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
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) (D 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 (D 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,

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**Figure 1.** Summary of mechanisms of obesity on the male reproductive system.
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 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 Linn. (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 spermatoeza HFD mice (Ongwisepaiboon 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.

<table>
<thead>
<tr>
<th>S. no</th>
<th>Natural Products</th>
<th>Part used</th>
<th>Bioactive phytochemical component</th>
<th>Obesity model</th>
<th>Dose/Duration of treatment</th>
<th>Anti-obesity standard</th>
<th>Effect on adipose tissue and lipid profile</th>
<th>Effect on reproductive function parameters</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><em>Achyranthes aspera</em> Linn. (Amaranthaceae)</td>
<td>Seed</td>
<td>Saponins</td>
<td>HFD-induced obese Mice</td>
<td>900 mg/kg (6 weeks)</td>
<td>-</td>
<td>↓ TC, TG, LDL</td>
<td>↑ HDL level</td>
<td>(Rani et al., 2012)</td>
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<tr>
<td>2.</td>
<td><em>Achyranthes bidentata</em> Blume (Amaranthaceae)</td>
<td>Roots</td>
<td>Steroids, alkaloids</td>
<td>HFD-induced obese in Mice</td>
<td>25 and 50 mg/100 g (30 days)</td>
<td>-</td>
<td>↓ Phospho-Akt expression</td>
<td></td>
<td>(Kamble et al., 2017)</td>
</tr>
<tr>
<td>3.</td>
<td><em>Acorus calamus</em> Linn. (Araceae) (sweet flag)</td>
<td>Rhizome, roots, and leaves</td>
<td>α- and β-asarones</td>
<td>Glucose challenged db/db mice</td>
<td>100 mg/kg (3 weeks)</td>
<td>-</td>
<td>↓ Serum glucose, ↓ TC &amp; IFA levels and ↑ adiponectin levels</td>
<td>↑ Sexual performance and Inhibit PDE-5</td>
<td>(Wa et al., 2009)</td>
</tr>
<tr>
<td>4.</td>
<td><em>Acorus calamus</em> Linn. (Araceae) (sweet flag)</td>
<td>Rhizome, roots, and leaves</td>
<td>α- and β-asarones</td>
<td>Glucose challenged db/db mice</td>
<td>100 mg/kg (3 weeks)</td>
<td>-</td>
<td>↓ Serum glucose, ↓ TC &amp; IFA levels and ↑ adiponectin levels</td>
<td>↑ Sexual performance and Inhibit PDE-5</td>
<td>(Wa et al., 2009)</td>
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<td>5.</td>
<td><em>Aloe vera</em></td>
<td>Leaves (Gel powder)</td>
<td>Phytosterol</td>
<td>HFD-induced obese rats</td>
<td>20, 100, and 200 mg</td>
<td>-</td>
<td>↓ Body fat accumulation</td>
<td></td>
<td>(Misawa et al., 2012)</td>
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<tr>
<td>6.</td>
<td><em>Alpinia galanga</em> Linn. (Zingiberaceae)</td>
<td>Rhizome</td>
<td>Flavonoid</td>
<td>HFD-induced obese mice</td>
<td>300 mg/kg (56 days)</td>
<td>-</td>
<td>↓ Serum lipids, liver weight, lipid peroxidation, and accumulates hepatic TGs.</td>
<td>↑ Testicular functions and sexual behavior</td>
<td>(Focho et al., 2009)</td>
</tr>
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<td>7.</td>
<td><em>Alpinia officinarum</em> Hance (Zingiberaceae)</td>
<td>Root</td>
<td>Curcumin (polyphenol)</td>
<td>HFD-induced obese mice</td>
<td>2% and 5% extract (6 weeks)</td>
<td>-</td>
<td>↓ TC, TG, and LDL levels</td>
