Bee-Products in Male Reproductive Impairment

Subjects: Chemistry, Medicinal

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Bee products are sources of functional food that have been used in complementary medicine to treat a variety of acute and chronic illnesses in many parts of the world. The products vary from location to location as well as country to country.

bee products preventive therapeutic male reproductive impairment

1. Introduction

Honeybees produce various products containing many biochemical components such as minerals, vitamins, and polyphenols, which are biologically active [1]. These compounds have served as preventive and therapeutic agents in the last four decades and have been used in apitherapy [2]. Bee products are used for the treatment of some conditions such as multiple sclerosis, arthritis, wounds, pain, gout, shingles, burns, tendonitis, and infections [3]. Therefore, apitherapy being a simple, convenient, and available method is practiced in traditional self-heath care and also holds promise for the treatment of periodontal diseases, mouth ulcers, and other diseases of the oral cavity as well [4]. The bee products include bee venom, honey, pollen, royal jelly, propolis, bee bread, bee brood, and beeswax, which are produced by four types of insects: honeybees (Apis), stingless bees, honey wasps, and honey ants [5]. Usually, honey bees are of four species, namely *A. mellifera*, *A. cerana*, *A. dorsata*, and *A. florea*.

Honey is a light or dark amber liquid formed by bees from the nectar of flowers [6], while propolis is a sticky, greenish–brown product used as a coating to build their hives. The royal jelly is a milky substance that contains water, proteins, sugar, fats, vitamins, salts, and amino acids. Similarly, bee pollen is a pellet from flower pollen gathered by worker honeybees and used as the nutritional sources for the beehive. Additionally, bee venom is an acidic colorless liquid made up of enzymes, sugars, minerals, and amino acid, beeswax is a mixture of pollen oils and wax to form a yellow or brown color, while bee bread is a mixture of pollen and nectar or honey [7][8][9][10][11].

Meanwhile, nowadays, there are many studies investigating the potential protective and therapeutic roles of these bee products in health, including male infertility [12][13][14][15]. The World Health Organization guidelines revealed that 15–25% of couples struggle to conceive, and approximately half of these cases are caused by infertility in males due to alteration in sperm concentration, motility, and/or morphology, which is present in samples collected [16]. Several mechanisms have also been identified as possible cause(s) of infertility, which include defects in the steroidogenic pathway, the imbalance in the pro and antioxidant activity, the irregularities in the apoptotic pathway, the imbalance of the pro and anti-inflammatory markers, and the generation of the reactive oxygen species.

2. Role of Bee Products in Male Reproductive Impairment

There are a lot of studies of bee products used in ameliorating male reproductive impairment. Table 1, Table 2, Table 3, Table 4, Table 5 and Table 6 show the summary of various effects of bee products on the male reproductive system in various animal models and human.

2.1. Effects of Bee Pollen on Male Reproductive Parameters

The administration of 100 mg/kg bw/day of bee pollen on streptozotocin (STZ)-induced diabetic rats for 4 weeks caused significant increases in testis weight, testosterone, LH, and FSH as well as sperm count, motility, and viability, which is suggested partly by scavenging toxic and mutagenic electrophiles and free radicals/modification of antioxidant pathways due to the presence of flavonoids [12]. Algerian bee pollen (100 mg/kg bw) administered for 15 days showed an increase in spermatogenesis and a decline in Sertoli cells destruction by lowering lipids, and it also showed anti-inflammatory and protective effects against testis cell injury due to the potentiated synthesis of proteins. Similarly, 60 mg/animal/day of Turkish bee pollen over a 30-day period showed increases in testosterone level and sperm counts in a rats model via its antioxidant activity [17].

Furthermore, the Indian bee pollen of 100 mg/kg/bw caused a decrease in MDA levels, while there were increases in SOD, GR, GPx, GST, CAT, and GSH in rifampicin and isoniazid-induced toxicity in rats through its antioxidant activity. In addition, lead-induced rats treated with 100 mg/kg bw of Algerian bee pollen showed an increase in spermatogenesis and a decline in the destruction of Sertoli cells (Table 1).

