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Review on effects of obesity on male reproductive system and the role of natural products

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ABSTRACT

Obesity is a major complex disease caused by the interaction of a myriad of genetic, dietary, lifestyle, and environmental factors that lead to increased body fat mass. Over the years, it has grown to pandemic proportions affecting many children, adolescents, and young adults exposed to this disorder for a longer period. Overactivity of aromatase cytochrome P450 enzyme which leads to increases of estrogen disrupting the hypothalamus–pituitary axis, leptin secretion in testicular tissues, scrotal temperature, adipocytes' environmental toxins/other toxic species, and vascular endothelial dysfunction have been implicated in obesity. The use of natural products and their derivatives has been historically valuable as sources of therapeutic agents in the treatment of several metabolic disorders including obesity. This review aims at looking the effect of natural products on obesity at pre-testicular, testicular, and post-testicular levels of the male reproductive system which will be discussed.

INTRODUCTION

Obesity is a disease condition associated with a significant disturbance in hormonal levels that can affect various systems leading to various diseases such as diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, lung diseases, osteoarthritis, some types of cancer, and certain reproductive and metabolic disorders (Hammoud *et al*., 2008). It can be caused by a combination of factors such as excessive food intake, lack of physical activity, medications, endocrine disorders, mental disorders, genes and genetic susceptibility (Guyenet and Schwartz, 2012). The prevalence of obesity has reached an alarming rate in many developing countries, including Malaysia, in which 29.1% were overweight while 14% were obese based on previous National Health and Morbidity Surveys (NHMSs) carried out in Malaysia (Chan *et al*., 2017; Mohamed, 2012; Nor *et al*., 2008). In men, the relationship between the male reproductive system and obesity is poorly understood (Fernandez *et al*., 2011; 2015). Some reports have shown that obesity in men is associated with a decrease in serum levels of total and free testosterone leading to a low sperm count (Du Plessis *et al*., 2010; Fernandez *et al*., 2011). On the other hand, there is a negative correlation between obesity and various semen parameters (Oliveira *et al*., 2017), while a recent study has suggested that there is no relationship between increased body mass index (BMI) and sperm DNA (Bandel *et al*., 2015). Natural products are chemical compounds or substances produced by living organisms which could be from plants, animal, microorganisms, and marine sources. For many years, natural products have been used in the prevention of diseases and have also played a very important role in health. The ancient civilizations of the North Africans, Indians, and Chinese provide written evidence for the use of natural sources for treating various diseases (Moudgil and Khalil, 2016). In those early times, mandrake was prescribed for pain relief, turmeric possessed blood clotting properties, roots of the endive

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plant were used for the treatment of gallbladder disorders, and raw garlic was prescribed for circulatory disorders. These natural products are still being used in several countries as alternative medicines (Arafat and Rahman, 2017). The role of these products in the treatment of obesity and fertility has received increased attention owing to the recent and rapid increase in the prevalence of obesity in the developed world (Hruby and Hu, 2015). In this review, information on obesity, natural products, pre-testicular, testicular, and post-testicular mechanisms of obesity, and male reproductive impairment were obtained through the following search databases: PubMed, Google Scholar, ScienceDirect, EBSCOhost, SCOPUS, and SpringerLink from 2000 to 2018. The keywords in single or in combination were also searched in these various databases based upon which the effects of natural products on obesity and male reproductive system were reviewed.

Classification of Obesity

Obesity can be generally classified into the following: Underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), and overweight which is further divided into Class I Obesity (25.0–29.9 kg/m^2), Class II Obesity (30.0–34.9 kg/m^2), Class III obesity (35.0–39.9 kg/m^2), and extreme obesity (40 kg/m^2) (De Lorenzo *et al*., 2016). There are also several types of obesity, which include central/abdominal, android or apple peripheral/visceral, gynecoid or pear, diffuse, localized, formerly obese, childhood, morbid, and sarcopenic obesity (Mazidi and Kengne, 2017).

Effects of Obesity on Male Reproductive System and their Mechanisms

Obesity has been studied using different obesity models. These include monogenic obesity models (ob/ob mouse, obese Zucker rats, and s/s mouse), polygenic obesity models [high fat diet (HFD)-induced obese rats, diet-induced obese (DIO) rats, and New Zealand Obese (NZO) mouse], surgical models, seasonal models (Syrian and Siberian hamsters), and lipodystrophy model. Generally, obesity affects the male reproductive system at pre-testicular, testicular, and the post-testicular levels leading to impaired male reproductive and fertility potentials, which are summarized in Figure 1.