<td>↓ Epididymal fat</td>
<td>(Jung et al., 2012)</td>
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<td>8.</td>
<td><em>Angelica gigas</em> Nakai (Apiaceae)</td>
<td>Roots</td>
<td>Coumarin compound decursin</td>
<td>HFD-induced obese mice</td>
<td>400 mg/kg (4 weeks)</td>
<td>-</td>
<td>↓ Secretion adipocytokines such as leptin, resistin, IL-6, and MCP-1.</td>
<td>Protects TM3 cells,</td>
<td>(Bae et al., 2016)</td>
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<td>9.</td>
<td><em>Arachis hypogaea</em> nutshell extract and pumpkin oil</td>
<td>Nutshell</td>
<td>Flavonoids (luteolin and eriodictyol apigenin 44 and chrysin) coumarin and phenolic acid</td>
<td>HFD-induced obese rats</td>
<td>5 mg/kg/day pumpkins and 2 mg/kg/day peanut shell extract (22 weeks)</td>
<td>-</td>
<td>↓ Body weight and BMI</td>
<td>↑ Sperm count and testicular histology</td>
<td>(Galaly et al., 2014)</td>
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<td>10.</td>
<td><em>Argyreia nervosa</em> Bojer (Convolvulaceae)</td>
<td>Roots</td>
<td>flavonoids, steroids, ergoline alkaloids, and triterpenoids</td>
<td>DIO rats</td>
<td>100 and 200 mg/kg (single dose)</td>
<td>-</td>
<td>↓ Serum leptin, TC, LDL, and TG.</td>
<td>Promotes fertility through increased sperm count, sperm motility, FSH release, and synthesis</td>
<td>(Galani et al., 2010)</td>
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<td>11.</td>
<td>Artemisia iwayomogi (Compositae)</td>
<td>Whole plant</td>
<td>Scopoletin</td>
<td>HFD-induced obese mice</td>
<td>0.5% extract (11 weeks)</td>
<td>-</td>
<td>Down-regulates PPARγ2 and C/EBPα and their target genes CD36, aP2, and FAS.</td>
<td>↓ TNFα, MCP1, IL-6, IFNα, and INFβ</td>
<td>(Choi et al., 2013)</td>
</tr>
<tr>
<td>12.</td>
<td>Atractylodes lancea (Thunb.) DC (Compositae)</td>
<td>Rhizome</td>
<td>Atractylone, hinesol, β-eudesmol, and atrctylodin</td>
<td>HFD-induced obese mice</td>
<td>250 and 500 mg/kg (24 days)</td>
<td>Orlistat</td>
<td>Inhibits human pancreatic lipase.</td>
<td>↓ epididymal fat</td>
<td>(Patra et al., 2015)</td>
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<td>13.</td>
<td>Bombax ceiba L. (Malvaceae)</td>
<td>Stem bark</td>
<td>Flavonoids</td>
<td>HFD-induced obese rats</td>
<td>100, 200, and 400 mg/kg</td>
<td>Gemfibrozil 50 mg/kg</td>
<td>↓ TC, TG, PL, and fasting blood glucose</td>
<td>↑ Sperm count</td>
<td>(Gupta et al., 2013)</td>
</tr>
<tr>
<td>14.</td>
<td>Camellia sinensis (L.) Kuntze (Theaceae)</td>
<td>Leaves, twigs and stems, flower buds</td>
<td>Epicatechin, epicatechin gallate, and epigallocatechin gallate (EGCG)</td>
<td>HFD-induced obese rats</td>
<td>2% aqueous (35 days)</td>
<td>-</td>
<td>Inactivation of acetyl-CoA carboxylase causes AMPK activation that mediates thermogenesis and FAS inhibition.</td>
<td>↑ Testicular function</td>
<td>(El-Sweedy et al., 2007)</td>
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<td>15.</td>
<td>Cardiospermum halicacabum</td>
<td>Leaves</td>
<td>Flavonoids and phenolic acids</td>
<td>HFD-induced obese in rats</td>
<td>100 and 200 mg/kg (30 days)</td>
<td>-</td>
<td>↓ Weight gain</td>
<td>↑ Testosterone level, sperm count, and motility</td>
<td>(Peiris et al., 2015)</td>
</tr>
<tr>
<td>16.</td>
<td>Cinnamomum zeylanicum</td>