Table 1. Effects of bee products on male reproductive parameters.

s/n	Bee Products	Dose/Duration of Treatment	Substance Used to Induce Stress	Animal Model Used	Route of Administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
1.	Bee pollen (Egypt)	100 mg/kg bw/day for 4 weeks	Streptozotocin (STZ)-injection (single dose)	Rats	i.p	-	↑ Testis weight, testosterone, LH, FSH, sperm count, motility and viability, ↓ MDA, ↑ (SOD, GR, GPx, GST, CAT, and GSH)	Act by scavenging toxic and mutagenic electrophiles and free radicals/modification of antioxidant pathways due to presence of flavonoids	[12]
2.	Bee pollen (India)	100 mg/kg bw	Rifampicin 100 mg/kg bw/day and isoniazid 50 mg/kg bw/day	Rats	Oral	-	↓ MDA, ↑ (SOD, GR, GPx, GST, CAT, and GSH)	Presence of bioactive elements (caffeic acid phenethyl ester, myricetin, kaempherol, isoquercetin, and flavonoids) convert	[18]

s/n	Bee Products	Dose/Duration of Treatment	Substance Used to Induce Stress	Animal Model Used	Route of Administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
								the reactive free radicals to inactive products	
3.	Bee pollen (Algeria)	100 mg/kg bw for 15 days	30 mg mg/kg bw of lead acetate	Rats	Oral	-	↑ Spermatogenesis and ↓ Sertoli cells destruction	Acts by lowering lipid, anti-inflammatory, and protective effect against testis cell injury due to potentiated synthesis of proteins	[19]
4.	Bee pollen (Turkey)	60 mg/per animal (30-day)		Rats	Oral		↑ Testosterone level and sperm counts	Beneficial effects	[17]

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release the adrenocorticotropic hormone, which causes release of the sex hormones such as testosterone in blood circulation, which have significant effects on spermatogenesis and fertility [20]. In a related study carried out in mice treated with Iraqi bee sting, it provided protection and the maintenance of some sexual efficiency parameters via its ability to release cortisol that inhibits Sertoli cells from releasing activin-B, which normally stimulates spermatogonia to induce mitosis to form spermatocytes [10] (Table 2).

Table 2. Effects of bee venom and bee wax on male reproductive parameters.

In	Bee Products	Dose/Duration of Treatment	Substance used to Induce Stress	Animal Model Used	Route of Administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
1.	Bee Venom (Egypt)	0.1 (G1), 0.2 (G2) and 0.3 (G3) mg/rabbit twice weekly over 20 wks	High temperature	Rabbits	Intravenous injection	-	↑ TAC, GST, GSH, IgA, IgM, Testosterone, spermatogenesis and fertility	These effects could be attributed to pituitary gland stimulation to release the adrenocorticotropic hormone, which causes release of the sex hormones such as testosterone in blood circulation, which has significant effects on spermatogenesis and fertility	[20]
2.	Bee Venom (Iraq)	155 stings	hydrogen peroxide	Mice	Stings	-	Protection and maintenance of some sexual efficiency parameters	Cortisol inhibits Sertoli cells from releasing activin-B, which normally stimulates	[10]

In	Bee Products	Dose/Duration of Treatment	Substance used to Induce Stress	Animal Model Used	Route of Administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
								spermatogonia to induce mitosis to form spermatocytes	
3.	Bee venom (Romania)	700 µg BV/kg		Rats	Injection	-	↓ Testicular weight and Sertoli cells, ↑diameter in seminiferous tubules	Mellitin interacts with the proteins in tight junctions between the adjacent Sertoli cells	[13]
[22]	Bee wax (USA)	15 mg bees wax pellet containing 3.0 mg		Mice	Injection	-	Differential testicular response to photoperiod	Post-pineal mechanism	[21]

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SOD, catalase, and TAC concentrations through its antioxidant, anti-inflammatory, and anti-apoptotic properties due to the presence of phenols and flavanoids [23]. Similarly, 1.0 mL/100 g body weight of honey administered in nicotine-induced old rats showed increases in the fertility of juvenile male rats by increasing sperm motility and the number of morphologically normal sperm; however, the exact mechanisms require further study [24].