Pre-testicular Mechanisms of Obesity

Obesity has been recognized to interfere with the hypothalamic–pituitary–gonadal axis leading to secondary hypogonadism. Studies have also revealed that increased adipose tissue results in increased aromatase activity and a consequent elevation in estradiol levels, which inhibits gonadotropin follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion from the anterior pituitary (Dimitriadis *et al*., 2017; Rosenblatt *et al*., 2017; Roth *et al*., 2008), Studies in experimental models in animals indicate that the most common cause of leptin insensitivity in the hypothalamus is obesity, which is responsible for the decreased KISS1 expression, and consecutively changes the release of gonadotropin-releasing hormone (GnRH) (Stefater *et al*., 2010). Pre-testicular mechanism involves two conditions,

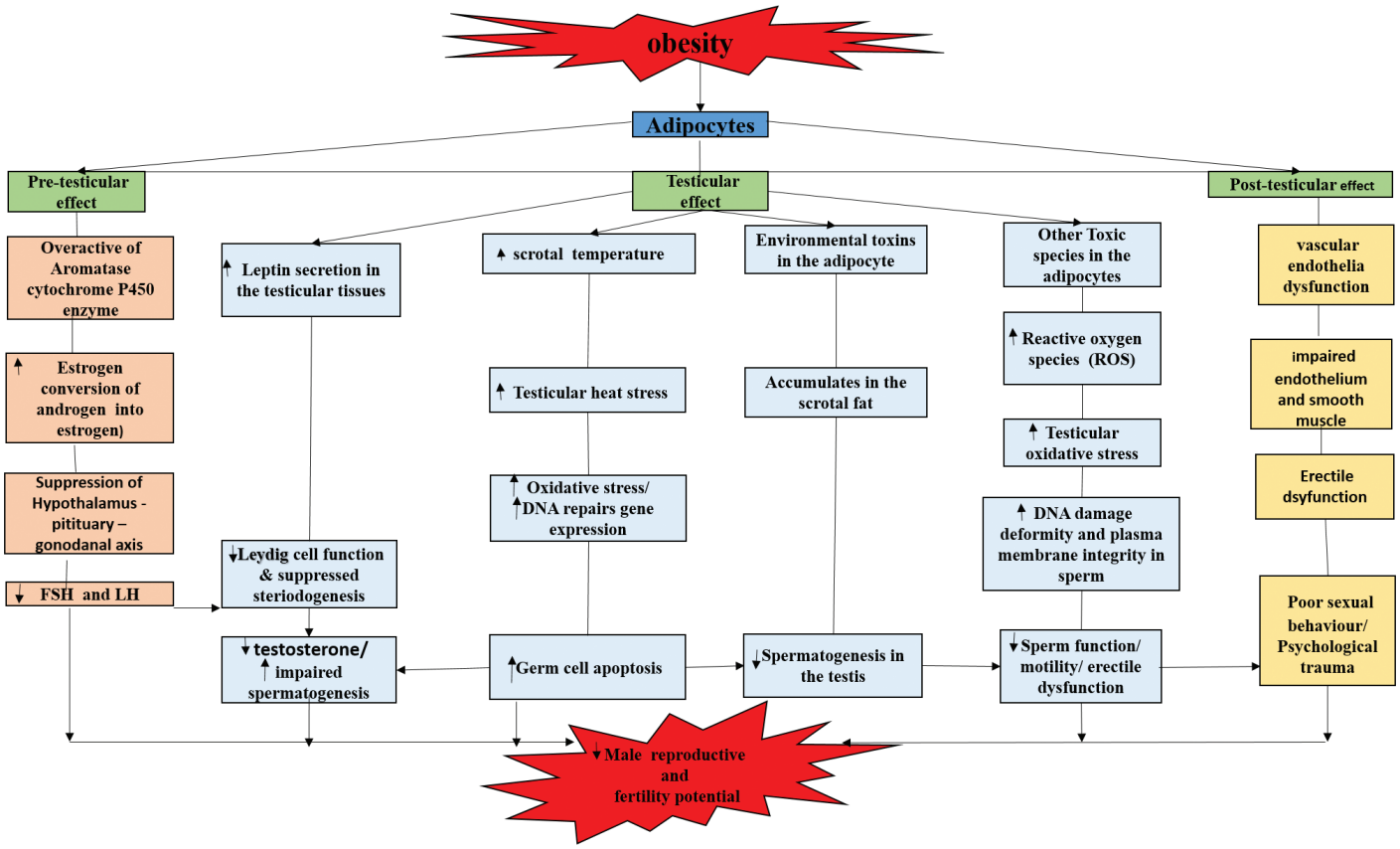

Figure 1. Summary of mechanisms of obesity on the male reproductive system.

namely hypergonadotropic hypogonadism and hypogonadotropic hypogonadism. Hypogonadotropic hypogonadism/primary hypogonadism is caused by testicular deficit leading to reduced testosterone level and impaired spermatogenesis (Condorelli *et al*., 2015; Dimitriadis *et al*., 2017). This attenuates the attenuation of the testosterone-induced negative feedback loop to the secretory activities of the hypothalamus and pituitary, which in turn leads to increased amounts of GnRH and FSH/LH secretions. On the other hand, hypogonadotropic hypogonadism/secondary hypogonadism is caused by the deficit at the hypothalamus and/or pituitary. FSH and LH are secreted at reduced levels, which also lead to decreased stimulation of Leydig cells to secrete testosterone (Santi *et al*., 2017).

