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Review Article

Endocrine Pharmacology Research in India: Scientific Progress in Last Five Years

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During the last five years, significant scientific effort has been made in the field of endocrine pharmacology by Indian researchers. Endocrine disorders like diabetes and disorders of the reproductive systems and melatonin are the major areas of research interest of the Indian scientists. Though the researchers have investigated both natural products and synthetic compounds, the reported studies have focused primarily on plant extracts to substantiate their use scientifically based on their folklore use. Diabetes is fast gaining the status of a potential epidemic in India with approximately 69 million people in the world. Various pharmacological investigations on herbal and synthetic compounds have been carried out for the treatment of diabetes and its complications. Saroglitazar, a novel PPARα/γ agonist is the first indigenously developed synthetic antidiabetic drug by an Indian pharmaceutical company as approved for the treatment of type 2 diabetes in June 2013. The potential of certain cell based therapies and nanoformulations were also investigated for different diabetes treatment. The scientific rationale for the use of various herbs on male and female reproduction with respect to aphrodiasic, fertility and antifertility properties has been explored. In addition to role of melatonin in chronobiology, it has been reported to possess multiple pharmacological actions such as antioxidant, anti-inflammatory and neuroprotective actions. Only few Indian scientists have studied on endocrine pharmacology related to adrenal, tyroid and parathyroid gland disorders. In addition, the effects of some endocrine disruptors, toxic chemicals and heavy metals on endocrine systems were also studied. In this review, we have compiled the research articles on scientific progress made in the field of endocrine pharmacology from India between years 2012-2017.

Keywords: Endocrine Pharmacology; Diabetes; Reproduction; Melatonin, Endocrine Disruptors

Introduction

The scientific progress in the field of endocrinology is greatly linked with the efforts made by the researchers working in the area of endocrine pharmacology. Even though research work relevant to endocrine glands had started much earlier, this branch of science gained major attention only when Brown Sequard published "organotherapy", which was initially carried out with testicular extracts. Other animal glands such as the adrenal, thyroid and pancreas were also used with varying degrees of success to treat hormone deficiency. Improvements in chemistry, pharmacy, and allied sciences led to innovations in endocrine pharmacology. Researchers began using a variety of compounds, both natural and synthetic, to treat endocrinopathies. As our understanding of the pathophysiological basis of metabolic and hormonal diseases improved, newer drugs were invented on purpose, rather than discovered by chance. The field of endocrine pharmacology has also witnessed the pharmacological exaptation meaning that some endocrine drugs, apart from their indications for the treatment of endocrinopathies, are also shown to be effective and indicated for the treatment of other non-endocrine ailments (Kalra *et al*., 2012, Katare and Banerjee 2016). Similarly, certain non-endocrine drugs have also been exapted for the treatment of endocrine disorders. In this review, we have analyzed and compiled the research articles published by the researchers from India between years 2012-2017 in the field of endocrine pharmacology. There are only some institutions and laboratories in India that keep

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working in the area of endocrine pharmacology. The main research areas of the Indian scientists were on diabetes and other disorders associated with reproductive system and melatonin. As we focused more on the pharmacological research in the field of endocrine pharmacology, few important clinical reports have only been incorporated in this review.

Diabetes Mellitus

Diabetes mellitus, a chronic metabolic noncommunicable disease has attained epidemic proportions worldwide. As of 2015, more than 415 million adults have diabetes and this number is expected to increase to around 642 million by the end of 2040. India is one of the epicentres of the global diabetes mellitus epidemic and has the second highest number of people with the disease in the world (~69 million individuals as of 2015) after China (IDF 2015, Unnikrishnan *et al*., 2016). Despite the current use of synthetic drugs and progress being made in allopathic drug research and development as reviewed, the use of herbal remedies is gaining importance because of synthetic drugs have drawbacks and limitations (Chaudhury *et al*., 2017, Kumar and Bharti 2017). Many of the pharmacological investigations from India during the last 5 years (2012-17) have been undertaken on the effects of herbal and natural products on diabetes. The conventional and induced animal models of diabetes such as high dose streptozotocin (STZ) and combined high fat diet (HFD) and low dose STZ-induced animals were mostly used in the studies.

