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Naturally Based Nano Formulation in Metabolic and Reproductive Disorders: A Review

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ABSTRACT

Metabolic and reproductive disorders are pervasive all over the world. There are common causes between them as obesity, the surplus of nutrients, and reduced energy expenditure. Depending on the amount and location of body fat, obesity has severe repercussions for the reproductive system. Obesity is linked to menstruation abnormalities, infertility, miscarriage, poor pregnancy outcomes, reduced fetal well-being, and diabetes mellitus. Their consequences have an impact on a huge portion of the reproductive population. Individuals and society bear a huge social, medical, and economic burden due to reproductive and metabolic disorders. Diabetes causes multiple ranges of reproductive health disorders, like delayed puberty and menarche, menstrual cycle abnormalities, subfertility, poor pregnancy outcomes, and perhaps early menopause. Reproductive disorders are conditions that disturb the reproductive system, such as infections of the reproductive tract, congenital anomalies, reproductive system malignancies, and sexual dysfunction. Obesity, hyperlipidemia, insulin resistance, hepatic steatosis, and hypertension are examples of metabolic disorders, which are diseases characterized by metabolic malfunction and abnormal energy homeostasis. Each disease has its specific physiological and clinical signs; they share some pathological aspects as over nutrition, which is commonly exacerbated by a modern, sedentary lifestyle, causes intracellular stress and inflammation due to metabolic disruption. Because of chemical therapies' adverse effects, natural products are becoming more popular as alternative options to chemical therapies. Nano sizing can improve the solubility, bioavailability, and effectiveness of any product. In this review, we discuss the relationship in some types of metabolic and reproductive disorders of both males and females by summarizing in vivo and in vitro studies and focusing on nano-natural products or their involvement in treatment. Suggesting further studies explaining the potential impact of some nano elements and molecular, metabolic parameters and their role in reproduction. Supplementing the female or male reproductive system would be highly advisable and valuable.

Key words: Metabolic disorder; Reproductive disorder; Nano Formulation; Natural products.

INTRODUCTION

A metabolic disorder affects the body's ability to digest and distribute macronutrients including proteins, lipids, and carbohydrates. Metabolic disorders occur when the body's normal metabolic process is disrupted by abnormal chemical reactions. It can also be characterized as a hereditary single gene aberration, the majority of which are autosomal recessive (Zheng et al. 2021). Physical inactivity, cigarette smoking and an elevated BMI are all lifestyle risk factors. Other causes include hypertension, poor glucose metabolism and high blood pressure and cholesterol concentration contribute to these disorders (Akhuemonkhan and Lazo 2017). Lethargy, weight loss, jaundice, and seizures are some of the signs of metabolic diseases. Symptoms would differ depending on the type of metabolic disease. Acute symptoms, late-onset acute symptoms, gradual general symptoms, and persistent symptoms are the four types of symptoms (Agana et al. 2018; Mendrick et al. 2018). Inherited metabolic diseases are a type of metabolic disorder caused by a faulty gene that results in an enzyme deficit. Inborn errors of metabolism are a group of disorders with a variety of subtypes. When the liver or pancreas does not function properly, metabolic disorders might develop. Fig. 1 represented some types of metabolic disorders (Hernández-Granados et al. 2018).

Any sickness or disorder that affects the human reproductive system is referred to as reproductive disorders. Improper hormone yielding via ovaries or testes, as well as other endocrine glands is among them. Genetic or congenital defects, infections, tumors, or disorders of unknown sources can all cause these diseases (Hutson et al. 2014).

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Genetic abnormalities, genital anomalies, infections, structural differences, and cancers are the primary divisions of these disorders (Rawal and Austin 2015; Elshazly et al. 2019). Symptoms of reproductive disorders are bleeding in between periods and within it, itching, burning of the genital area, and pain during sex, severe pelvic/abdominal pain, vaginal discharge, and frequent urination (Hutson et al. 2014). Common reproductive conditions for human females are anomalies of the clitoris, vagina and uterus, abnormalities of menstrual cycle endometriosis, cancers, polycystic ovarian syndrome and diseases as AIDS, syphilis, gonorrhea, chlamydia, and genital herpes. And in men are pseudo hermaphroditism, anomalies of the penis, urethra, testes, prostate gland and seminal vesicles, Impotence, benign prostatic hyperplasia, Priapism, testicular cancer and prostate disease. Intersexuality syndrome as Klinefelter, Turner, and testicular feminization. Delayed and precocious puberty in both (Rawal and Austin 2015). Infertility is one of the most serious issues that is worsening by the day and endangering the human generation's future. Varicocele reduces sperm morphology and improves sperm count in people with aberrant morphology. Ovarian, cervical and prostate cancers are the deadliest of reproductive cancers. Some risk factors for this malignancy include age, history of family and late menopause. While pregnant and breastfeeding, the likelihood of occurrence is reduced (Salehi et al. 2008).

