Plant Extract and Infertility

Subjects: Others

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Infertility is a couple’s inability to conceive after one year of unprotected regular intercourse.

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1. Infertility

Female infertility can be caused by failures at various steps, including ovulation, fertilization, embryo development, embryo transport, and implantation [1]. The different responses of environment toxicity include reduced fertility, spontaneous abortions, low birth weight, impaired folliculogenesis, and even damage to the ovaries [2]. OS induces infertility in woman through a variety of mechanisms [3], having a direct effect on the oocyte, embryo, and implantation by causing cell membrane lipid peroxidation, cellular protein oxidation, and DNA damage [4]. Excess ROS in the follicle may overwhelm follicular fluid antioxidant defense and hinder the endometrium which normally functions to support the embryo and its development [3]. Appropriate development of embryo and receptive endometrium are crucial factors for successful implantation [5]. Endometrial receptivity is critical for blastocyst adhesion and invasion during the complex process of implantation. Leukemia inhibitory factor (LIF) in particular is one of the major factors that regulates endometrial receptivity. Defects of LIF expression is involved in multiple implantation failures in patients with female infertility. OS is also associated with conditions such as endometriosis, hydrosalpinges, polycystic ovary syndrome (PCOS), and unexplained subfertility [4]. In addition, there is a lack of specific genetic markers because of the absence of an inherited syndrome that could implicate a gene in the pathogenesis of female infertility [6]. Mutations in the human LH P-subunit gene recently have been reported and linked with infertility. Endometriosis is noted in up to 30–40% of infertile women. Luteinizing hormone (LH) and its receptors have been linked with endometriosis-associated infertility. Reproduction is tightly controlled by hypothalamic–pituitary–gonadal axis [7]. Reproduction systems respond to hormonal signals from the pituitary gland which, in turn, is controlled by hormones produced in the hypothalamus [8]. Interruption of these processes, in any of the functional events in either sex, leads to fertility impairment [7] including gonadal dysgenesis, amenorrhea, premature ovarian failure [8]. Mammalian reproductive physiology is primarily regulated by the gonadotrophins luteinizing hormone (LH) and follicle stimulating hormone (FSH) secreted from the anterior pituitary which act on the gonads to produce sex steroids [9]. These pituitary hormones in turn enhance the proliferation of the follicular cells and the production of estrogens (principally estradiol) by ovarian cholesterol catabolism [10]. Additionally, they can lead to and restore spermatogenesis [11]. The initiation and maintenance of mammalian infertility are connected with G-protein coupled receptor 54 (GPR54) [12]. The mutation in GPR 54 is characterized by the absence of sexual maturation and low levels of gonadotropin releasing hormones (GnRH). Abnormal GnRH secretion induces anovulation, luteal insufficiency, and premature oocyte maturation, leading to menstrual disorders, polycystic ovary syndrome (PCOS), recurrent miscarriage, and infertility [6]. Additionally, it could affect the testicular function with decrease in T release [13]. Estrogen affects granulosa cells by promotion of proliferation, suppression of apoptosis, and augmentation of FSH effects. Homeostatic maintenance of prolactine (PRL) is essential since this hormone performs multiple physiological functions [14]. Increased PRL levels can cause infertility and bone loss in both women and men. It has been reported that E2 increases serum and pituitary PRL in ovariectomized rats. In addition, precursor of E2 and P4, pregnelone sulfate also increases prolactin production in the rat pituitary. On the other hand, compounds derived from natural food and herbal medicine showing promising antioxidant and antiapoptotic potentials have been considered an alternative therapy for disease [15].

The antioxidant system plays an importance role in protecting reproductive and other biological tissues below a critical threshold of ROS, preventing negative effects on reproduction [16]. Herbal medicines possessing antioxidants reduced ROS levels, protecting germ cells from OS-mediated apoptosis [17]. They could be used as complementary, alternative medicines to promote pregnancy [18].