Antidiabetic Investigations on Herbal Drugs and Natural Products

Various plants and herbal products have been used as a folk medicine in India for the treatment of diabetes. Many of the pharmacological investigations were carried out to provide a scientific rationale for the use of the plant to treat diabetes in folk medicine (Table 1). The ethyl extract of *Ficus carica* leaves was evaluated in HFD-fed and low dose STZ-treated type 2 diabetic rats. It exhibited significant antidiabetic effects by restoring the altered carbohydrate metabolizing enzymes such as glucose-6-phosphatase, fructose-1,6-bisphosphatase and hexokinase in the liver tissue of HFD/STZ diabetic rat (Stephen Irudayaraj *et al*., 2017). Further, ficusin isolated from *F. carica* is reported to produce antidiabetic effects via enhancing glucose transporter (GLUT)-4 translocation and peroxisome proliferator-activated receptor (PPAR)-γ-expression in adipose tissue (Irudayaraj *et al*., 2016). The ethanolic extract of *Allium cepa* stimulates GLUT4 translocation-mediated glucose uptake by the activation of the phosphatidylinositol 3-kinase (PI3K)/Akt dependent pathway (Gautam *et al*., 2015).

Oral administration of *Aegle marmelos* (L.) Corr. bark extract showed significant hypoglycaemic activity which was associated with reduction in blood glucose, increase in insulin levels and pancreatic β-cells regeneration in STZ-induced diabetic rats (Gandhi *et al*., 2012). Aegeline, alkaloidal-amide isolated from *Aegle marmelos* exhibited antihyperglycemic activity which may be via stimulating glucose transport and cytoskeletal rearrangement through PI3K/Rac1 signaling (Gautam *et al*., 2015). The aqueous extract of tamarind seeds selectively increased GLUT-2 (liver), GLUT-4 (skeletal muscle), islets' intracellular calcium levels and β-cell neogenesis resulting in improved glucose homeostasis in STZ diabetic rats (Sole and Srinivasan 2012). The anti-inflammatory action of tamarind seeds contributes toward its antidiabetic activity via repressing pancreatic beta-cell damage and normalizing sterol regulatory element-binding transcription factor (SREBP-1c) concentration in liver (Sole *et al*., 2013).

Polyphenols-rich *Cyamopsiste tragonoloba* (L.) Taub. beans were reported to possess hypoglycemic and β-cells protective effects in HFD/STZ type 2 diabetic rats (Gandhi *et al*., 2014). The investigators from Annamalai University have demonstrated that oral treatments of some plant derived components such as myrtenal (monoterpene) and naringin (flavonoid) caused significant reduction in the levels of plasma glucose, blood glycosylated hemoglobin (HbA1c) and improvement in plasma insulin. Myrental acts by enhancing GLUT2 in liver, GLUT4 and Akt in the skeletal muscle where as naringin acts by modulating hepatic enzymes involved in carbohydrate metabolism of diabetic rats (Pari and Chandramohan 2017, Rathinam and Pari 2016).

Prasath and co-workers from the University of Madras have made extensive studies on antidiabetic