Testicular Mechanisms of Obesity

Testis is an important site of hormone production and metabolism, and accumulation of large amounts of body fat may interfere with the hormonal regulation of testicular function. Several studies on obesity suggest that high levels of plasma cholesterol and/or triglycerides have direct adverse effects on testicular function, leading to poor semen quality and infertility (Teerds *et al*., 2011). Kasturi *et al*. (2008) have reported the presence of 65% incidence of dyslipidemia as defined by isolated hypercholesterolemia, triglyceridemia, or both, in 106 male partners from infertile couples. Reactive oxygen species (ROS) resulting in lipid peroxidation, are extremely toxic to human spermatozoa, implicating a significant role of oxidative stress in causing of male infertility as spermatozoa from infertile men show signs of greater oxidative injury compared with normal fertile controls (Agarwal *et al*., 2003). Elevated DNA fragmentation index noted in obese men may reflect an abnormal oxidative state in the testicular microenvironment (Aitken *et al*., 2014). Similarly, *in vitro* study suggests that endogenously generated ROS in the adipocytes lead to an increase in sperm DNA fragmentation. This finding also suggests that oxidative stress may result in lipid peroxidation in the sperm plasma membrane. This may, in turn, lead to decreased motility, membrane dysfunction, and excessive oxidative stress in DNA of the affected sperm (Zhou *et al*., 2014).

Post-Testicular Mechanisms of Obesity

Over the years obesity has been linked to post-testicular etiology that may cause male infertility by affecting the male genital system after sperm production. The affected post-testicular structures include defects of the genital tract like vas deferens obstruction, congenital absence of vas deferens, prostatitis, ejaculatory duct obstruction, retrograde ejaculation, hypospadias, and impotence. In a study carried out by Ouvrier *et al*. (2011), 3-month-old male mice are fed with a lipid-enriched diet containing 1.25% cholesterol for 4 weeks. The result shows complete infertility in dyslipidemic male mice (the Liver X Receptor-deficient mouse model). The infertility results from post-testicular defects affecting the fertilizing potential of spermatozoa which are less viable and motile and highly susceptible to undergo a premature acrosome reaction. It suggests that obesogens may also cause erectile dysfunction (ED), apart from inflammatory responses, androgen deficiency, and endothelial dysfunction (Petrakis *et al*., 2017). Researchers suggest that visceral obesity contributes to ED via three interdependent (overlapping) pathophysiological mechanisms:

i. inflammatory cytokines that contribute to endothelial dysfunction and microvascular disease and reduced androgen levels,
ii. the insult on the endothelium resulting in endothelial injury and reduced nitrogen oxide (NO) synthase activity and NO production, leading to reduced tissue relaxation and poor hemodynamics, and
iii. disruption of the endocrine milieu, with a concomitant decrease in testosterone levels and increased E2 level, thus disrupting tissue homeostasis, tissue histo-architecture, and erectile tissue compliance (Siragusa and Fleming, 2016).

Natural Products and Obesity-induced Impairment in Male Reproductive Function

Natural products are used for the treatment of various diseases including to improve male reproductive health for several decades. They are shown to be effective, inexpensive, and available. The extraction and development of several drugs and chemotherapeutics from these natural products have been widely observed. Several researchers have suggested that two-thirds of the world's plant species have medicinal value and many of them have great antioxidant potential. These products have shown to have significant effects at the pre-testicular, testicular, and post-testicular levels which are listed in Tables 1 and 2 (whole extracts and pure compounds isolated from plants, respectively).

Natural Products with Pre-Testicular hypothalamic-pituitary gonadal axis (HPG axis) Beneficial Effects in Obesity

The administration of *Argyreia nervosa* Bojer (Convolvulaceae) in DIO rats increased the synthesis and release of FSH (Galani *et al*., 2010). On the other hand, the messenger ribonucleic acid (mRNA) levels of GnRH mRNA and LH are significantly increased in HFD mice treated with *Epimedium* Herb (Zhang *et al*., 2011). In addition, administration of *Nigella sativa* increases testosterone and FSH in HFD-induced obese mice (Barakat and El-Masry, 2016) (Tables 1 and 2).

Natural Products with Testicular Beneficial Effects in Obesity

There are also studies showing the beneficial effects of natural products at the testicular level. A study on the seed of *Achyranthes aspera* Linn. (Amaranthaceae) has shown an increase in spermatogenesis in HFD-induced obese mice (Rani *et al*., 2012). In another study, the leaf of *Aloe vera* significantly increases the number of stem cells and primary spermatocytes in HFD-induced obese rats (Misawa *et al*., 2012). The rhizome of *Alpinia galanga* Linn. also increases the number of spermatozoa HFD mice (Ongwisespaiboon and Jiraungkoorskul, 2017). The root of *Angelica gigas* Nakai (Apiaceae) administered in HFD-induced obese mice increased sperm count, motility, and spermatogenic cell density (Bae *et al*., 2016). Leaf of *Danae racemose* (Khojasteh *et al*., 2016) and seeds of *a* combination of *Cinnamomum zeylanicumon* (Barakat and El-Masry, 2016; Fathiazad *et al*., 2013) and *Citrullus vulgaris* (Watermelon) (Khaki *et al*., 2013) administered in HFD-induced obese mice increase sperm concentration and sperm motility, respectively. Leaf of *Murraya koenigii* (L.) Spreng. (Rutaceae) in HFD-induced obese mice for 2 weeks (Birari *et al*., 2010) and roots of Panax ginseng C. A. Mey.