In addition, 0.05 mL of honey administered for 4 weeks showed diminished degenerative changes of seminiferous tubules and increased plasma levels of testosterone significantly in CCL-induced rats via reduction of the elevated levels of free radicals and an increased antioxidant defense system [25]. Furthermore, rats treated with 1.0 mL/100 g of Egyptian honey for 60 days showed significant increases in sperm count and the number of sperm with normal morphology, the honey acted as a physiologic modulator of spermatogenic cells proliferation, which influence the cell cycle of the seminiferous epithelium; thereby, it increases spermatogenesis [14]. Similarly, studies carried out in Iran by Hadi and Mohammed [26][27] revealed that 10% of honey (1 mL of honey and 9 mL of IVF culture medium) with doses of 1.2 and 1.8 g/kg bw enhances sperm motility, increases testosterone, FSH, and LH hormones as well as diameters of seminiferous tubules; this might be a result of the antioxidant properties of honey.

Conversely, 1.2 g/kg of Malaysian honey showed increases in the percentages of rats achieving intromission, ejaculation, mating, and fertility indexes as well as increases in testis, epididymis weights, percentages of abnormal spermatozoa, and sperm motility; in this case, the mechanism through which honey acts is by its counteraction on oxidative stress within penile tissues via its antioxidant property due to the possession of phenols [28][29].

Likewise, 0.2, 1.2, and 2.4 g/kg^{-1} of Malaysian honey administered for 4 weeks in rats revealed increases in epididymal sperm count without affecting spermatid count and reproductive hormones [30][31]. Furthermore, 1, 2, and 2.5 mL of Nigerian honey administered to rats for 21 days improved the sperm quality and spermatogenesis rate, and there was no sign of degeneration or cellular loss in the testicular histoarchitecture. It is imperative to note that the presence of zinc in honey and its accumulation in the testis during early spermatogenesis may be important in DNA synthesis and regulate spematogonial proliferation [32]. In other similar studies, 1 mL/100 g of bw of Nigerian honey administered for 65 days increases the sperm count and sperm motility, and it also improves the sperm morphology through the reduction of lipid peroxidation and oxidative stress on the sperm cells by reactive

oxygen species such as superoxide and hydrogen peroxide. The authors of [33][34][35] revealed that rats treated with 100 mg/kg bw of Nigerian honey for 35 days had improvements in sperm motility, viability, morphology, counts, FSH, LH, and testosterone. The rats treated with 5% Palestinian honey for 20 days induced spermatogenesis in rats by increasing epididymal sperm count, relative weight of the epididymis, SDH activity, and reducing LDH activity; however, the mechanisms require further study [36].

Saudi Arabian honey (20 mg/kg bw/day) ameliorates octylphenol toxic effects and reduces the histopathological stress toxicity on the testis in rats; also, the combined administration of honey and royal jelly reduces sperm abnormality and chromosomal aberrations as well as ameliorates GSH and MDA in cyclophosphamide toxicity in mice; therefore, the presence of CAPE served as a protective agent against chemotherapy-induced oxidative stress [9][37]. The honey drone milk is a product that is secreted by honey bees through their hypopharyngeal and mandibular glands; thus, the Hungarian honey drone milk (110 mg/kg/day) increases the relative weights of the androgen-dependent organs and the plasma testosterone level in castrated rats and then increases the tissue mRNA and protein level of SLAP (Spot14-like androgen-inducible protein). This was done through the scavenging of free radicals by polyphenols before they can interact with DNA [38], while 70 g of honey supplement administered to humans for 8 weeks in Iran increases seminal IL-1b, IL-6, IL-8, TNF-α, ROS, and MDA levels and significantly decreases the levels of seminal SOD, catalase. Kelulut honey 2.0 g/kg weight administered 28 days to diabetic rats revealed significant increases in SOD activity and GSH level as well as significant decreases in protein carbonyl and MDA levels in sperm and testis, whereas the histology of the epididymis showed a decrease in spermatozoa and spermatogenic cells density in the testis of the diabetic group [11] (Table 3).