There is a relation between metabolic and reproductive disorders as diabetic complications can lead to some reproductive disorder as subfertility, delayed puberty or disturbance in the menstrual cycle. Reproductive difficulties can appear early in adolescence, later, or during the climacteric period, relying on the age at which diabetes is discovered. Decreased concentrations of LH, FSH and estradiol occurred in type 2 human studies (Gnanadass et al. 2021).

Because of central hypogonadism, women with type 1 diabetes sometimes have amenorrhoea, polycystic ovarian syndrome and hyperandrogenism, and infertility that can be controlled by insulin administration and improved metabolic disorder (Codner et al. 2012). Also, type 2 diabetes is related to other reproductive disorders like obesity and insulin resistance related to polycystic ovarian syndrome due to improper lifestyle. Although pubertal breast development appears to be delayed in type 1 diabetes, some people with type 1 diabetes still experience a small delay in menarche due to diabetic nephropathy and retinopathy (Calcaterra et al. 2021). The most common menstrual cycle abnormalities are oligomenorrhoea and prolonged cycle length that are related to patients with type 1 and 2 diabetes, studies revealed that these disturbances are more than six times than normal women without diabetes. Disturbance in BMI, sex steroid and sex hormone-binding globulin concentrations is also related to type 2 diabetes (Thong et al. 2021).

Mechanisms of Interactions between Diabetes and Reproductive Function

Insulin plays a crucial role in the hypothalamic–pituitary–gonadal axis so insulin insufficiency leads to hypogonadotropic and hypogonadism. Insulin promotes gonadotropin-releasing hormone (GnRH) release in cell lines obtained from hypothalamus cells (Edem et al. 2021). Hypogonadotropic hypogonadism and infertility are seen in knockout mice with a particular deletion of the brain insulin receptor. These animals respond to exogenous gonadotropin-releasing hormone injection by increasing LH concentrations, implying that the absence of insulin action lowers pituitary gonadotropin-releasing hormone release (Castellano et al. 2009). Uncontrolled hyperglycemia in animal models causes a catabolic condition with decreased fat mass and serum leptin concentrations, which inhibits central nervous system expression of kisspeptin, a key GnRH stimulant. Kisspeptin has been demonstrated to reverse hypogonadism after administration (Castellano et al. 2009).

Insulin receptors are expressed in the ovary and bind to insulin-like growth factor 1 receptors, thus FSH and LH are secreted. Insulin has been found *in vitro* to trigger these receptors, and to produce more androgen, estrogen, and progesterone. Insulin and testosterone levels in the blood are associated, with insulin levels (Nandi and Poretsky 2013). Diabetes has an impact on male reproductive function, by affecting the endocrine control of spermatogenesis, spermatogenesis itself, and compromising penile erection and ejaculation (Mohammad and Ameen 2021). The impacts have been studied in several studies. Diabetes is, however, a well-known cause of male sexual dysfunction. Previous research has put the prevalence of type 1 diabetes in subfertile men at around 1%. A decline in sperm numbers and quality has been seen in animal research employing mouse models of streptozotocin-induced DM (Carvalho et al. 2021).

When DM is induced in pre-pubertal animals, the related loss in infertility is more significant. Furthermore, in the BB Wistar rat, naturally occurring DM is linked to considerable loss of infertility, ruling out any putative confounding effects of diabetogenic drugs as a major cause. These findings back up the theory that DM affects male reproductive function (Komeilifard 2016). The gonadosomatic index (GSI) and the relative weights of the testis, epididymis and seminal vesicles were all significantly reduced in the streptozotocin (STZ) produced animal model of diabetes, indicating severe testicular injury (Adedara et al. 2015).

Diabetic mice showed longer mounting latency (ML) and intromission latency (IL) but lower mounting frequency (MF) and intromission frequency (IF) in animal studies. Diabetes is known as one of the risk factors for reduced sexual function, but it may also be the most difficult to treat; nonetheless, many elements of its pathophysiology and therapy have yet to be extensively studied (Suresh and Prakash 2012).

Insulin deficiency in STZ diabetic rats influenced spermatogenesis by altering serum FSH levels rather than directly impacting the seminiferous tubule epithelium. Previous research has found denatured and disintegrated sertoli cell cytoplasm in DM caused by intraperitoneal injection of streptozotocin (STZ) in animal models. As a result, both clinical and laboratory testing are required (Wagner et al. 2021). In an animal model of fertility, diabetic mice had a lower pregnancy rate, mating rate, and fertility index when compared to the control group, which had female mice mate with healthy male mice. These findings imply that diabetes can have a significant impact on male fertility (Nadi et al. 2021).

Table 1: Some nanoparticles of natural plant extract and corresponding pharmacological effects in some metabolic and reproductive disorders.