Table 1. Summary of some selected natural products and their effects on obesity and male reproductive system.

S. no	Natural Products	Part used	Bioactive phytochemical component	Obesity model	Dose/Duration of treatment	Anti-obesity standard	Effect on adipose tissue and lipid profile	Effect on reproductive function parameters	References
1.	*Achyranthes aspera* Linn. (Amaranthaceae)	Seed	Saponins	HFD-induced obese Mice	900 mg/kg (6 weeks)	-	↓ TC, TG, LDL ↑ HDL level.	↑ Spermato-genesis	(Rani *et al*., 2012)
2.	*Achyranthes bidentata* Blume (Amaranthaceae)	Roots	Steroids, alkaloids	HFD-induced obese in Mice	25 and 50 mg/100 g (30 days)	-	↓ Phospho-Akt expression	↓ Spermato-genesis and inhibits testicular function in mice without side effects to act as a potential contraceptive agent	(Kamble *et al*., 2017)
3.	*Acorus calamus* Linn. (Araceae) (sweet flag)	Rhizome, roots, and leaves	α- and β-asarones	Glucose challenged db/db mice	100 mg/kg (3 weeks)	-	↓Serum glucose, TG, ↓ TC & FFA levels and ↑ adiponectin levels	↑ Sexual performance and Inhibit PDE-5	(Wu *et al*., 2009)
4.	*Allium sativum* Linn. (Amaryllidaceae)	Stem, bulb, and roots	Saponins such as alloside B, polyphenols	HFD-induced obese mice	500 and 1,000 mg/kg (28 days)	-	↑ Antioxidant enzymes and suppresses glutathione depletion and lipid peroxidation in hepatic tissue.	↑ Testicular functions and sexual behavior	(Focho *et al*., 2009)
5.	*Aloe vera*	Leaves (Gel powder)	Phytosterol	HFD-induced obese rats	20, 100, and 200 mg	-	↓ Body fat accumulation	↑ The number of stem cells and primary spermatocytes	(Misawa *et al*., 2012)
6.	*Alpinia galanga* Linn. (Zingiberaceae)	Rhizome	Flavonoid	HFD-induced obese mice	300 mg/kg (56 days)	-	↓ Serum lipids, liver weight, lipid peroxidation, and accumulates hepatic TGs.	↑Spermatozoa and testosterone production	(Ongwisespaiboon and Jiraungkoorskul, 2017)
7.	*Alpinia officinarum* Hance (Zingiberaceae)	Root	Curcumin (polyphenol)	HFD-induced obese mice	2% and 5% extract (6 weeks)	-	↓ TC, TG, and LDL levels ↓ leptin content.	↓ Epididymal fat	(Jung *et al*., 2012)
8.	*Angelica gigas* Nakai (Apiaceae)	Roots	Coumarin compound decursin	HFD-induced obese mice	400 mg/kg (4 weeks)	-	↓ Secretion adipocytokines such as leptin, resistin, IL-6, and MCP-1.	Protects TM3 cells, ↑ sperm counts, motility, and spermatogenic cell density, ↓ 8-OHdG, SOD, ↓ Nrf2 and heme oxygenase-1 (HO-1), and apoptosis	(Bae *et al*., 2016)
9.	*Arachis hypogaea* nutshell extract and pumpkin oil	Nutshell	Flavonoids (luteolin and eriodictyol apigenin 44 and chrysin) coumarin and phenolic acid	HFD-induced obese rats	5 mg/kg/day pumpkins and 2 mg/kg/day peanut shell extract (22 weeks)	Orlistat	↓ Body weight and BMI	↑ Sperm count and testicular histology	(Galaly *et al*., 2014)
10.	*Argyreia nervosa* Bojer (Convolvulaceae)	Roots	flavonoids, steroids, ergoline alkaloids, and triterpenoids	DIO rats	100 and 200 mg/kg (single dose)	-	↓ Serum leptin, TC, LDL, and TG.	Promotes fertility through increased sperm count, sperm motility, FSH release, and synthesis	(Galani *et al*., 2010)