<td>Extracted oil (seed)</td>
<td>Tannins, terpenoids</td>
<td>HFD-induced obese mice</td>
<td>75 mg/kg (28 days)</td>
<td>-</td>
<td>↓ TC, LDL, and fasting blood glucose</td>
<td>↑ Sperm concentrations, motility, and viability</td>
<td>(Barakat and El-Masry, 2016; Fathiazad et al., 2013)</td>
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<td>17.</td>
<td>Citrullus vulgaris (Watermelon)</td>
<td>Seed</td>
<td>Lycopene, beta carotene</td>
<td>HFD-induced obese rats</td>
<td>55 mg/kg (28 days)</td>
<td>-</td>
<td>↓ Weight gain, serum TC, TG, LDL level.</td>
<td>↑ Sperm concentrations, motility, and viability</td>
<td>(Khaki et al., 2013)</td>
</tr>
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<td>18.</td>
<td>Curcuma longa (Turmeric)</td>
<td>Leaves</td>
<td>Curcuminoid</td>
<td>Cafeteria rats</td>
<td>25 mg/kg (35 days)</td>
<td>-</td>
<td>Prevents adipocyte differentiation</td>
<td>↓ Testicular weight</td>
<td>(El-Sweedy i., 2007)</td>
</tr>
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<td>19.</td>
<td>Danae racemose</td>
<td>Leaves</td>
<td>Phenolic compounds (phenols, sterol, lignans)</td>
<td>HFD-induced obese rats</td>
<td>200 and 400 mg/kg (28 days)</td>
<td>-</td>
<td>↓ TG, TC, and LDL levels</td>
<td>↑ Sperm motility and viability</td>
<td>(Khojasteh et al., 2016)</td>
</tr>
<tr>
<td>20.</td>
<td>Epimedium Herb (Berberidaceae)</td>
<td>Leaves</td>
<td>Isoptenyl flavonoids, icarine, and icariside</td>
<td>HFD-induced obese mice</td>
<td>0.2 and 0.4 g/kg (8 weeks)</td>
<td>-</td>
<td>-</td>
<td>↑ mRNA expressions of GnRH and LH.</td>
<td>(Zhang et al., 2011)</td>
</tr>
<tr>
<td>21.</td>
<td>Epimedium</td>
<td>Leaves</td>
<td>Icariside II</td>
<td>Zucker's rat</td>
<td>1.5 mg/kg/day (4 weeks)</td>
<td>-</td>
<td>-</td>
<td>Improves erectile function and pathologic changes through endogenous progenitor cell preservation and proliferation</td>
<td>(Ruan et al., 2018)</td>
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<tr>
<td>S. no</td>
<td>Natural Products</td>
<td>Part used</td>
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<td>22.</td>
<td><em>Garcinia cambogia</em></td>
<td>Fruits</td>
<td>Flavonoids, particularly hesperidin, naringin, and alkaloids</td>
<td>Zucker rats</td>
<td>(154 mmol HCA/kg diet) (92 or 93 days)</td>
<td>-</td>
<td>↓ Epididymal fat and toxicity.</td>
<td>Causes testicular atrophy and toxicity.</td>
<td>(Saito <em>et al</em>., 2005)</td>
</tr>
<tr>
<td>23.</td>
<td><em>Guibourtia tessmannii</em> (Caesalpiniaceae)</td>
<td>Stem barks</td>
<td>Phenols</td>
<td>HFD-induced obese rats</td>
<td>55, 110, 220 mg/kg (21 or 56 days)</td>
<td>Clomiphene citrate (2 mg/kg)</td>
<td>↓ TG, TC, LDL, and VLDL levels</td>
<td>Promotes LXRs/ABCA1 pathway, stimulates cholesterol removal from macrophages, and delays atherosclerosis.</td>
<td>(Defo <em>et al</em>., 2017)</td>
</tr>
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<td>24.</td>
<td><em>Hibiscus sabdariffa</em> L. (Malvaceae)</td>
<td>Leaf</td>
<td>Flavonoids</td>
<td>HFD-induced obese rats</td>
<td>1.15, 2.3, and 4.6 mg/kg (12 weeks)</td>
<td>-</td>
<td>-</td>
<td>Causes testicular toxicity</td>
<td>(Höper <em>et al</em>., 2013)</td>
</tr>
<tr>
<td>25.</td>
<td><em>Ligustrum lucidum</em> (Oleaceae)</td>