Nanoparticles	Model	Benefits	References
TQ-loaded nanocapsule	STZ-induced diabetic rats.	Decrease blood glucose and HbA1c, Improvements in body weight and lipid profile.	Rani et al. (2019)
Capsicum Oleoresin nanoemulsion	High-fat (HF)-diet-induced obesity in rats.	↓Adipogenic gene expression, ↑PPAR-α, UCP2 and CPT-1α.	Kim et al. (2014)
Curcumin PLGA-based NPs with Q10	STZ-induced diabetic rats.	↓CRP, IL-6, total cholesterol, ↓plasma triglycerides ↑HDL.	Devadasu et al. (2011)
Emodin PEGMA-DMAEMA-MAMMAM Nanomacromolecule	T2DM induced by HF diet with low dose of STZ injection in rats.	↓Upregulation of TNF-α protein, 2X3 receptor, and the phosphorylation of ERK1/2 in the DRG of T2DM.	Li et al. (2017b)
Gymnemic acid Nanosuspension	Diabetes-induced rats.	↓Blood glucose levels.	Ravichandran (2012)
Scutellarin amphiphilic chitosan derivatives (Chit-DC-VB12)	Caco-2 cells and STZ induced diabetic rats.	Downregulation of expression of VEGFR2, VEGF and vWF.	Wang et al. (2017)
Stevioside Pluronic-F-68 copolymer-based PLA Nanoparticles	*In vitro* release study.	↑Intestinal absorption, bioavailability ↑Biocompatibility controlled release.	Li et al. (2017a)
Resveratrol Nanocapsule	HF-diet- induced diabetic Mice.	Regulation of systolic and diastolic blood pressure.	Shahraki et al. (2017)
Marrubiin-SLNs	Umbilical vein endothelial cells.	Marrubiin nanoparticles are proposed as a preventive/therapeutic remedy against disorders elicited by increased levels of intracellular ROS in CVDs.	Nakhlband et al. (2018)
Nanostructured lipid carriers (NLCs) of Leonotis leonurus	INS-1 cells.	The plant extract encapsulated in NLC improved the uptake of glucose and enhanced the insulin sensitivity in vitro, compared to the extract.	Odei-Addo et al. (2017)
Ficus religiosa L. extract loaded solid lipid nanoparticles (SLN)	Diabetes induced Wistar rats.	SLN significantly reduced diabetes induced higher levels of blood glucose and increased diabetes induced lower level of plasma insulin.	Priyanka et al. (2018)
Curcumin Chitosan-coated solid lipid nanoparticles	BALB/c mice.	Administration prevents the onset of cancer.	Thakkar et al. (2016)
solid lipid nanoparticle suspensions of Plicosepalus acaciae and P. curviflorus,	HF-diet- induced diabetic Mice.	Significant blood glucose-lowering effect associated with antioxidant effects in the diabetic rats.	Aldawsari et al. (2014)
Poly (lactic-co-glycolic) acid (PLGA)-encapsulated nano-Syzygium jambolanum (NSJ)	L6 cells and in mice.	NSJ had a greater potential than that of SJ, and management of arsenic-induced hyperglycemia and stress.	Samadder et al. (2012)
Eysenhardtia polystachya-loaded silver nanoparticles (EP/AgNPs)	Pancreatic β cells, INS-1 cells, and zebrafish.	EP/AgNPs promote pancreatic β-cell survival, insulin secretion, enhanced hyperglycemia, and hyperlipidemia in glucose-induced diabetic zebrafish. EP/AgNPs also showed protection of the pancreatic β-cell line INS-1 against hydrogen peroxide-induced oxidative injury.	Campoy et al. (2018)
AgNPs and leaf extract of Pouteria sapota	Diabetes-induced rats.	A significant reduction in blood sugar levels in rats treated with leaf extract or AgNPs.	Prabhu et al. (2018)
Nasturtium officinale and ZnO nanoparticles	Alloxan-diabetic Wister rats.	The application of Nasturtium officinale leaf extract can strongly empower ZnO nanoparticles towards superior antidiabetic and enhanced antibacterial activities.	Bayrami et al. (2019)
Copper nanoparticles supported on titania (CuNPs/TiO2), plant extracts (buckwheat (Fagopyrum esculentum) and vitex (Vitex agnus-castus)	Ovarian cell.	CuNPs/TiO2 can directly stimulate ovarian cell functions, promoting ovarian cell proliferation, apoptosis, turnover, viability, and steroid hormones release; the plants buckwheat and vitex, as well as rutin and apigenin, can promote some of these ovarian functions.	Sirotkin et al. (2020)
SLN containing myricitrin	Adult male mice.	Total antioxidant capacity and superoxide dismutase levels increased in diabetic mice. SLN containing myricitrin recovered LH, FSH, testosterone, and sperm count. Diabetes induced vacuoles and apoptosis in testicular cells, were improved.	Oroojan et al. (2021)
Terminalia arjuna Reduced Gold Nanoparticles	Male Wistar rat.	Effective significant recovery in the reproductive disorder caused due to acetaminophen toxicity.	Mitra et al. (2020)
Gadolinium orthovanadate nanoparticles	Rats with neonatally-induced reproductive disease	Restoring the quality of sperm and male fertility and improves reproductive potential.	Belkina et al. (2017)