Continued

S. no	Natural Products	Part used	Bioactive phytochemical component	Obesity model	Dose/Duration of treatment	Anti-obesity standard	Effect on adipose tissue and lipid profile	Effect on reproductive function parameters	References
11.	*Artemisia iwayomogi* (Compositae)	Whole plant	Scopoletin	HFD-induced obese mice	0.5% extract (11 weeks)	-	Down-regulates PPARγ2 and C/EBPα and their target genes CD36, aP2, and FAS. ↓ TNFα, MCP1, IL-6, IFNα, and INFβ	↑ Epididymal functions	(Choi *et al*., 2013)
12.	*Atractylodes lancea* (Thunb.) DC (Compositae)	Rhizome	Atractylone, hinesol, β-eudesmol, and atrctylodin	HFD-induced obese mice	250 and 500 mg/kg (24 days)	Orlistat	Inhibits human pancreatic lipase.	↓ epididymal fat	(Patra *et al*., 2015)
13.	*Bombax ceiba* L. (Malvaceae)	Stem bark	Flavonoids	HFD-induced obese rats	100, 200, and 400 mg/kg	Gemfibrozil 50 mg/kg	Inactivation of acetyl-CoA carboxylase causes AMPK activation that mediates thermogenesis and FAS inhibition.	↑ Sperm count	(Gupta *et al*., 2013)
14.	*Camellia sinensis* (L.) Kuntze (Theaceae)	Leaves, twigs and stems, flower buds	Epicatechin, epicatechin gallate, and epigallocatechin gallate (EGCG)	HFD-induced obese rats	2% aqueous (35 days)	-	↓ TC, TG, PL, TBARS, and NO Inhibits pancreatic lipase activity	↑ Testicular function	(El-Sweedy *et al*., 2007)
15.	*Cardiospermum halicacabum*	Leaves	Flavonoids and phenolic acids	HFD-induced obese in rats	100 and 200 mg/kg (30 days)	-	↓ Weight gain	↑ Testosterone level, sperm count, and motility	(Peiris *et al*., 2015)
16.	*Cinnamomum zeylanicumon*	Extracted oil (seed)	Tannins, terpenoids	HFD-induced obese mice	75 mg/kg (28 days)	-	↓ TC, LDL, and fasting blood glucose	↑ Sperm concentrations, motility, and viability	(Barakat and El-Masry, 2016; Fathiazad *et al*., 2013)
17.	*Citrullus vulgaris* (Watermelon)	Seed	Lycopene, beta carotene	HFD-induced obese rats	55 mg/kg (28 days)	-	↓ Weight gain, serum TC, TG, LDL level.	↑ Sperm concentrations, motility, and viability	(Khaki *et al*., 2013)
18.	*Curcuma longa* (Turmeric)	Leaves	Curcuminoid	Cafeteria rats	25 mg/kg (35 days)	-	Prevents adipocyte differentiation	↓ Testicular weight	(El-Sweedy i., 2007)
19.	*Danae racemose*	Leaves	Phenolic compounds (phenols, sterol, lignans	HFD-induced obese rats	200 and 400 mg/kg (28 days)	-	↓ TG, TC, and LDL levels	↑ Sperm motility and viability ↑ Caudal epididymal sperm count	(Khojasteh *et al*., 2016)
20.	*Epimedium Herb (Berberidaceae)*	Leaves	Isopentenyl flavonoids, icariine, and icariside	HFD-induced obese mice	0.2 and 0.4 g/kg (8 weeks)	-	-	↓ MDA level ↑ mRNA expressions of GnRH and LH.	(Zhang *et al*., 2011)
21.	Epimedium	Leaves	Icariside II	Zuckers rat	1.5 mg/kg/day (4 weeks)	-	-	Improves erectile function and pathologic changes through endogenous progenitor cell preservation and proliferation	(Ruan *et al*., 2018)