2. Plant Extract and Infertility

Several herbal extracts and plant-derived pure molecules have shown their protective effects in various types of diseases [19], including those that affect the reproductive system [20]. Recent studies have shown that the administration of plant extracts improve semen parameters, androgen status, fertility index, and have positive influence on sperm quality in male [21][22]. In female, herbal medicine affects the molecular mechanism and prevents estrogen-dependent endometrial hyperplasia improving ovarian dysfunction, ovarian follicle [23], and increased endometrial receptivity [1][5]. Additionally, herbal therapy that has actions on the hypothalamic–pituitary–gonadal axis may influence reproductive physiology and ameliorates some infertility problems [7]. The gonadotrophic-like effects of the extracts were characterized by the following biological parameters: increase in the weight of the ovary and uterus; induction of ovulation; increase in estradiol, progesterone, protein levels; decrease in cholesterol level, and so forth [10]. The antimutagenic or protective effects have been attributed to many classes of phytocompounds mainly flavonoids and phenolic compounds [24]. The natural antioxidants with free radical scavenging ability have received much attention as potential remedies to treat oxidative stress and abnormal hormone functions [8][25]. Antioxidants can directly scavenge ROS, inactivate them, and repair the damage [4]. Additionally, they showed diverse biological activities resulting from their ability to mimic endogenous estrogen actions, inhibit hormone actions, and modulate hormone productions [8]. The antioxidant capacity of phenolic compounds, flavonoids, and foods rich in these compounds, has been repeatedly demonstrated in various in vitro and in vivo systems. In this present study, we aimed to investigate the effects and mechanisms of various plants extracts and natural products on the reproductive system. A large number of plants have been used to treat infertility for thousands years worldwide, including Korea [26][27]. Additionally, numerous natural products, including plant extracts were discovered to possess potential effects in reversing reproductive activity in both males and females. Natural products originated from plants, animals, and fungi, and their forms varied from compounds, extracts, as well as multiple formulas. Studies have discovered structural and functional improvements in the reproductive system while identifying the specific mechanisms of effects. However, adverse effects were also observed to be related with the utilization of some natural products.

2.1. Natural Products That Reverse Male Infertility

2.1.1. Plant Derived Natural Products for Treatment of Male Infertility

In Vitro Studies

Several studies reported the efficacy of plant derived natural products through in vitro examination (Table 1).

Table 1. Plant derived natural products and male infertility (in vitro studies).

Classification	Compound/Extract	System	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Plant	Date palm pollen extract	In vitro	*Phoenix dactylifera* Linn.	Sertoli cells, spermatogonial stem cells from mice	0.06, 0.25, 0.62 mg/mL; 14 days	Increase of proliferation of spermatogonia		[28]
Plant	5H-purin-6-amine, *Sedum sarmentosum* extract	In vitro	*Sedum sarmentosum*	Spermatogonial stem cells C57BL. 6-TG-EGFP	0.01, 0.1, 1, 10 mg/mL; 1 week	Increase of self-renewal in SSCs	↑ PLZF, GFRα1, VASA, Lhx1 ↓ Pgk2	[29]
Plant	Licorice extract	In vitro	*Glycyrrhiza uralensis* Fisch.	Testis tissue from C57BL/6N mice	0.2, 2, 20 μmol/L; 72 h	Increase of proliferation of spermatogonia	↑ PCNA, SCP3, Spo11	[30]
Plant	*Lycium barbarum* polysaccharide	In vitro	*Lycium barbarum* Linn.	Leydig MLTC-1	50 μg/mL; 48 h	Increase of cell viability	↑ Testosterone, ↓ p-PERK/PERK, p-eIF2α/eIF2α, ATF4/β-actin, apoptosis rate, LC3II/I, Atg5/β-actin	[31]

In Vitro and in Vivo Studies

Seveal studies were conducted both in vitro and in vivo to prove the effectiveness of natural substances of plant origin (Table 2).

Table 2. Plant derived natural products and male infertility (in vitro and in vivo studies).