Table 3. Effects of honey on male reproductive parameters.

s/*n*	Bee Products	Dose/Duration of Treatment	Substance used to Induce stress	Animal Model Used	Route of Administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
1.	Honey (Nigeria)	100, 200, and 400 mg/kg	-	Rat	Oral	2.5, 5, and 7.5 mg/kg of testosterone i.p	↑ Sperm count	Chrysin (5,7-dihydroxyflavone) blocked the conversion of androgens into oestrogens with a consequent increase in testosterone	[22]
2.	Honey (Egypt)	0.05 mL (4 weeks)	5 mL/kg of 0.3% CCL 4 daily subcutaneously (4 Weeks)	Mice	Oral	-	↓ Degenerative changes of seminiferous tubules and ↑ plasma levels of testosterone significantly	Via reduction of the elevated levels of free radicals and increase in the antioxidant defense system	[25]

s/n	Bee Products	Dose/Duration of Treatment	Substance used to Induce stress	Animal Model Used	Route of Administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
3.	Honey (Malaysia gelam honey)	1.0 mL/100 g (60 days)	-	Rats	Oral	-	↑ Sperm count and number of sperm with normal morphology	Acts as a physiologic modulator of spermatogenic cells proliferation, which influence the cell cycle of the seminiferous epithelium thus, ↑ spermatogenesis	[14]
4.	Honey (Malaysia)	1.2 g/kg bw/daily	Cigarette 8 min 3 times/day	Rats	Oral	-	↑ Intromission and ejaculation, mating, and fertility indexes	Acts as a physiologic modulator of spermatogenic cells proliferation, which influence the cell cycle of the seminiferous epithelium and thus increase spermatogenesis	[29]
5.	Honey (Malaysia)	1.2 g kg^{-1} bw daily (21 days)	Prenatal restraint stress (three times per day) from day 11 of pregnancy until delivery	Rats	Oral	-	↑ Testis and epididymis weights as well as improved the percentages of abnormal spermatozoa and sperm motility	Acts partly by its counteraction on oxidative stress within penile tissues via its antioxidant property	[28]
6.	Honey (Malaysian honey)	0.2, 1.2, and 2.4 g kg^{-1} (4 weeks)	-	Rats	Oral	-	↑ Epididymal sperm count without affecting spermatid count and reproductive hormones	Due to its one or more constituents that could protect germ cells against oxidative stress. This might have further enhanced spermiogenesis	[30]
7.	Honey (Nigeria)	1, 2, and 2.5 mL of honey daily for 21 days	-	Rats	Oral	0.3 mL FSH drug for 6 days	Improves the sperm quality and spermatogenesis rate and no sign	Suggestive of zinc accumulating in the testis during early	[32]

s/n	Bee Products	Dose/Duration of Treatment	Substance used to Induce stress	Animal Model Used	Route of Administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
							of degeneration or cellular loss in the testicular histoarchitecture	spermatogenesis, and important in DNA synthesis and the regulation of spematogonial proliferation	
8.	Honey (Nigeria)	1 mL of honey per 100 g of bw (65 days)	-	Rat	Oral	Manix capsules (6220 mg/100 mL of drug solution)	↑ Sperm count, sperm motility, and improves sperm morphology	↓ Lipid peroxidation and oxidative stress on the sperm cells by reactive oxygen species such as super oxide, hydrogen peroxide	[34]
9.	Honey (Nigeria)	(100 mg/kg bw) (35 days)	Nicotine (1.0 mg/kg bwt)	Rats	Oral	-	↑ Sperm motility, viability, morphology, counts, FSH, LH, and testosterone	Mediated by its counteraction on oxidative stress	[35]
10.	Honey supplements (Iran)	70 g (8 weeks)	8 weeks of intensive cycling training	Humans	Oral	-	↓ Seminal interleukin (IL)- 1 b, IL-6, IL-8, tumor necrosis factor (TNF)-α, ROS, MDA, ↑ Levels of seminal SOD and catalase	↓ Seminal plasma cytokines and oxidative stress biomarkers as well as increasing seminal antioxidant levels	[23]
11.	Honey (Palestinian Honey)	5% honey for 20 days	-	Rats	Oral	-	Induces spermatogenesis in rats by ↑ epididymal sperm count, relative weight of the epididymis, SDH activity, and ↓ LDH activity	Needs further experiments to establish mechanism	[36]
12.	Honey (Saudi Arabia)	20 mg/kg body weight/day) for 4 weeks	Octylphenol (0.1 and 1.0 mg kg_1 bw)	Rats	Oral	-	Ameliorates toxic effects and ↓ histopathological stress toxicity	Further studies required	[9]