Continued

S. no	Natural Products	Part used	Bioactive phytochemical component	Obesity model	Dose/Duration of treatment	Anti-obesity standard	Effect on adipose tissue and lipid profile	Effect on reproductive function parameters	References
22.	Garcinia cambogia	Fruits	Flavonoids, particularly hesperidin, naringin, and alkaloids	Zucker rats	(154 mmol HCA/kg diet) (92 or 93 days)	-	↓ Epididymal fat	Causes testicular atrophy and toxicity.	(Saito *et al*., 2005)
23.	*Guibourtia tessmannii* (Caesalpiniaceae)	Stem barks	Phenols	HFD-induced obese rats	55, 110, 220 mg/kg (21 or 56 days)	Clomiphene citrate (2 mg/kg)	↓ TG, TC, LDL, and VLDL levels	Improves sexual behavior and performance	(Defo *et al*., 2017)
24.	*Hibiscus sabdariffa* L. (Malvaceae)	Leaf	Flavonoids	HFD-induced obese rats	1.15, 2.3, and 4.6 mg/kg (12 weeks)	-	Promotes LXRα/ABCA1 pathway, stimulates cholesterol removal from macrophages, and delays atherosclerosis.	Causes testicular toxicity	(Höper *et al*., 2013)
25.	*Ligustrum lucidum* (Oleaceae)	Fruits	(8-E)-niizhenide, a secoiridoid	HFD-induced C58BL/6J obese mice	300 and 30 mg/kg (6 weeks)	-	↓Fats and TG.	↓ Epididymal fat	(Chen *et al*., 2012)
26.	*Morinda citrifolia L. (Rubiaceae)*	Fruit	Phenolic acids and polysaccharides	HFD-induced obese mice	150 and 350 mg/ kg bw (12 weeks)	-	↓ Body weight fat mass and TG level. ↑ glucose tolerance and ↓ plasma TG level.	↑ Sperm motility, viability, and count	(Saminathan *et al*., 2013)
26.	*Murraya koenigii* (L.) Spreng. (Rutaceae)	Leaves	Carbazole alkaloids, phenols, carotenoids, terpenoids	HFD-induced obese mice	30 mg/kg (2 weeks)	-	↓ Body weight gain, plasma TC and TG levels in mice.	↑ Testicular function	(Birari *et al*., 2010)
28.	*Nigella sativa* (Black Cumin, Fennel Flower, Black Caraway)	Extracted oil (Seed)	Thymoquinone	HFD-induced obese rats	(0.5 and 1.5 g/kg) (50 days)	-	↓ TG, LDL, and fasting blood glucose levels	↑ Sperm parameters and levels of testosterone and FSH	(Barakat and El-Masry, 2016)
29.	*Ocimum basilicum*	Leaves	Flavonoids, alkaloids (1-deoxynojirimycin), and polysaccharides	HFD-induced obese mice	800 mg/kg (24 days)	-	↓ Adipose TG	↑ Sperm motility, viability and count, ↓ MDA and ↑ TAC.	(Umar *et al*., 2012)
30.	*Panax ginseng* C. A. Mey. (Araliaceae)	Roots	Isoginsenoside-Rh3	HFD-induced obese C57BL6/J mice0	0.75 g/kg (16 weeks)	-	Activates lipase via Protein Kinase A.	↑ Testicular functions	(Park *et al*., 2013)
31.	*Perilla frutescens* (L.) Britton (Lamiaceae)	Leaves	Anthocyanins, malonylshisonin	HFD-induced obesity. C57BL/6J mice	1% and 3% extract (4 weeks)	-	↑ Weight gain, food efficiency ratio, and relative liver and epididymal fat mass	↓ Epididymal adipose tissue	(Kim and Kim, 2009)
32.	*Sida rhombifolia* L. (Malvaceae)	Leaves	Alkaloids	HFD-induced obese in C57BL/6J mice	1% extract (20 weeks)	-	Up-regulation of PPARγ 2 and SREBP-1c expression in the epididymal adipose tissue, leading to attenuation of adipogenesis.	↑ Testicular function	(Thounaojam *et al*., 2011)
33.	*Spirulina Platensis*	Blue-green algae	Phenolic compounds like phlorotannins	HFD-induced obese rats	3% extract (60 days)		↓ TC levels	↑ Spermatogenesis and testicular structure	(Esener *et al*., 2017)

Continued

S. no	Natural Products	Part used	Bioactive phytochemical component	Obesity model	Dose/Duration of treatment	Anti-obesity standard	Effect on adipose tissue and lipid profile	Effect on reproductive function parameters	References
34.	*Tamarindus indica* L. (Leguminosae)	Fruit	Polyphenols (especially procyanidins) and flavonoids	DIO Sprague-Dawley rats	5, 25, and 50 mg/kg (10 weeks)	-	↓ TC, LDL, and TG	↑ Testicular function	(Azman *et al*., 2012)
35.	*Vaccinium corymbosum* L. (Ericaceae)	Peel	Flavonoids	HFD-induced obese rats	0, 50, 200, or 300 µg/ml (7 days)	-	Inhibits lipid accumulation and ↓ C/EBPβ, C/EBPα, and PPARγ genes	↓ Epididymal adipose tissue	(Song *et al*., 2013)
36.	Zingiber Officinale (Ginger)	Rhizome	Zingiberolpenols (gingerol, zingerone, and shogaol) and resin	HFD-induced obese rats	50 and 100 mg/kg (22 days)	-	↓ Plasma TG, TC, and LDL levels	↑ Sperm functions sperm count, motility, and viability)	(Khaki *et al*., 2009)

aP2 = Activating protein 2; ABCA1 = Adenosine triphosphate binding cassette transporters A1; AMPK = 5'AMP-activated protein kinase; HFD = High-fat diet-induced obese; DIO = diet-induced obesity; C/EBPα and C/EBPβ = CCAAT-enhancer-binding proteins; CD36 = cluster of differentiation 36; FAS = fatty acid synthase; GSH = Gonodotropic stimulating hormone; TC = Total cholesterol, TG = triacylglycerides; HDL = high-density lipoprotein; IFNα = Interferon-alpha; IL-6 = interleukin-6; LDL-C = low-density lipoprotein cholesterol; TAC = Total antioxidant capacity; ROS = Reactive oxygen species, MDA = Malondialdehyde; GnRH = Gonadotropin-releasing hormone; mRNA = messenger ribonucleic acid; LH = Luteinizing hormone; LXRα = Liver X receptor α; MCP1 = Monocyte chemotactic protein-1; NO = Nitrogen oxide; PPAR-γ = Peroxisome proliferator-activated receptor gamma; SREBPs = Sterol regulatory element-binding proteins; TBARS = Thiobarbituric acid reactive substances; TNFα = Tissue necrotic factor.

Table 2. Summary of some selected isolated compounds from natural products and their effects on obesity and male reproductive system.