Classification	Compound/Extract	System	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Plant	*Morindae* radix aqueous extract	In vitro	*Morinda officinalis*	TM3 cells, mouse Leydig cells	10, 50, 100, 250 mg/mL; 24 h	Increase of testosterone production. Decrease of H$_2$O$_2$ induced cytotoxicity, and lipid peroxidation	↑ SOD, CAT ↓ MDA	[32]
Plant	*Taraxacum officinale* aqueous extract	In vitro	*Taraxacum officinale*	TM3, ATCCNoCRL	1, 10, 25, 50 mg/mL; 12, 48 h	Increase of the levels of steroidogenic enzymes	↑ STAR, CYP11A1, CYP17A1	[33]
Plant	*Typha capensis* rhizome extract F1 fraction	In vitro	*Typha capensis (Rohrb.) N.E.Br.*	TM3-Leydig cells	10, 100 µg/mL; 96 h	↑ Testosterone		[34]
Plant	*Echinacea purpurea* aqueous extract (encapsulated chitosan/silica nanoparticle)	In vitro and in vivo studies	*Echinacea purpurea* Linn.	(1) LC540 (2) SD rats	(1) 25 µg/mL; 24 h (2) 270, 465 mg/kg; 7 weeks	(1) Increase of seminiferous tubules diameter, germinal cell layer thickness, area of seminiferous tubules, area of seminiferous lumen, sperm motility, sperm DNA integrity Decrease of sperm abnormality (2) Increase of seminiferous tubules diameter, germinal cell layer thickness, area of seminiferous tubules, area of seminiferous lumen, sperm motility, sperm DNA integrity Decrease of sperm abnormality	(1) ↓ NO (2) ↓ TNF-α, IL-1β	[35]
Plant	Echinacoside	In vitro and in vivo studies	*Cistanche tubulosa* (Schrenk) Hook. f. II.	(1) LC-540, TM3 (2) SD rats	(1) 5, 10 µM (2) 160, 320 mg/kg; 6 weeks	(1) Increase of cell viability (2) Increase of sperm number, sperm motility, seminiferous tubule thickness Decrease of sperm abnormality	(1) LC-540, TM3: ↓ Superoxide anion, LC-540: ↑ StAR, CYP11A1, CYP17A1, HSD17β3 ↓ RAGE, NF-*κB*, H$_2$O$_2$ (2) ↑ LH, KISS1, SIRT1, GPR54, SOCS -3, SOD, CAT ↓ NO, TNF-α, IL-6, superoxide, MDA	[12]

PCNA, proliferating cell nuclear antigen; PERK, protein kinase-like endoplasmic reticulum kinase; p-PERK, phospho-PERK; eIF2α, eukaryotic initiation factor 2; p-eIF2α, phospho-eIF2α; ATF4, activating transcription factor 4; SCP3, synaptonemal complex protein 3; SOD, superoxide dismutase; CAT, catalase; MDA, malondialdehyde; StAR, steroidogenic acute regulatory protein; CYP17A1, cytochrome P450 17A1; CYP11A1, cytochrome P450 11A1.

2.1.2. Animal Derived Natural Products for Treatment of Male Infertility

Natural products from animal origin were also mentioned to have profertility effects upon males in various studies (Table 3).

Table 3. Animal derived natural products and male infertility.

Classification	Compound/Extract	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Insect	Drone milk	*Apis mellifera*	SD rats	110 mg/kg; 5, 10 days	Increase of weight of androgen-sensitive organs (glans penis, seminal vesicle, muscles)	↑ Testosterone, SLAP	[36]

NO, nitric oxide; TNF-α, tumor necrosis factor α; IL-1β, interleukin 1 beta; CYP17A1, Cytochrome P450 17A1; CYP11A1, cytochrome P450 11A1; HSD17β3, hydroxysteroid dehydrogenase 17β3; RAGE, receptor for advanced glycation end products; NF-*κB*, nuclear factor kappa-light-chain-enhancer of activated B cells; H$_2$O$_2$, hydrogen peroxide; LH, luteinizing hormone; Kiss1, kisspeptin 1; SIRT1, sirtuin 1; GPR54, G protein-coupled receptor; SOCS-3, suppressor of cytokine signaling 3; SOD, superoxide dismutase; CAT, catalase; IL-6, interleukin 6.