<td>Fruits</td>
<td>(8-E)-nizhenide, a secoiridoid</td>
<td>HFD-induced obese mice</td>
<td>300 and 30 mg/kg (6 weeks)</td>
<td>-</td>
<td>↓ Fats and TG.</td>
<td>↓ Epididymal fat</td>
<td>(Chen <em>et al</em>., 2012)</td>
</tr>
<tr>
<td>26.</td>
<td><em>Murraya koenigii</em> (L.) Spreng. (Rutaceae)</td>
<td>Leaves</td>
<td>Carbazole alkaloids, phenols, carotenoids, terpenoids</td>
<td>HFD-induced obese mice</td>
<td>30 mg/kg (2 weeks)</td>
<td>-</td>
<td>↓ Body weight gain, plasma TC and TG levels in mice.</td>
<td>↑ Testicular function</td>
<td>(Bitari <em>et al</em>., 2010)</td>
</tr>
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<td>27.</td>
<td><em>Nigella sativa</em> (Black Caraway)</td>
<td>Fruits</td>
<td>Phenolic acids and polysaccharides</td>
<td>HFD-induced obese mice</td>
<td>150 and 350 mg/kg bw (12 weeks)</td>
<td>-</td>
<td>↓ Body weight, fat mass and TG level.</td>
<td>↑ Sperm motility, viability, and count</td>
<td>(Saminathan <em>et al</em>., 2013)</td>
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<td>28.</td>
<td><em>Perilla frutescens</em> (L.) Britton (Lamiaceae)</td>
<td>Leaves</td>
<td>Phenols, alkaloids (1-deoxynojirimycin), and polysaccharides</td>
<td>HFD-induced obese mice</td>
<td>0.5 and 1.5 g/kg (50 days)</td>
<td>-</td>
<td>↓ TG, LDL, and fasting blood glucose levels</td>
<td>↑ Sperm parameters and levels of testosterone and FSH</td>
<td>(Barakat and El-Masyr, 2016)</td>
</tr>
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<td>29.</td>
<td><em>Ocimum basilicum</em></td>
<td>Leaves</td>
<td>Flavonoids, alkaloids (1-deoxynojirimycin), and polysaccharides</td>
<td>HFD-induced obese mice</td>
<td>800 mg/kg (24 days)</td>
<td>-</td>
<td>↓ Adipose TG</td>
<td>↑ Sperm motility, viability and count, ↓ MDA and ↑ TAC.</td>
<td>(Umar <em>et al</em>., 2012)</td>
</tr>
<tr>
<td>30.</td>
<td><em>Panax ginseng</em> C. A. Mey. (Araliaceae)</td>
<td>Roots</td>
<td>Isoginsenoside-Rh3</td>
<td>HFD-induced obese mice</td>
<td>0.75 g/kg (16 weeks)</td>
<td>-</td>
<td>Activates lipase via Protein Kinase A.</td>
<td>↑ Testicular functions</td>
<td>(Park <em>et al</em>., 2013)</td>
</tr>
<tr>
<td>31.</td>
<td><em>Perilla frutescens</em> (L.) Britton (Lamiaceae)</td>
<td>Leaves</td>
<td>Anthocyanins, malonylshisonin</td>
<td>HFD-induced obesity.</td>
<td>1% and 3% extract (4 weeks)</td>
<td>-</td>
<td>↑ Weight gain, food efficiency ratio, and relative liver and epididymal fat mass</td>
<td>↓ Epididymal adipose tissue</td>
<td>(Kim and Kim, 2009)</td>
</tr>
<tr>
<td>32.</td>
<td><em>Sida rhombifolia</em> L. (Malvaceae)</td>
<td>Leaves</td>
<td>Alkaloids</td>
<td>HFD-induced obese in C57BL/6J mice</td>
<td>1% extract (20 weeks)</td>
<td>-</td>
<td>Up-regulation of PPARγ 2 and SREBP-1c expression in the epididymal adipose tissue, leading to attenuation of adipogenesis.</td>
<td>↑ Testicular function</td>
<td>(Thounaojam <em>et al</em>., 2011)</td>
</tr>
<tr>
<td>33.</td>
<td><em>Spirulina Platensis</em></td>
<td>Blue-green algae</td>
<td>Phenolic compounds like phlorotannins</td>
<td>HFD-induced obese rats</td>
<td>3% extract (60 days)</td>
<td>-</td>
<td>↓ TC levels</td>
<td>↑ Spermatogenesis and testicular structure</td>
<td>(Esener <em>et al</em>., 2017)</td>
</tr>
</tbody>
</table>