One of the established pathways in diabetic reproductive damage is oxidative stress. Several studies have shown that oxidative stress plays a role in the development of diabetic reproductive system damage and that antioxidants can help. According to the evidence, oxidative stress was the primary cause of the testicular malfunction, which resulted in male hypogonadism and infertility (Allam et al. 2021). Hyperglycemia boosted mitochondrial glucose oxidation by releasing a large amount of superoxide and other free radicals into the cytoplasm, according to a study. The principal source of ROS in the testes is NADPH oxidase (NOX),

METABOLIC DISORDERS	
CONGENITAL	ACQUIRED AND CONGENITAL
Fabry disease	Diabetes
Phenylketonuria	Obesity
Prader-Willi syndrome	Dyslipidemia
Galactosemia	Hipolipidemia
Tay-Sachs's disease	Hyperthyroidism
Porphyria	Hypoparathyroidism
Pompe disease	Hypothyroidism
Niemann-Pick disease	Cushing's syndrome
Morquio's syndrome	Hyperuricemia
Maroteaux-lamy syndrome	Hemochromatosis
Hunter Syndrome	Hyperparathyroidism
Lesh-Nyhan syndrome	
Hurler syndrome	
Homocystinuria	
Hartnup	
Gaucher disease	

Fig. 1: The congenital and acquired metabolic disorders (Hernández-Granados et al. 2018).

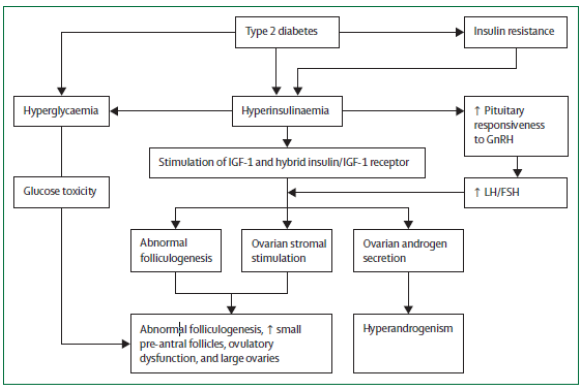

Fig. 2: Mechanisms of interactions between type 2 diabetes and reproductive function (Thong et al. 2020).

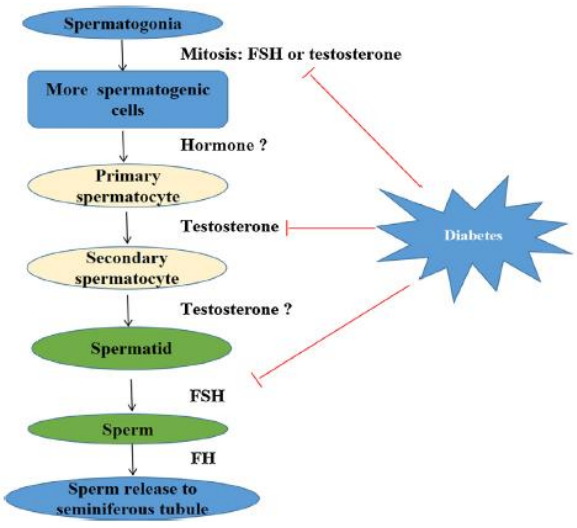

Fig. 3: Schematic diagram of endocrine effects on spermatogenesis (Shi et al. 2017).

which generates an electron current that passes from intracellular NADPH to oxygen, resulting in superoxide production (Miguel-Jiménez et al. 2021). Endothelin (ET) is required for the modulation of testicular activity, which increases ROS generation by activating NADPH oxidase, as seen in germ cells. This imbalance between the generation of reactive oxygen species (ROS) and their

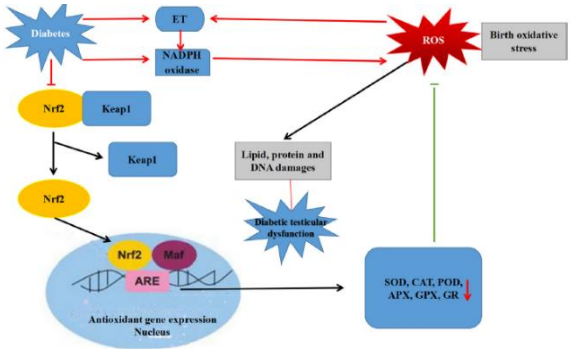

Fig. 4: The relationship between diabetes-mediated oxidative stress (mitochondrial dysfunction and ER stress) and the onset of diabetic reproductive damages (Shi et al. 2017).