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, serum testosterone, FSH, and LH levels with a significant increase in sperm abnormalities in acrylamide-induced toxicity in rats through the antioxidative effectiveness of propolis mainly by its flavonoids and phenolic content [39]. Egyptian propolis extract (50 mg/kg bw) decreases LPO levels and normalizes CAT, SOD, GPx, and GST activities, while GSH content was increased in testicular tissue in chlorpyrifos-induced toxicity in rats. The protective effect can be due to scavenging MDA molecules by propolis active ingredients or inhibition of mitochondrial and cytosolic lipoperoxidation chain reactions [40]. Egyptian propolis of 200 mg/kg p.o. for 3 weeks decreases testicular oxidative stress, inflammatory, and apoptotic markers in doxorubicin-induced toxicity in rats due to its possession of phenolic compounds [15]. Egyptian propolis (50 mg/kg bw/day extract decreases dead and abnormal sperm and TBARS, and it increases testosterone, GSH, 17-ketosteroid reductase, CAT, and GST in aluminum chloride-induced toxicity in rats through its antioxidant properties [41].

Turkish propolis (100 mg/kg/day) prevented the rise in malondialdehyde, xanthine oxidase levels, and HSP-70 expression and improved testicular morphology and JTBS in methotrexate-induced toxicity in rats through

s/n	Bee Products	Dose/Duration of Treatment	Substance used to Induce stress	Animal Model Used	Route of Administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
13.	Honey (Taulang) (Malaysia)	0.2, 1.2, or 2.4 g/kg/day of honey for 28 days	[43] -	Rats	Oral	- [44]	↑ Sperm counts significantly.	Further studies required	[31]
14.	Honey bee and pollen grains (Saudi Arabia) [45]	(1 g/kg) 2 weeks	Cyclophosphamide (10 mg/kg) i.p	Mice	Oral	-	↓ Sperm abnormality, chromosomal aberrations, ameliorates GSH and MDA	Presence of CAPE as protective agent against chemotherapy-induced oxidative stress	[37]
15.	Honey bee Drone milk (Hungary)	110 mg/kg/day	-	Castrated Rats [47]	Oral	-	↑ Relative weights of the androgen-dependent organs and the plasma testosterone level in castrated rats and tissue mRNA and protein level of SLAP	Scavenging of free radicals by polyphenols before free radicals can interact with DNA	[46] [38]
16.	Honey (Iran)	10% of honey [40]	-	Mice	IVF	-	Enhances sperm motility and pregnancy rate of female mice	Antioxidant activity	[26]
17.	Honey (Gelam) (Malaysia)	1.0 mL/100 g bw	Nicotine (N) group were intraperitoneally (i.p.) injected with 5.0 mg/kg	Rats (4–5 weeks old)	[48] Intra peritoneal		↑ Fertility of juvenile male rats by increasing sperm motility and number of morphologically normal sperm	Further study required	[24]

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MDA, TAS levels, PON1, and CAT activities in testis tissue, it acted through its protective effect of antioxidant mechanisms [43]. Furthermore, Malaysian propolis (300 mg/kg bw) administered on streptozotocin-induced rats caused increases in testosterone level, steroidogenic, and sperm parameters by increasing penile cGMP and serum testosterone levels due to the presence of phenols [49] (Table 4).