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

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

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 |
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Anthocyanins</td>
<td>-</td>
<td>C57BL/6J Mice</td>
<td>2.9 mg/g</td>
<td>-</td>
<td>15-fold increase in necrotic-like adipocyte death and formation of macrophage synovia, coincident with increased tumor necrosis factor-α gene expression.</td>
<td>↓ Epididymal fat</td>
</tr>
<tr>
<td>2.</td>
<td>Curcumin</td>
<td>-</td>
<td>HFD-induced obese rats</td>
<td>250 mg/kg (4 weeks)</td>
<td>-</td>
<td>↓ Liver weight, TG and FFA levels</td>
<td>↑ Sperm concentration, normal sperm morphology, semen volumes</td>
</tr>
<tr>
<td>3.</td>
<td>Ethyl caprylate</td>
<td>-</td>
<td>C57BL/6J mice</td>
<td>0.05 and 0.1 g/kg (12 weeks)</td>
<td>Rosiglitazone</td>
<td>↓ Accumulation of ROS.</td>
<td>↑ Testicular function</td>
</tr>
<tr>
<td>4.</td>
<td>Friedelin</td>
<td>-</td>
<td>HFD-induced obese rats</td>
<td>(50 and 70 mg/kg)</td>
<td>Fenofibrate</td>
<td>↓ Levels of TC, TG, HDL, and LDL</td>
<td>↑ Testicular functions</td>
</tr>
<tr>
<td>5.</td>
<td>Kaempferol glycoside</td>
<td>-</td>
<td>HFD-induced obese Mice</td>
<td>0.15% of dietary (92 days)</td>
<td>-</td>
<td>↑ Lipid metabolism through the down-regulation of PPAR-γ and SREBP-1c</td>
<td>↑ Testicular functions</td>
</tr>
<tr>
<td>6.</td>
<td>Letrozole</td>
<td>-</td>
<td>Human model</td>
<td>2.5 mg letrozole (once a week for 6 months)</td>
<td>-</td>
<td>Aromatase inhibitor</td>
<td>Normalization of serum total testosterone</td>
</tr>
<tr>
<td>7.</td>
<td>Quercetin</td>
<td>-</td>
<td>C57BL/6J mice</td>
<td>(16 weeks)</td>
<td>-</td>
<td>Attenuates adipogenesis and ↓ expression of adipogenesis-related factors and enzymes</td>
<td>↓ Epididymal fat</td>
</tr>
<tr>
<td>8.</td>
<td>Resveratrol</td>
<td>-</td>
<td>Human Model</td>
<td>0.100 µmol/l (30 minutes)</td>
<td>-</td>
<td>Down-regulation of C/EBPα and PPARγ</td>
<td>↑ Sperm concentration, normal sperm morphology, semen volumes</td>
</tr>
</tbody>
</table>

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; SREBP1c = Sterol regulatory element-binding proteins; VLDL = Very low-density lipoprotein.

Notes:
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 = Glutathione; TC = Total cholesterol, TG = triacylglycerides; LDL = 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; SREBP1c = Sterol regulatory element-binding proteins; TBARS = Thiobarbituric acid reactive substances; TNFα = Tissue necrotic factor.
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 activates 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

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 Guibourdia tessmannii (Caesalpiniaaceae) is administered in HFD-induced obese rats for 21 or 36 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).
HPT hypothalamic–pituitary–testicular axis
IFNα Interferon-α
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

No conflict of interest.

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ETHICS APPROVAL

Not applicable.

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