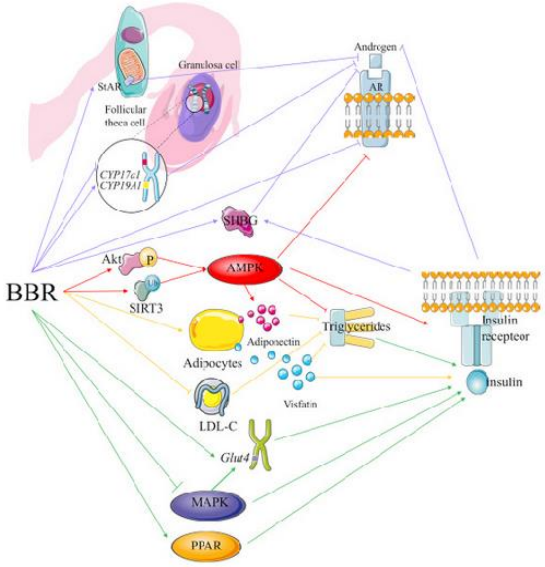

Fig. 5: BBR's major method of action against PCOS is to block androgen binding to AR while promoting insulin binding to insulin receptors. Furthermore, the action of BBR on lipid metabolism is an intermediary connection that alters insulin binding to its receptor .Furthermore, greater insulin sensitivity can prevent androgen from binding to AR (Zhang et al. 2021).

degradation eventually leads to germ cell death and spermatogenesis failure (Brewer et al. 2011).

Plant extracts have a long history of being used to treat infertility, sexual dysfunction, and other reproductive diseases. Plant active components such as phenols, alkaloids, flavonoids, terpenoids, tannins, and saponins improve the reproductive system in animals, according to science. Medicines that lower blood glucose, TGs, and blood pressure, as well as lifestyle changes, are common treatments for metabolic disorders. However, these drugs have side impacts. Nanoformulation of natural and synthetic substances can be used to reduce these side effects and increase therapeutic delivery efficiency (Kaur 2014). A therapeutic method is to use nanosized the drug made up of phytochemicals with good pharmacological and pharmacokinetic properties. The nano-vehicles have unique qualities such as increased medication bioavailability and solubility, reduced systemic side effects, increased time in circulation, and preferential aggregation in the body (Torchilin 2006). Therefore, different plants including curcumin, berberine, *Centella Asiatica*, *Hemidesmus indicus*, *Celastrus paniculatus* and

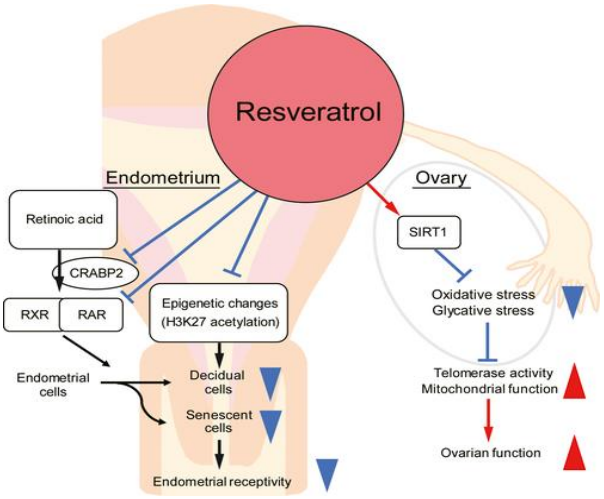

Fig. 6: Effects of resveratrol on ovaries and endometrium. Resveratrol increases the production of SIRT1 in the ovary, which is linked to protection against oxidative and glycation stress. Furthermore, it improves ovarian function by activating telomerase activity and mitochondrial function. Resveratrol inhibits decidual senescence and decidualization by speeding up the downregulation of the CRABP2-RAR pathway in the decidualized endometrium (Ochiai and Kuroda 2020).

Hibiscus rosa-sinensis and others have been used in diverse strategies for curing and prevention of metabolic and reproductive disorders (Hossen et al. 2016; Taghipour et al. 2019).

Curcumin

Curcumin, a polyphenol derived from turmeric (Curcuma longa): related to the curcuminoid group of polyphenols having anticancer, antioxidant, anti-inflammatory, hypolipidemic, and anticarcinogenic properties. Curcumin's low water solubility is a concern that needs to be resolved by formulating this phytochemical in a nanosized structure (Ashtary-Larky et al. 2021).