Table 4. Effects of propolis on male reproductive parameters.

s/n	Bee Products	Dose/Duration of Treatment	Substance Used to Induce Stress	Animal Model Used	Route of administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
1.	Propolis (Iraq)	200 mg/kg bw (4 weeks)	Acrylamide (150 mg/kg BW)	Rats	Oral	-	↓ Sperm concentration, sperm motility, rate of viability, normal sperms, weights of testes, epididymis, prostate gland, seminal vesicles, serum testosterone,	Anti-oxidative effectiveness of propolis mainly via its flavonoids and phenolic content	[39]

s/n	Bee Products	Dose/Duration of Treatment	Substance Used to Induce Stress	Animal Model Used	Route of administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
							FSH, LH levels with significant ↑ sperm abnormalities		
2.	Propolis (Egypt)	50 mg/kg bw extract (70 days)	Chlorpyrifos (9 mg/kg) (insecticide)		Oral	-	↓ LPO level, normalized CAT, SOD, GPx, and GST activities, ↑ GSH content in testicular tissue	Protective effect can be due to scavenging MDA molecules by propolis active ingredients or inhibition of mitochondrial and cytosolic lipoperoxidation chain reactions	[40]
3.	Propolis (Egypt)	Propolis extract (200 mg kg 1; p.o.) for 3 weeks	Doxorubicin 18 mg kg 1 total cumulative dose of Dox i.p.	Rats	Intraperitoneal	-	↓ Testicular oxidative stress, inflammatory and apoptotic markers	Tumor necrosis factor-related apoptosis inducing ligand via phenolic compounds	[15]
4.	Propolis (Egypt)	50 mg propolis/kg bw/day	Aluminium chloride 34 mg $AlCl_3$/kg bw (70 days)	Rats	Oral	-	↓ Dead and abnormal sperm and TBARS, and ↑ testosterone, GSH, 17-ketosteroid reductase, CAT, and GST	Antioxidant property of propolis	[41]
5.	Propolis (Turkey)	100 mg/kg/day (oral gavage) (15 days)	Methotrexate (20 mg/kg)	Rats	Oral	-	↓ Malondialdehyde, xanthine oxidase levels, and HSP-70 expression and improves testicular morphology and JTBS	Scavenging free radicals and thereby protection against lipid peroxidation	[42]
6.	Propolis (Balikesir, Turkey)	Propolis (200 mg/kg/days, gavage) and	L-NAME (40 mg/kg, i.p.) for	Rats	Oral	-	↓ Levels of TOS, NF-κB, and MDA	Inhibiting the functioning of	[43]

s/n	Bee Products	Dose/Duration of Treatment	Substance Used to Induce Stress	Animal Model Used	Route of administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
		pollen (100 mg/kg/days	induction of hypertension					inflammatory pathways	
7.	Propolis (Chilean propolis)	-	benzo[a]pyrene, hydrogen peroxide (H_2O_2) and hydrogen peroxide in combination with adenosine 5 V-diphosphate (ADP) and ferrous sulfate ($FeSO_4$)	Human spermatozoa	In vitro	-	Protects sperm membrane from the deleterious action of oxidative attack, reducing TBARS formation and LDH release	Exhibited a strong antioxidant activity	[44]
8.	Propolis (Czech Republic)	(1 uL) 10 participants		Human spermatozoa (0.1 mL of fresh ejaculate)	In vitro	-	Maintains sperm motility and improves the total mitochondrial respiratory efficiency	Antioxidant property	[45]
9.	Propolis (Egypt)	50 mg/kg bw/day	-	Rats	Oral	Intraperitoneal injection of genta micin (5 mg/kg bw/day)	Improves structure of seminiferous tubules and ↑ daily sperm production	↓ Level of free radicals and lactate dehydrogenase	[46]
10.	Propolis (Egypt)	100, 200, and 300 mg/kg bw/day, respectively for two weeks (one week before and after mating) for five consecutive times	-	New Zealand White (NZW) rabbit		-	Improves all studied traits	Substantial levels of antioxidant nutrients, including vitamins, minerals, phenolic constituents, and enzymes	[47]
11.	Propolis (green brazallian propolis)	3, 6, and 10 mg/kg/day (56 days)	-	Rats	Oral	-	↑ Sperm production and greater epithelium height of the epididymis	Mechanism still under investigation	[48]