Classification	Compound/Extract	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Animal	Gelam Honey	*Apis mellifera*	SD rats	1.0 mL/100 g; 60 days	Increase of fertility	↑ Fructose	[11]
Insect	Hydroethanolic extract of Indian propolis	*Apismellifera*	Swiss albino mice	400 mg/kg; 4 weeks	Increase of testis weight, sperm count, total motility, spermatozoa with normal head morphology, spermatozoa with normal DNA, number of tubules with complete spermatogenesis, diameter of seminiferous tubule, number of germ cells Decrease of sperm DNA damage, chromatin immaturity, apoptosis in spermatogonial germ cell	↑ Testosterone, GSH, CAT ↓ MDA, RAD51	[37]
Animal	Spermaturin	Scorpion *Scorpio maurus palmatus*	(1) Bovine sperm (2) Monkey sperm (3) Mouse oocytes	(1) dilution 1/20; 10 min (2) dilution 1/40; 10 min (3) dilution 1/40; 4 h	Improvement of sperm motility		[38]
Fungi	*Antrodia cinnamomea* ethanol extract	*Antrodia cinnamomea* Chang.	SD rats	385, 770, 1540 mg/kg; 5 weeks	Increase of total sperm count, motility rate Decrease of abnormal sperm count, DNA damage in sperm	↑ LH, testosterone, StAR, CYP11A1, 17β-HSD, SOD ↓ RAGE, GRP-78, H_2O_2, NO, MDA	[39]

SD, Sprague Dawley; SLAP, spot14-like androgen-inducible protein; TBRAS, thiobarbituric acid-reactive substances; LDH, lactic dehydrogenase; GSH, glutathione; CAT, catalase; MDA, malondialdehyde.

SD, Sprague Dawley; LH, luteinizing hormone; StAR, steroidogenic acute regulatory; CYP11A1, cytochrome P450 11A1; 17β-HSD, 17β-hydroxysteroid dehydrogenase; SOD, superoxide dismutase; RAGE, receptor for advanced glycation end products; GRP-78, glucose-regulated protein-78; H_2O_2, hydrogen peroxide; NO, nitric oxide; MDA, malondialdehyde.

2.1.3. Fungus Derived Natural Products for Treatment of Male Infertility

One study was found to elucidate the efficacy in male fertility of fungus derived natural product (Table 4).

Table 4. Fungus derived natural product and male infertility.

2.2. Natural Products That Reverse Female Infertility

2.2.1. Animal Derived Natural Products for Treatment of Female Infertility

A single study mentioned a natural product from an animal that showed the capacity to recover infertility problems in females (Table 5). Royal jelly is a dietary substance originated from *Apis mellifera* [40]. Elham Ghanbari et al. demonstrated that administration of royal jelly to Wistar rats (100, 200, 400 mg/kg for 14 days) resulted in the folliculogenesis by a significant increase of uterine and ovarian weights, the serum levels of progesterone, estradiol, FRAP, and a decrease in NO level.

Table 5. Animal derived natural products and female infertility.

Classification	Compound/Extract	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Animal	Royal jelly	*Apis mellifera*	Wistar rats	100, 200, 400 mg/kg; 14 days	Increase of ovarian hormones and folliculogenesis	↑ FRAP, progesterone, estradiol ↓ NO	[40]

FRAP, ferric reducing antioxidant power assay; NO, nitric oxide.

3. Conclusions

In conclusion, this study aimed to investigate natural products that showed effective improvement on infertility and subfertility in men and women. Natural compounds, extracts, and various formulations were discovered to show efficacy in the production of gonadotropic hormones and the activation of antioxidative processes including lipid peroxidation and glutathione synthesis. Several natural products also showed efficacy in the regulation of glucose and the apoptotic pathways. This study deals with natural substances, extracts, and prescriptions of various origins, and attempted to establish a balanced view by examining drugs that showed opposite (contraceptive) effects. However, there are still limitations in that research on infertility lacks clinical studies and the dosage and utilization methods of formulations were indistinguishable. Future studies are expected to clarify the mechanisms of the profertility effects and to refine pharmacological effects of natural products for clinical use.