Curcumin-loaded on nanomicelles pluronic were created and characterized for the elimination of diabetes in another study because they significantly increased the expression of the genes of Pdx-1 and NKx6.1, which are essential transcription factors in the expression of the insulin gene (El-Far et al. 2017). Nanoemulsion of curcumin was produced as an antihypercholesterolemic and antihypertensive drug in another study. In an *in vitro* investigation, the efficiency of curcumin versus hypertension was evaluated via ACE suppression (Rachmawati et al. 2016). In the therapy of cancer, cardiovascular, and neurological illnesses, nanoformulations of curcumin have shown therapeutic benefits over free curcumin (Gera et al. 2017). Increased MMP-2/TIMP-2 ratio was directly connected to endometriotic development, which was slowed by curcumin pretreatment (Jana et al. 2012). Through the reduction of the inflammatory response, nano curcumin can prevent the production of anti-sperm antibodies in testicular injuries (Pramudhito et al. 2021). Nanocurcumin has promising potential against polycystic ovary syndrome-related pancreatic molecular and histological pathologies via decreasing oxidative indicators, glycemic indices, and TNF-α level considerably. It restored normal sex hormonal levels by restoring PI3K/AKT/mTOR levels, alleviating insulin resistance, and preserving islet intact (Abuelezz et al. 2020).

Berberine (BBR)

BBR is a benzylisoquinoline alkaloid found in the Coptis chinensis plant. Infections in the intestine, hypertension, cardiac failure and arrhythmia, tumors, increasing cholesterol level, and diabetes have all been treated with BBR (Xu et al. 2021). BBR treatment enhanced TG levels, obesity, and insulin-resistant animals, according to studies. BBR increases genes expression related to energy utilization while decreasing the one related to lipogenesis. BBR that has been nano formulated is proved to have a higher bioavailability greater than that of simple BBR (Xue et al. 2013).

The cytoprotective effects of O-hexadecyldextran encapsulated BBR NPs on rat primary hepatocytes induced apoptosis were investigated. PCSK-9 mRNA was efficiently regulated by oral administration of a nanoformulation made from PLGAPEG-PLGA copolymers containing BBR chloride for the treatment of elevated LDL cholesterol (Kapoor et al. 2014). The use of NPs of BBR and bulk formulations of BBR significantly improve obesity and increase insulin homeostasis also fasting blood glucose level, and resistance evaluated (Ochin and Garelnabi 2018). Intake of BBR corrected some metabolic and hormonal abnormalities in PCOS-affected women (Wei et al. 2012). BBR has been shown to decrease the level of androgen in rats and PCOS people. Many studies have shown that BBR can raise sex hormone-binding globulin levels, which helps to stabilize androgen levels and alleviate hyperandrogenism signs including acne and hairiness in patients (Maliqueo et al. 2007; Zhang et al. 2021).

Naringenin

Naringenin known also as 5,7,4'-trihydroxyflavanone belongs to the flavanone family of flavonoids found in grapefruit, oranges and most vegetables. Also act against inflammation, mutation hyperglycemia and oxidation (Arafah et al. 2020). Naringenin is poorly dissolved in water and poorly absorbed through the intestine because the action of many enzymes leads to rapid clearance in the gut and liver. As a result, nano sizing this substance by loading onto NPs, or encapsulating it in a nanoformulation is a strong technique for improving its targeting and absorption. In STZ-induced diabetic rats, core-shell NPs loaded with naringenin revealed no toxicity or harm to cells and had good anti-diabetic benefits after oral supplementation (Maity et al. 2017).

Naringenin enhanced the production of reactive oxygen species and lipid peroxidation in the testis, resulting in a dose-dependent decrease in sperm count and motility. It also acts as a pro-oxidant, causing damage to testicular tissue (Ranawat and Bakshi 2017). Caspase 3 decreased and enhancing anti-apoptotic (Bcl-2) genes by naringenin at and increased the quality and fertility of rooster sperm after thawing (Mehdipour et al. 2020). It also blocked gonadotoxicity-induced Cisplatin and doxorubicin in male rats (Fouad et al. 2019).

Ginseng

Ginseng is a plant that grows in Korea, northeastern China; it has possible impacts on memory, fatigue,

menopause symptoms, atherosclerosis, erectile disorder, immune disorders, cancer disease, and stress physiology and insulin response in people with mild diabetes (Chen et al. 2019; Sung et al. 2005). Plant nanoparticles are helping to improve drug bioactivity within cells and tissues by acting as less toxic and efficient carriers for delivery. Furthermore, supplementation with KRG extract has been shown to improve testicular function, sperm viability, and sperm quality in guinea pigs (Linjawi 2015). According to a study, Panax ginseng and Panax ginseng nanoparticles administration improved male rat fertility by increasing serum-free testosterone, LH, and FSH secretion and decreasing sperm abnormalities. Furthermore, Panax Ginseng treatment reduced DNA damage and enhanced fertility gene expression levels (Kim et al. 1999).

Myricitrin

Myricitrin known as myricetin-3-O-rhamnosid is a flavonol glycoside found in plants that are extracted. Anti-nociceptive, anxiolytic, antioxidant, anti-carcinogenic and anti-inflammatory properties are all found in myricitrin. It is regarded as an essential supplement in medicine due to its high antioxidant activity (Sun et al. 2014; Devi et al. 2015). SLNs containing myricitrin were found to protect against cytotoxicity caused via streptozocin supplementation. In addition, SLNs containing myricitrin were found to have antioxidant and anti-diabetic properties in a diabetic animal STZ-nicotinamide and cell of male mouse myotube (Ahangarpour et al. 2018). Diabetes caused reproductive problems by increasing oxidative stress and lowering antioxidant capacity; however, myricitrin or SLN containing myricitrin relieved these symptoms (Oroojan et al. 2021).