humans shows an increase in pregnancy rate due to increase in sperm capacitation through its antioxidant and scavenging activities against free oxygen species [51]. The administration of Egyptian royal jelly (1 g/kg bw) for 1 month increased the testicular weight and the body of epididymus, sperm count, testosterone hormone, and glutathione level, and it also caused a decrease in sperm deformity percentage, while there were no significant differences in the prostate weight, seminal vesicles, percentage of live sperm, malondialdehyde level, and body weight through the central effect of royal jelly because it contains acetylcholine [52] in hydrogen peroxide (0.5%) in drinking water induced rats. Meanwhile, 100 mg/kg of royal jelly causes a decrease in the toxic effect of cyclosporine in testis of rats due to its antioxidant property [53]. Egyptian royal jelly administered at 200, 400, or 800 mg/kg body weight once a week (6 weeks) significantly boosts testosterone level, ejaculated volume, and seminal plasma fructose; improves sperm motility and sperm total output; reduces abnormal sperm and dead sperm due to the presence of vitamin C and amino acids; and increases spermatic concentration [54].

Turkish royal jelly (50 and 100 mg/kg) for 10 days decreases the malondialdehyde level and increases superoxide dismutase, catalase, and glutathione–peroxidase activities and increases the weights of testes, epididymis,

s/n	Bee Products	Dose/Duration of Treatment	Substance Used to Induce Stress	Animal Model Used	Route of administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
							initial segment and no induction of oxidative stress		
[55]									
12.	Propolis (Egypt)	50 mg kg/bw (4 weeks)	Paclitaxel 5 mg/kg/bw	Rats	Oral	-	↑ Sperm count, motility, viability, and sperm morphology [7]	Scavenging the free radicals and enhancing the antioxidant activities	[8]
13.	Propolis (India)	400 mg/kg bw (5 days a week for 4 weeks)	Mitomycin C (2, 4, and 8 mg/kg bodyweight, single dose) (i.p)	Mice	Oral	-	↓ Oxidative stress and DNA damage, ↑ testicular testosterone and inhibin B	Strong antioxidant activity	[50]
14.	Propolis + Bee pollen (Turkey)	Propolis (200 mg/kg/day) and pollen (100 mg/kg/day) [57] the last 14 of 28 days	[56] N(ω)-nitro-L-arginine methyl ester (L-NAME) (40 mg/kg, i.p.)	Rats	Oral		↓ TOS, NF-κB, MDA, TAS levels, PON1, and CAT activities in the testis tissue	Protective effect of antioxidant mechanisms against oxidative mechanisms on the reproductive system	[43] [58]
15. [61]	Propolis (Malaysia)	Propolis (300 mg/kg bw for 4 weeks	streptozotocin (60 mg/kg bw [59]	Rats	Oral [60]	Metformin (300 mg/kg/day	↑ Testosterone level, steroidogenic and sperm parameters	↑ In penile cGMP and serum testosterone levels due to presence of phenols	[49]

CAT and FRAP activities [62]. Rats induced with hydroxylurea (225 or 450 mg kg/bw/day) followed by administration of royal jelly (100 mg kg/bw/day) for 60 days revealed improved sperm quality, hormonal, and antioxidant status as well as histology architecture [63] (Table 5).

Table 5. Effects of royal jelly on male reproductive parameters.

s/n	Bee Products	Dose/Duration of Treatment	Substance Used to Induce Stress	Animal Model Used	Route of Administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
1.	Royal jelly (Iraq)	1 g/kg bw (1 month)	hydrogen peroxide (0.5%) in drinking water		Oral	-	↑ Testicular weight and the body of epididymis, sperm count, testosterone hormone and glutathione levels; ↓ sperm deformity percentage, while there were no significant differences in the	Central effect of royal jelly because it contains acetylcholine	[52]