S/n	Natural products	Part used	Obesity model	Dose/Duration of treatment	Anti-obesity standard	Effect on adipose tissue and lipid profile	Effect on reproductive function parameters	References
1.	Anthocyanins	-	C57BL/6J Mice	2.9 mg/g	-	15-fold increase in necrotic-like adipocyte death and formation of macrophage syncytia, coincident with increased tumor necrosis factor-α gene expression.	↓ Epididymal fat	(Meydani and Hasan, 2010)
2.	Curcumin	-	HFD-induced obese rats	250 mg/kg (4 weeks)	-	↓ Liver weight, TG and FFA levels	↑ Sperm concentration, normal sperm morphology, semen volumes	(Meydani and Hasan, 2010)
3.	Ethyl caprylate	-	C57BL/6J mice	0.05 and 0.1 g/kg (12 weeks)	Rosiglitazone	↓ Accumulation of ROS.	↑ Testicular function	(Hong and Lee, 2009)
4.	Friedelin	-	HFD-induced obese rats	(50 and 70 mg/kg)	Fenofibrate	↓ Levels of TC, TG, HDL, and LDL	↑ Testicular functions	(Duraipandiyan *et al*., 2016)
5.	Kaempferol glycoside	-	HFD-induced obese Mice	0.15% of dietary (92 days)	-	↑ Lipid metabolism through the down-regulation of PPAR-γ and SREBP-1c	↑ Testicular functions	(Zhang *et al*., 2011)
6.	Letrozole	-	Human model	2.5 mg letrozole (once a week for 6 months)	-	Aromatase inhibitor	Normalization of serum total testosterone	(Loves *et al*., 2008)
7.	Quercetin (flavonoid)	-	C57BL/6J mice	(16 weeks)	-	Attenuates adipogenesis and ↓ expression of adipogenesis-related factors and enzymes	↓ Epididymal fat	(Ahn *et al*., 2008)
8.	Resveratrol (phenol)	-	Human Model	0100 µmol/l (30 minutes)	-	Down-regulation of C/EBPα and PPARγ	↑ Sperm concentration, normal sperm morphology, semen volumes	(Aguirre *et al*., 2014)

HFD = High fat diet; DIO = Diet-induced obesity; FFA = Free fatty acid; C/EBPα and C/EBPβ = CCAAT-enhancer-binding proteins; TC = Total cholesterol; TG = triacylglycerides; LDL = low-density lipoprotein cholesterol; ROS = Reactive oxygen species, MDA = Malondialdehyde; PPAR-γ = Peroxisome proliferator-activated receptor gamma; SREBPs = Sterol regulatory element-binding proteins; VLDL = Very low-density lipoprotein.

(Araliaceae) (Park *et al*., 2013) in HFD C57BL6/J mice increase testicular function. *Spirulina platensis* (Esener *et al*., 2017) in HFD-induced obese rats increases spermatogenesis and testicular structure (Thounaojam *et al*., 2011). The treatment with Curcumin (Meydani and Hasan, 2010) in HFD-induced obese rats for 4 weeks has increased sperm concentration, normal sperm morphology, and semen volumes while treatments of ethyl caprylate, friedelin, and kaempferol glycoside in C57BL/6J mice, HFD-induced obese rats, and HFD-induced obese mice, respectively, also show an increase in testicular functions (Duraipandiyan *et al*., 2016; Hong and Lee, 2009; Zhang *et al*., 2011). However, leaf of *Hibiscus sabdariffa* L. (Malvaceae) (Hoper et al., 2013), fruits of *Ligustrum lucidum* (Oleaceae), and fruits of *Garcinia cambogia* (Saito *et al*., 2005) administered on Zucker rats cause potent testicular atrophy and toxicity (Chen *et al*., 2012; Höper *et al*., 2013). In various studies conducted on rhizome of *Zingiber Officinale* (Ginger), *Alpinia officinarum* Hance (Zingiberaceae), *Artemisia iwayomogi* (Compositae), *Atractylodes lancea*, *Ligustrum lucidum* (Oleaceae), *Perilla frutescens* (L.) Britton (Lamiaceae), *Vaccinium corymbosum* L. (Ericaceae), and isolated compounds like flavonoids, anthocyanins, and quercetin in the epididymal adipose fats are decreased (Ahn *et al*., 2008; Chen *et al*., 2012; Choi *et al*., 2013; Jung *et al*., 2012; Khaki, 2015; Khaki *et al*., 2009; Kim and Kim, 2009; Meydani and Hasan, 2010; Patra *et al*., 2015; Song *et al*., 2013). Nutshells of Arachis hypogaea and extracts of pumpkin oil (Galaly *et al*., 2014), stem bark of *Bombax ceiba* L. (Malvaceae) (Gupta *et al*., 2013), leaves, stems, and flower buds of *Camellia sinensis* (L.) Kuntze (Theaceae) (El-Sweedy *et al*., 2007), leaves of *Cardiospermum halicacabum* (Peiris *et al*., 2015) and *Curcuma longa* (Turmeric) (El-Sweedy *et al*., 2007) have increased sperm count, testicular histology, and functions in HFD-induced obese rats/mice. Leaves of *Sida rhombifolia* L. (Malvaceae) (Thounaojam *et al*., 2011) and fruits of *Tamarindus indica* L. (Leguminosae) (Azman *et al*., 2012; Esener *et al*., 2017) have increased testicular function in HFD-induced obese mice and DIO rats, respectively. Fruits of *Morinda citrifolia L.* (Rubiaceae) (Saminathan *et al*., 2013) and leaves of *Ocimum basilicum* (Umar *et al*., 2012) have increased sperm motility, viability, sperm count, and total antioxidant capacity but decrease malondialdehyde in HFD-induced obese mice. Letrozole (Loves *et al*., 2008) on the other hand, normalizes serum total testosterone while resveratrol (Aguirre *et al*., 2014) increases sperm concentration, normal sperm morphology, and semen volumes.