Resveratrol

Resveratrol also named 3,5,4-trihydroxylstilbene is a polyphenol found in grapes and nuts that exhibits anti-inflammatory, strong antioxidant, antiplatelet, analgesic, neuroprotective, cardioprotective, and antiaging properties. It has a significant impact on glucose metabolism and oxidative stress. Resveratrol appears to be a viable adjuvant therapy for type 2 diabetes management (Bremer 2014). The nanoliposomes loaded with resveratrol were covalently PEGylated to improve plasma half-life and residence time. Liposomes increased levels of GSH-Px and SOD that are ROS-inactivating enzymes; these NPs protect and help in the treatment of patients with type 2 diabetes mellitus (Yücel et al. 2018). Another NPs combination had resveratrol was formed, and the effect of this formulation on mice with metabolic disorders was studied. The results showed that mice treated with nanocapsules had their systolic and diastolic blood pressures controlled (Shahraki et al. 2017; Sobhy et al. 2021).

Resveratrol has been shown to have an inhibiting effect on female reproductive processes in several studies. The rat sociosexual behavior was impacted by Resveratrol. It interrupts the ovarian cycle and lowers ovarian weight, ovarian follicular development, and the number of ovarian follicles were demonstrated in rats *in vivo*. It inhibited DNA synthesis and, as a result, cell growth in cultured ovarian cells (Ortega and Duleba 2015; Macedo et al. 2017; Sirotkin et al. 2019). Gold nanoparticles added to resveratrol enhanced anti-tumor potency versus breast, pancreatic and prostate cancers via its anti-angiogenesis character of AuNPs and the phytochemical (Thipe et al. 2019).

Quercetin (QUE)

QUE is an antioxidant and anti-inflammatory flavonoid present in foods as onions, citrus fruits, apples, and tea. QUE affects adipokinesis and lipolysis via mitochondrial mechanisms. Some reports revealed that QUE decreased blood pressure, insulin resistance, and cholesterol (Leiherer et al. 2016). Poly (ethylene glycol) - block - (poly (ethylenediaminel - glutamate) - graft - poly (-benzyloxycarbonyl-l-lysine)) with QUE was synthesized in a study and its abilities in the form of nanosized complexes were investigated in several models in diabetic nephropathy (Tong et al. 2017).

In diabetic mice, the administration of these NPs reduced fasting blood glucose levels. The production of lipid peroxidation products was reduced by QUE (Alam et al. 2016). In mice, QUE in conjunction with other antioxidants such as rutin and resveratrol, as well as QUE nanoemulsion, reduced inflammation, decrease pain, and regulate apoptosis generated by oxaliplatin, and protected the brain and liver (Schwingel et al. 2014). QUE has a cytotoxic impact on cancer cells line of ovarian and prostate in several models. Specific oncogenes and genes governing the G1, S, G2, and M stages of the cell cycle were strongly suppressed by quercetin (Nair et al. 2004; Vafadar et al. 2020). On ovarian cancer cell line named PA-1, QUE may have a synergistic effect with gefitinib's anti-cancer properties. Furthermore, it was discovered that QUE reduced the viability in a dose and time-dependent mechanism of ovarian cancer cells. QUE regulates the intrinsic apoptotic pathway, causing anti-apoptotic genes like Bcl-2 and Bcl-xL to be suppressed while pro-apoptotic elements like caspase-3 -9, cyto-c, Bid, Bad, and Bax are enhanced in expression (Teekaraman et al. 2019).

Thymoquinone (TQ)

Thymoquinone (TQ) is an antioxidant, anti-inflammatory, neuroprotective, anti-allergic, anti-viral, anti-diabetic, and anti-carcinogenic chemical found in the Nigella Sativa plant. This compound is an antioxidant phytochemical that scavenges free oxygen radicals, particularly superoxide anion and hydroxyl radicals (Ashraf et al. 2011). After ischemia and reperfusion, TQ improves histological changes in testicular tissue as well as the rate of apoptosis. TQ protects the testicles against the damaging consequences of obesity by raising healthy sperm count and lowering sperm abnormalities, according to another study studying the effect of obesity on testicular tissue and sperm parameters. TQ's antioxidant activities have been found in another investigation to prevent methotrexate-induced histopathological alterations. In the medical treatment of varicocele, thymoquinone has the potential to be employed as a preventive and therapeutic pharmacological agent (Tufek et al. 2015).

