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/m²), normal (18.5–24.9 kg/m²), and overweight which is further divided into Class I Obesity (25.0–29.9 kg/m²), Class II Obesity (30.0–34.9 kg/m²), Class III obesity (35.0–39.9 kg/m²), and extreme obesity (40 kg/m²) (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.](image-url)
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 (Siragus 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 zeylanicum (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.         | 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      | Roots                          | Steroids, alkaloids                    | HFD-induced obese in Mice | 25 and 50 mg/100 g (30 days) | -                      | ↓ Phospho-Akt expression                   | -                                         | (Kamble et al., 2017) |
| 3.    | Acorus calamus Linn. (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.            | Rhizome                        | Flavonoid                              | HFD-induced obese mice | 300 mg/kg (56 days)       | -                      | ↓ Serum lipids, liver weight, lipid peroxidation, and accumulates hepatic TGs. | ↑Spermatozoos and testosterone production | - (Ongwisespaiboon and Jiraungkoorskul, 2017) |
| 7.    | Alpinia officinarum Hance        | Root                           | Curcumin (polyphenol)                  | HFD-induced obese mice | 2% and 5% extract (6 weeks) | - | ↓ TC, TG, and LDL levels ↓ leptin content. | ↑ Epididymal fat Protects TM3 cells, ↑ sperm counts, motility, and spermatogénic cell density, ↓ 8-OHdG, SOD, ↓ Nrf2 and heme oxygenases-1 (HO-1), and apoptosis | (Jung et al., 2012) |
| 8.    | Angelica gigas Nakai             | Roots                          | Coumarin compound decursin             | HFD-induced obese mice | 400 mg/kg (4 weeks)       | - | ↓ Secretion adipocytokines such as leptin, resistin, IL-6, and MCP-1. | -                                        | (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           | 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/EBPs and their target genes CD36, ap2, and FAS.                      | ↑ Epididymal functions                                         | (Choi et al., 2013) |
|       |                                   |           |                                   |                            |                           |                             | ↓ TNFα, MCP1, IL-6, IFNα, and INFβ                               |                                                                  |                   |
| 12.   | Atractylodes lancea (Thunb.) DC  | Rhizome   | Atractyline, hinesol, β-eudesmol, and atretyloid | 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       | ↑ Epididymal functions                                         | ↑ 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)      | -                          | ↑ Testicular function                                         | ↑ Testosterone level, sperm count, and motility                  | (El-Sweedy et al., 2007) |
| 15.   | Cardioespernum halicacabum       | Leaves    | Flavonoids and phenolic acids     | HFD-induced obese in rats | 100 and 200 mg/kg (30 days) | -                          | ↑ Weight gain                                                   | ↓ TC, TG, PL, TBARS, and NO Inhibits pancreatic lipase activity | (Peiris et al., 2015) |
| 16.   | Cinnamomum zeylanicomon          | Extracted oil (seed) | Tannins, terpenoids              | HFD-induced obese mice    | 75 mg/kg (28 days)        | -                          | ↓ Weight gain, serum TC, TG, LDL level.                      | ↑ Sperm concentrations, motility, and viability                | (Barakat and El-Masry, 2016; Fathiazad et al., 2013) |
| 17.   | Citrus vulgaris (Watermelon)     | Seed      | Lycopene, betacarotene           | HFD-induced obese rats    | 55 mg/kg (28 days)        | -                          | Prevents adipocyte differentiation                            | ↓ Testicular weight                                             | (El-Sweedy i., 2007) |
| 18.   | Curcuma longa (Turmeric)         | Leaves    | Curcuminoid                       | Cafeteria rats            | 25 mg/kg (35 days)        | -                          | ↓ Sperm motility and viability                                | ↑ Caudal epididymal sperm count                                 | (Khojasteh et al., 2016) |
| 19.   | Danae racemose                   | Leaves    | Phenolic compounds               | HFD-induced obese rats    | 200 and 400 mg/kg (28 days) | -                          | ↓ TG, TC, and LDL levels                                     | ↓ MDA level                                                    |                   |
|       |                                   |           | (phenols, sterol, lignans)       |                            |                           |                             |                                                                  | ↑ mRNA expressions of GnRH and LH.                             | (Zhang et al., 2011) |
| 20.   | Epimedium Herb (Berberidaceae)   | Leaves    | Iosopentenyl flavonoids, icarine, and icariside | HFD-induced obese mice    | 0.2 and 0.4 g/kg (8 weeks) | -                          | Improves erectile function and pathologic changes through endogenous progenitor cell preservation and proliferation |                                                                  |                   |
| 21.   | Epimedium                       | Leaves    | Icariside II                     | Zucker rat               | 1.5 mg/kg/day (4 weeks)   | -                          |                                                                  |                                                                  | (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) | -                     | ↓ TG, TC, LDL, and VLDL levels           | Promotes LXRα/ABCA1 pathway, stimulates cholesterol removal from macrophages, and delays atherosclerosis. | (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) | -                     | -                                      | Causes testicular toxicity                    | (Höper et al., 2013) |
| 25.   | *Ligustrum lucidum* (Oleaceae) | Fruits    | (8-E)-nizhenide, a secoiridoid | HFD-induced 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) | -                     | ↑ Sperm motility, viability, and count     | ↑ Testicular function                        | (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                        | (Bitari 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 | ↑ Testicular function                        | (Barakat and El-Masyry, 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 mice | 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, malonylshisbonin    | 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 Up-regulation of PPARγ 2 and SREBP-1c expression in the epididymal adipose tissue, leading to attenuation of adipogenesis. | (Kim and Kim, 2009) |
| 32.   | *Sida rhombifolia* L. (Malvaceae) | Leaves    | Alkaloids                         | HFD-induced obese in C57BL/6J mice | 1% extract (20 weeks) | -                     | ↑ Testicular function                     | (Thounaojam et al., 2011) |
| 33.   | *Spirulina Platensis* | Blue-green algae | Phenolic compounds like phlorotamins | HFD-induced obese rats | 3% extract (60 days) | -                     | ↑ TC levels                             | ↑ Spermatogenesis and testicular structure   | (Esener et al., 2017) |

Continued
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 synectia, 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 (50 and 70 mg/kg) | Fenofibrate | ↓ Levels of TC, TG, HDL, and LDL | ↑ Testicular functions | (Duraiapandian 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       | -         | C57BL/6J mice | 16 weeks | - | Attenuates adipogenesis and ↓ expression of adipogenesis-related factors and enzymes | ↓ Epididymal fat                          | (Ahn et al., 2008) |
| 8.  | Resveratrol      | -         | Human Model | 0.1 µmol/L (30 minutes) | - | Down-regulation of CEBPα 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; CEBPα and CEBPβ = 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; SREBP-1c = Sterol regulatory element-binding protein-1; CD36 = Cluster of differentiation 36; FAS = Fatty acid synthase; GSH = Glutathione; TC = Total cholesterol; TG = triacylglycerides; HDL = high-density lipoprotein; TNFα = Tissue necrotic factor.
(Araliaceae) (Park et al., 2013) in HFD C57BL/6J 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 (Duraiappan 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 epidydimal 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. (Rubiacaeae) (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* (Caesalpiniaaceae) 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

| Symbol | Description |
|--------|-------------|
| 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 |
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Conflict of interest

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Ethics approval

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