s/n	Bee Products	Dose/Duration of Treatment	Substance Used to Induce Stress	Animal Model Used	Route of Administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
							prostate weight, seminal vesicles, the percentage of live sperm, MDA level, and body weight		
2.	Royal jelly (Iraq)	100 mg/kg (5, 10, and 15 days	20, 40, and 60 m/kg cyclosporine A for 5, 10 and 15 days (i.p)	Rats	Oral	-	↓ Toxic effect	Antitumor, antioxidant	[53]
3.	Royal jelly (Egypt)	200, 400, or 800 mg royal jelly (RJ)/kg body weight once a week (6 weeks)	-	Rabbits	Oral	-	↑ Testosterone level, ejaculated volume, seminal plasma fructose, improves sperm motility, sperm total output, ↓ abnormal sperm, and dead sperm	Presence of vitamin C and amino acids have increased spermatic concentration	[54]
4.	Royal jelly (Turkey)	50 and 100 mg/kg (10 days)	Cisplatin (single dose of 7 mg/kg i.p)	Rats	Oral	-	↓ MDA level and ↑ SOD, catalase, and glutathione peroxidase activities and weights of testes, epididymides, seminal vesicles, and prostate along with epididymal sperm concentration and motility	Antioxidant property	[64]
5.	Royal jelly (Japan)	50 µg/g diet or 500 µg/g diet for 12 weeks	-	Hamsters	Oral (food)	-	↑ Intensity of spermatogenesis and testosterone levels	Inhibited the age-associated decline and testosterone-secreting cells	[59]
6.	Royal jelly (Turkey)	(400 mg/kg daily for 4 weeks)	a single intraperitoneal injection of STZ (60 mg/kg)	Rats	Oral	-	↓ Caspase-3-positive cells in testicular apoptosis	Estrogenic effect	[61]

s/n	Bee Products	Dose/Duration of Treatment	Substance Used to Induce Stress	Animal Model Used	Route of Administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
7.	Royal jelly (Chinese)	50, 100, or 150 mg of Chinese royal jelly (RJ)/kg twice per week, respectively, over a 20-week period	temperatures ranging from 23 to 36 °C	Rabbits	Oral	-	↑ Sperm concentration, total sperm output, sperm motility, live sperm, and normal sperm	Amino acids and vitamins may play a role	[55]
8.	Royal jelly (Egypt)	100 g of Egyptian bee honey mixed with 3 g of royal jelly and 1 teaspoon of bee bread	Asthenozoospermia	Humans	Intravaginal	-	↑ Pregnancy rate due to ↑ in sperm capacitation	Antioxidant and scavenging activities against free oxygen species	[51]
9.	Royal jelly (Egypt)	0.4% royal jelly + heparin	-	Buffalo (Bubalus Bubalis)	IVF	-	Induces sperm acrosome reaction but also is effective for in vitro fertilizing capacity of the cryopreserved buffalo spermatozoa	Contain motility stimulants such as adenosine and adenosine monophosphate ((AMP) N (1)-oxide)	[7]
10.	Royal jelly (Iran)	100 mg/kg bw	Streptozotocin (STZ) 60 mg/kg body weight (BW) i.p	Rats	Oral	-	↑ Testicular weight, sperm count, motility, viability, and serum testosterone levels and ↑ sperm deformity, DNA integrity, chromatin	Antioxidant activity due to the presence of vitamins E and C	[65][66] [56]

tioxidant well as able 6).

s/n	Bee Products	Dose/Duration of Treatment	Substance Used to Induce Stress	Animal Model Used	Route of Administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
1.	Bee bread (Malaysia)	0.5 g/kg/day bw (12 weeks)	High-fat diet	Rats	Oral	Orlistat	Upregulated testicular antioxidant enzymes, downregulated inflammation and apoptosis, and increased PCNA immunoexpression, as well as improving lactate transport	Antioxidant, anti-inflammatory, and antiapoptotic properties	[65][66]

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s/*n*	Bee Products	Dose/Duration of Treatment	Substance Used to Induce Stress	Animal Model Used	Route of Administration	Standard Drug	Effect on Reproductive Function Parameters	Possible Molecular Mechanisms	References
13.	Royal jelly (Iran)	100 mg/kg daily (48 days)	Bleomycin group (BLG) received BL (10 mg/kg twice a week) with i.p for 48 days	Rats	Oral	-	Improves bleomycin-induced toxicity on sperm parameters, testosterone, and MDA concentrations	Antioxidant activity	[57]
14.	Royal jelly (Iran)	(0, 50, 100, and 150 mg/kg bw)	Taxol 7.5 mg/kg body weight (bw), weekly	Rats	Oral	-	↑ Sperm and significant upregulation of transcription factor E2f1 mRNA	Antioxidant activity	[58]

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