References

1. Choi, H.J.; Chung, T.W.; Park, M.J.; Jung, Y.S.; Lee, S.O.; Kim, K.J.; Ha, K.T. Water-extracted tubers of cyperus rotundus l. Enhance endometrial receptivity through leukemia inhibitory factor-mediated expression of integrin alphavbeta3 and alphavbeta5. J. Ethnopharmacol. 2017, 208, 16–23.
2. Uchewa, O.O. Countering the effects of lead as an environmental toxicant on the microanatomy. J. Trace Elem. Med. Biol. 2019, 52, 192–198.
3. Adeoye, O.; Olawumi, J.; Opeyemi, A.; Christiania, O. Review on the role of glutathione on oxidative stress and infertility. JBRA Assist. Reprod. 2018, 22, 61–66.
4. Smits, R.M.; Mackenzie-Proctor, R.; Fleischer, K.; Showell, M.G. Antioxidants in fertility: Impact on male and female reproductive outcomes. Fertil. Steril. 2018, 110, 578–580.
5. Kim, E.Y.; Choi, H.J.; Chung, T.W.; Choi, J.Y.; Kim, H.S.; Jung, Y.S.; Lee, S.O.; Ha, K.T. Water-extracted perilla frutescens increases endometrial receptivity though leukemia inhibitory factor-dependent expression of integrins. J. Pharmacol. Sci. 2016, 131, 259–266.
6. Liao, W.X.; Roy, A.C.; Chan, C.; Arulkumaran, S.; Ratnam, S.S. A new molecular variant of luteinizing hormone associated with female infertility. Fertil. Steril. 1998, 69, 102–106.
7. Ajuogu, P.K.; Mgbere, O.O.; Bila, D.S.; McFarlane, J.R. Hormonal changes, semen quality and variance in reproductive activity outcomes of post pubertal rabbits fed Moringa oleifera lam. Leaf powder. J. Ethnopharmacol. 2019, 233, 80–86.
8. Mvondo, M.A.; Touomo Sakock, A.J.; Ateba, S.B.; Awounfack, C.F.; Nanbo Gueyo, T.; Njamen, D. Emmenagogue properties of Milicia excelsa (welw.) c.C. Berg (moraceae) based, at least in part, on its ability to correlate the activity of the hypothalamic-pituitary axis to that of the ovaries. J. Ethnopharmacol. 2017, 206, 283–289.
9. Naz, M.; Kamal, M. Classification, causes, diagnosis and treatment of male infertility: A review. Orient. Pharm. Exp. Med. 2017, 17, 89–109.
10. Lienou, L.L.; Telefo, B.P.; Bale, B.; Yemele, D.; Tagne, R.S.; Goka, S.C.; Lemfack, C.M.; Mouokeu, C.; Moundipa, P.F. Effect of the aqueous extract of Senecio biafrae (oliv. & hiern) j. Moore on sexual maturation of immature female rat. BMC Complementary Altern. Med. 2012, 12, 36.
11. AM, M.; HA, D.S.; MY, K.J. Effects of gelam honey on sperm quality and testis of rat. Sains Malays. 2011, 40, 1243–1246.
12. Kong, Z.L.; Johnson, A.; Ko, F.C.; He, J.L.; Cheng, S.C. Effect of cistanche tubulosa extracts on male reproductive function in streptozotocin(-)nicotinamide-induced diabetic rats. Nutrients 2018, 10, 1562.
13. Azza, M.; Elhabibi, E.-S.M.; El-Ghany, E.A. Preventing male infertility by marjoram and sage essential oils through modulating testicular lipid accumulation and androgens biosynthesis disruption in a rat model of dietary obesity. Egypt. J. Basic Appl. Sci. 2015, 2, 167–175.