The nano-drug delivery system improves the bioavailability of orally delivered therapeutic agents, allows for target-specific drug delivery, and extends the half-life of parenteral medications. TQ is the main active element in Nigella sativa and has been used in a variety of nano-formulations to test its pharmacological effectiveness

against a variety of human ailments, including cancer, hypertension (HTN): diabetes, allergies, eczema, and immunogenic disorders. The very hydrophobic property of TQ limits its solubility and bioavailability, which is a major challenge in producing TQ-based nanoformulation (Khan et al. 2021). Antitumor activities have been discovered in TQ. To increase TQ bioavailability and cytotoxicity, TQ nanostructured lipid carrier (TQ-NLC) was formed. These NPs has a cytotoxic impact on breast cancer (MDA-MB-231 and MCF-7) and cervical cancer cell lines in cell line HeLa and SiHa. Cell cycle arrest was also triggered by TQ-NLC.TQ-NLC was most cytotoxic against breast cell lines than cervical cancer cell lines (Keat 2015).

Stevioside

Stevioside is a glycoside- extracted from the Stevia rebaudiana plant's leaves (Goyal et al. 2010). This substance is anti-diabetic. Many studies have shown that stevioside has a significant response on the kidney and metabolism of glucose (Kujur et al. 2010). Stevioside treatment inhibited OVCAR-3 cell growth and produced cytotoxicity, both dose and time-dependently, and was related to increased ROS generation in the cell, indicating the onset of apoptosis. Furthermore, the drop in mitochondrial membrane potential indicated that the cell was affected by the stevioside-induced intrinsic apoptotic pathway. After stevioside supplementation, the levels of caspase-3, -9 in OVCAR-3 cancer cells enhanced. Furthermore, a flow cytometric analysis revealed stevioside's apoptotic activity and cell stop in the G2/M phase. The inhibition of the P13K/AKT signaling pathway was also discovered (Li et al. 2017a). This compound's nano-bioconjugation with Pluronic-F-68-based Polylactic acid (PLA) NPs was found to be effective in overcoming poor intestinal absorption and increasing bioavailability. This NPs formulation revealed strong anti-diabetic efficacy in streptozotocin-induced rats (Barwal et al. 2013).

Eurycoma Longifolia

The herb Eurycoma longifolia, a Southeast Asian native, has traditionally been used to cure a variety of diseases including tachycardia, malaria, fever, and reproductive problems. In the test animals, the herbal extract produced the anticipated benefits in terms of aphrodisiac, sexual prowess, and fertility. Furthermore, chemicals identified in the plant have been shown to boost testosterone levels, sperm concentration, and sperm quality in rats (Bhat and Karim 2010). The bioactive components present in its roots, the bulk of which are quassinoids, such as eurycomanone, 13 (21)- epoxyeurycomanone, and eurycomanol, 13, 21-dihydroeurycomanone, are responsible for these qualities. Eurycomanone ($C_{20}H_{24}O_9$) is a significant quassinoid found in E. longifolia root extracts that improve animal reproduction. This substance inhibits the enzymes aromatase and phosphodiesterase, which are required for estradiol synthesis, increasing testosterone production (Low et al. 2013).

When given orally or intravenously, this chemical has a limited bioavailability and half-life. To counteract this, the chemical was conjugated with chitosan nanoparticles to extend the duration of its impact. This compound proved to increase gonadal development, as evidenced by a higher GSI value. The eurycomanone nanoparticles were discovered to boost testosterone and reproduction success by acting on genes involved in steroid synthesis and metabolism in the gonads, as well as FSH and LH in the brain (Bhat et al. 2019a; Low et al. 2005). The effect of chitosan-conjugated EN in female fish was investigated and showed downregulation in different treatment groups, the mRNA expression of the genes implicated in the HPG axis was elevated. When compared to the control group, which had somewhat fully mature eggs, 17-estradiol levels were lower in EN treated groups, and the ovary contained eggs in the embryonic stage. According to the findings, EN is unlikely to be used in females for gonadal development. The cause is a decrease in the hormone estradiol, which is necessary for ovarian function and the development of female secondary sexual characteristics (Bhat et al. 2019b).

Costus Speciosus

Costus speciosus a medicinal herb from India belongs to the Costaceae (Zingiberaceae) family. It acts as an anti-inflammatory, anti-hyperlipidemic, anti-diabetic, and liver-protective drug. In the STZ- diabetic rat model, extracts of C. speciosus rhizome in ethyl acetate, hexane, and methyl alcohol dramatically lowered plasma glucose levels. Diabetes-induced hyperglycemia, body weight loss and testicular injury were considerably improved with a lower dose of NPs C. speciosus (Bahshwan et al. 2019).

Conclusions and Future Prospective

This review summarized several studies about the protective effects of some nano natural plants or their involvement in treatment and controlling some reproductive and metabolic disorders. Other studies should be done in different models in comparison with other treatments and also the crude plant. Suggesting further studies explaining the potential impact of some nano elements and molecular metabolic parameters and their role in reproduction. Its supplementation on the female or male reproductive system would be highly advisable and valuable.

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