteroid dehydrogenase; Akt: Protein kinase B; Bax: Bcl-2-associated X protein; cAMP: cyclic adenosine monophosphate; CAT: catalase; CYP11A1: cytochrome P450 family 11 subfamily A member 1; FasL: Fas ligand; FSH: Follicle-stimulating hormone; GPx: glutathione peroxidase; GR: glutathione reductase; Grp 78: glucose-regulated protein-78; GSH: glutathione; GST: glutathione S-transferase; HO-1: heme oxygenase-1; iNOS: inducible nitric oxide synthase; JNK: c-Jun N-terminal kinase; LH: luteinizing hormone; LPO: lipid peroxidation; MDA: malondialdehyde; NF-κβ: nuclear factor κB; NO: nitric oxide; Nrf2: nuclear factor erythroid 2-related factor 2; P450scc: Cholesterol side-chain cleavage enzyme; p-IRE1α: phosphorylated inositol-requiring transmembrane kinase/endoribonuclease 1α; RNS: reactive nitrogen species; ROS: reactive oxygen species; SF1: splicing factor 1; SHBG: sex hormone binding globulin; SMAD: Mothers against decapentaplegic; SOD: superoxide dismutase; StAR: steroidogenic acute regulatory; TBARS: thiobarbituric acid reactive substances; TGF-β - transforming growth factor-beta; TNFα: tumor necrosis factor alpha; γ-GT: gamma glutamyl transferase.