Natural Products with Post-Testicular Beneficial Effects in Obesity

Many natural products have also shown their potential beneficial effects in treating post-testicular impairment in male obesity as shown in Tables 1 and 2. A study carried out on HFD-induced obese mice for 30 days shows that *Achyranthes bidentata* Blume (Kamble *et al*., 2017) decreases spermatogenesis and inhibits testicular function without any side effects suggesting its potential contraceptive property (Rani *et al*., 2012). Another study carried out by Wu *et al*. (2009) on glucose challenged db/db mice treated with *Acorus calamus* Linn. (Araceae) for 3 weeks has shown an improved sexual performance, i.e., improved mount, intromission, and ejaculatory latencies, and their frequencies and inhibits prostaglandins E 5 (PDE-5) synthesis. *Allium sativum* Linn. administered on HFD-induced obese mice for 28 days also increases sexual behavior (Focho *et al*., 2009). Defo *et al*. (2017) have reported an improvement in sexual behavior and performance when *Guibourtia tessmannii* (Caesalpiniaceae) is administered in HFD-induced obese rats for 21 or 56 days. In addition, Icariside II (Epimedium) administered on Zuckers rat for 4 weeks also improves erectile function and pathologic changes through endogenous progenitor cell preservation and proliferation (Ruan *et al*., 2018).

Effects of Natural Products on Adipose Tissue and Lipid Profile

A large number of the natural products studied in this review demonstrated significant effects in reducing total cholesterol (TC), triacylglycerides (TG), high-density lipoprotein (HDL) (Jung *et al*., 2012), low-density lipoprotein (LDL) as well as fasting blood glucose (Table 1). Some pure isolated compounds also reduced the accumulation of ROS, attenuated adipogenesis (Zhang *et al*., 2011), and decreased expression of adipogenesis-related factors and enzymes (Table 2).

CONCLUSION AND FUTURE DIRECTION

There is enough evidence to show that male obesity has an impact on fertility through its effects on pre-testicular, testicular, and post-testicular mechanisms. Natural products, on the other hand, have been used over the years to improve obesity-induced male infertility at the aforementioned levels. This review identifies some selected natural products, with their effects and mechanisms on male reproductive functions in obesity. What does the future hold for the effect of natural products on the male reproductive system in obese men at these levels? With the exponential increase in the number of experiments in this area, it seems likely that many more will be conducted in the nearest future on natural plants, herbs, and other natural products emphasizing on new technologies which could help manage health and weight/energy balance more effectively and analyze the future impact of new technologies on lifestyle, dietary habits, thereby improving male fertility. However, the inclusion of studies on their phytochemical compounds and toxicity would further help appreciate their potentials to reduce obesity-induced impairment in the male reproductive system.

ABBREVIATIONS

aP2	activating protein 2
ABCA1	Adenosine triphosphate binding cassette transporters A1
AMPK	5' AMP-activated protein kinase
BMI	body mass index
C/EBPα and C/EBPβ	CCAAT-enhancer-binding proteins
C57BL/6J	C57 black 6
CD 36	cluster of differentiation 36
DIO	diet-induced obese; diet-induced obesity
FAS	fatty acid synthase
GnRH	Gonadotropin-releasing hormone
HDL	high-density lipoprotein
HFD	high fat diet

HPT	hypothalamic–pituitary–testicular axis
IFNα	Interferon-alpha
IL-6	interleukin-6
LDL	low-density lipoprotein
LH	Luteinizing hormone
LXRα	Liver X receptor α
MCP1	monocyte chemotactic protein-1
MDA	Malondialdehyde
mRNA	messenger ribonucleic acid
NHMSs	National Health and Morbidity Surveys
NO	nitrogen oxide
NZO	New Zealand Obese mouse
ob/ob mouse	obesity mouse
PPAR-γ	Peroxisome proliferator-activated receptor gamma
ROS	reactive oxygen species
SREBPs	Sterol regulatory element-binding proteins
TAC	total antioxidant activity
TBARS	Thiobarbituric acid reactive substances
TC	total cholesterol
TG	Triacylglycerides
TNFα	tissue necrotic factor
VLDL	very low-density lipoprotein

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CONFLICT OF INTEREST

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