14. Hong, S.H.; Li, M.; Jeung, E.B.; Lee, G.S.; Hong, E.J.; Choi, Y.W.; An, B.S. Therapeutic effects of schisandra chinensis on the hyperprolactinemia in rat. Int. J. Oncol. 2017, 50, 1448–1454.
15. Afrigan, L.; Jafari Anarkooli, I.; Sohrabi, D.; Abdanipour, A.; Yazdinezhad, A.; Sayyar, Z.; Ghorbanlou, M.; Arianmanesh, M.J.A. The effect of hydroethanolic extract of Matricaria chamomilla on the reproductive system of male rats exposed to formaldehyde. Andrologia 2019, 51, e13362.
16. Arafa, N.M. Efficacy of echinacea on the action of cyproterone acetate in male rats. Pak. J. Biol. Sci. 2010, 13, 966–976.
17. Yari, A.; Sarveazad, A.; Asadi, E.; Raouf Sarshoori, J.; Babahajian, A.; Amini, N.; Amidi, F.; Bahadoran, H.; Joghataei, M.T.; Asadi, M.H.; et al. Efficacy of Crocus sativus L. On reduction of cadmium-induced toxicity on spermatogenesis in adult rats. Andrologia 2016, 48, 1244–1252.
18. Nam, E.Y.; Kim, S.A.; Kim, H.; Kim, S.H.; Han, J.H.; Lee, J.H.; Kim, D.I. Akt activation by evodiae fructus extract protects ovary against 4-vinylcyclohexene diepoxide-induced ovotoxicity. J. Ethnopharmacol. 2016, 194, 733–739.
19. Rahmouni, F.; Daoud, S.; Rebai, T. Teucrium polium attenuates carbon tetrachloride-induced toxicity in the male reproductive system of rats. Andrologia 2019, 51, e13182.
20. Askaripour, M.; Hasanpour, A.; Hosseini, F.; Moshrefi, M.; Moshtaghi, G.; Hasannejad, M.; Rajabi, S.; Nematollahi-Mahani, S.N. The effect of aqueous extract of Rosa damascena on formaldehyde-induced toxicity in mice testes. Pharm. Biol. 2018, 56, 12–17.
21. Park, H.J.; Koo, Y.K.; Park, M.J.; Hwang, Y.K.; Hwang, S.Y.; Park, N.C. Restoration of spermatogenesis using a new combined herbal formula of epimedium koreanum nakai and angelica gigas nakai in an luteinizing hormone-releasing hormone agonist-induced rat model of male infertility. World J. Men’s Health 2017, 35, 170–177.
22. Fakher, S.; Seghatoleslam, A.; Noorafshan, A.; Karbalay-Doust, S.; Rahmanifard, M.; Rashidi, M. The impact of echium amoenum distillate on naturally boosting fertility: Potential ameliorative role in male mice reproductive parameters. Iran. J. Med. Sci. 2019, 44, 227.
23. Orkhon, B. Astragalus root induces ovarian betaoxidation and suppresses estrogendependent. Mol. Med. Rep. 2018, 18, 5198–5206.
24. Saleem, M.A.; Al-Attar, M.S. Protective effects of mentha spicata aqueous extract against ifosfamide induced chromosomal aberrations and sperm abnormalities in male albino mice. Trends Biotechnol. Res. 2013, 2, 1.
25. Sm, S.; Mahaboob Basha, P. Fluoride exposure aggravates the testicular damage and sperm quality in diabetic mice: Protective role of ginseng and banaba. Biol. Trace Elem. Res. 2017, 177, 331–344.
26. Heo, J. Dongui Bogam; Namsandang: Seoul, Korea, 1994; Volume 90.
27. Agbodjento, E.; Klotoé, J.R.; Sacramento, T.I.; Dougnon, V.; Tchabi, F.L.; Déguénon, E.; Atègbo, J.-M. Ethnobotanical knowledge of medicinal plants used in the treatment of male infertility in southern benin. Adv. Tradit. Med. 2020.
28. Mahaldashtian, M.; Naghdi, M.; Ghorbanian, M.T.; Makoolati, Z.; Movahedin, M.; Mohamadi, S.M. In vitro effects of date palm (Phoenix dactylifera L.) pollen on colonization of neonate mouse spermatogonial stem cells. J. Ethnopharmacol. 2016, 186, 362–368.
29. Jung, S.E.; Kim, Y.H.; Cho, S.; Kim, B.J.; Lee, H.S.; Hwang, S.; Kim, G.B.; Kim, Y.H.; Pang, M.G.; Lee, S.; et al. A phytochemical approach to promotion of self-renewal in murine spermatogonial stem cell by using sedum sarmentosum extract. Sci. Rep. 2017, 7, 11441.
30. Wang, C.; Jin, Y.; Jin, Y. Promoting effect of licorice extract on spermatogonial proliferation and spermatocytes differentiation of neonatal mice in vitro. In Vitro Cell. Dev. Biol. Anim. 2016, 52, 149–155.
31. Yang, F.; Wei, Y.; Liao, B.; Wei, G.; Qin, H.; Pang, X.; Wang, J. Lycium barbarum polysaccharide prevents cisplatin-induced mltc-1 cell apoptosis and autophagy via regulating endoplasmic reticulum stress pathway. Drug Des. Dev. Ther. 2018, 12, 3211–3219.
32. Chang, M.-S.; Kim, W.-N.; Yang, W.-M.; Kim, H.-Y.; Oh, J.-H.; Park, S.-K. Cytoprotective effects of Morinda officinalis against hydrogen peroxide-induced oxidative stress in leydig tm3 cells. Asian J. Androl. 2008, 10, 667–674.
33. Chung, H.J.; Noh, Y.; Kim, M.S.; Jang, A.; Lee, C.E.; Myung, S.C. Steroidogenic effects of taraxacum officinale extract on the levels of steroidogenic enzymes in mouse leydig cells. Anim. Cells Syst. 2018, 22, 407–414.
34. Ilfergane, A.; Henkel, R.R. Effect of Typha capensis (rohrb.)n.E.Br. Rhizome extract f1 fraction on cell viability, apoptosis induction and testosterone production in tm3-leydig cells. Andrologia 2018, 50, e12854.
35. Mao, C.F.; Zhang, X.R.; Johnson, A.; He, J.L.; Kong, Z.L. Modulation of diabetes mellitus-induced male rat reproductive dysfunction with micro-nanoencapsulated Echinacea purpurea ethanol extract. Biomed. Res. Int. 2018, 2018, 4237354.

36. Seres, A.B.; Ducza, E.; Bathori, M.; Hunyadi, A.; Beni, Z.; Dekany, M.; Hajagos-Toth, J.; Verli, J.; Gaspar, R. Androgenic effect of honeybee drone milk in castrated rats: Roles of methyl palmitate and methyl oleate. J. Ethnopharmacol. 2014, 153, 446–453.
37. Kumari, S.; Nayak, G.; Lukose, S.T.; Kalthur, S.G.; Bhat, N.; Hegde, A.R.; Mutalik, S.; Kalthur, G.; Adiga, S.K. Indian propolis ameliorates the mitomycin c-induced testicular toxicity by reducing DNA damage and elevating the antioxidant activity. Biomed. Pharmacother. 2017, 95, 252–263.
38. Martinez, G.; Hograindleur, J.P.; Voisin, S.; Abi Nahed, R.; Abd El Aziz, T.M.; Escoffier, J.; Bessonnat, J.; Fovet, C.M.; De Waard, M.; Hennebicq, S.; et al. Spermaurin, an la1-like peptide from the venom of the scorpion Scorpio maurus palmatus, improves sperm motility and fertilization in different mammalian species. Mol. Hum. Reprod. 2017, 23, 116–131.
39. Johnson, A.; Cheng, S.C.; Tsou, D.; Kong, Z.L. Attenuation of reproductive dysfunction in diabetic male rats with timber cultured Antrodia cinnamomea ethanol extract. Biomed. Pharmacother. 2019, 112, 108684.
40. Ghanbari, E.; Khazaei, M.R.; Khazaei, M.; Nejati, V. Royal jelly promotes ovarian follicles growth and increases steroid hormones in immature rats. Int. J. Fertil. Steril. 2018, 11, 263–269.