Table 1

Botanical name	Family	Common name	Part/extract used	Active ingredient/ principle(s)	Test model	Pharmacological effects	Suggested mode of action(s)	References
Ficus carica	Moraceae	Fig/Anjir	Leaves/ethyl acetate	Ficusin	HFD fed-low dose STZ-induced type 2 diabetic rats	Decrease (↓) in blood glucose, total cholesterol (TC), triglycerides (TG), and increase (↑) in hepatic glycogen	-Restoring carbohydrate metabolizing enzymes in liver -Enhancing GLUT-4 translocation-mediated glucose uptake and PPAR-γ expression in adipose tissue	Stephen Irudayaraj *et al*., 2017; Irudayaraj *et al*., 2016
Allium cepa	Amarylli-daceae	Onion	Whole onion/ ethanol	Allyl propyl disulphide and Diallyl-disulphide	*In-vitro*	-Stimulates glucose uptake by the rat skeletal muscle cells (L6 myotubes)	-Stimulating GLUT4 translocation and glucose disposal by the activation of PI3K/Akt dependent pathway	Gautam *et al*., 2015
Aegle marmelos	Rutaceae	Bael	Bark/ Methanol	Aegelin and Lupeol	STZ-induced diabetic rats	↓blood glucose, ↑insulin and pancreatic β-cells regeneration	-Stimulating the glucose transport through Akt/Rac1 pathway in the skeletal muscle cells	Gandhi *et al*., 2012; Gautam *et al*., 2015
Tamarindus indica	Fabaceae	Tamarind	Seeds/ Aqueous	Polyphenols and Flavonoids	Neonatal STZ-induced diabetic rats	↓blood glucose, ↑insulin and pancreatic β-cells regeneration ↓serum NO, HbA1c and TNF-α	-Improving GLUT-2 and SREBP-1c in the liver and GLUT-4 in the skeletal muscles	Sole and Srinivasan 2012; Sole *et al*., 2013
Cyamopsis tetragonoloba	Fabaceae	Guar/ cluster Bean	Beans/ methanol	Polyphenols (gallic acid and caffeic acid)	HFD/STZ-type 2 diabetic rats	hypoglycemic and β-cells protective effects	--	Gandhi *et al*., 2014
				Myrental	STZ-diabetic rats	↓plasma glucose, HbA1c and ↑plasma insulin	-Enhancing GLUT2 in liver, GLUT4 and Akt in the skeletal muscle	Rathinam and Pari 2016
				Naringin	HFD/STZ-type 2 diabetic rats	↓plasma glucose, HbA1c and ↑plasma insulin and blood Hb	-Modulating hepatic glucose metabolism	Pari and Chandramohan 2017
				Fisetin (3, 7, 3', 4'-tetrahy-droxyflavone)	STZ-induced diabetic rats	↓blood glucose, lipids, HbA1c and ↑circulating insulin	-Inhibiting gluconeogenic enzymes in hepatic and renal tissues -Antioxidant and anti-inflammatory actions via decreasing NF-kB p65, IL-1β, and lipid peroxidation	Prasath and Subramanian 2014; Prasath *et al*., 2014; Prasath and Subramanian 2013; Prasath *et al*., 2013
				Rosmarinic acid (polyphenol)	HFD/STZ-type 2 diabetic rats	↓blood glucose, lipids, HbA1c, AGE, TNF-α, IL-1β, IL 6, NO, ↑plasma insulin and ↑insulin sensitivity index	- Alleviating pancreatic β-cell dysfunction via increasing Nrf-2 and hemeoxyenase (HO-1) antioxidants levels	Govindaraj and Sorimuthu Pillai 2015; Jayanthy *et al*., 2017
				Morin	STZ-diabetic	↓blood glucose, lipids and ↑serum	-Antihyperglycemic action via	Vanitha *et al*.,

				(pentahydroxyflavone), and Zinc-Morin complex	rats HFD/STZ diabetic rats	insulin and preservation of β-cells ↓insulin resistance and ↑plasma adiponectin and ↓leptin and TNF-α levels	ameliorating hepatic glucose metabolizing enzymes -acting as antioxidant against pancreatic β-cells damage by Nrf2 signaling pathway	2014; Sendrayaperumal *et al*., 2014; Vanitha *et al*., 2017
Embelia ribes	Myrsinaceae	False black pepper	Fruits/ Chloroform	Embelin and its derivatives 6-bromoembelin and vilangin	HFD/STZ diabetic rats	Embelin decreases blood glucose, ↓TC, TG and FFA, ↓hyperinsulinemia, insulin resistance, β-cell dysfunction	-Partial agonism on PPAR-γ and stimulating glucose uptake in adipose tissue -Normalizing the hepatic glucose metabolizingenzymes	Gandhi *et al*., 2013; Stalin *et al*., 2016
Enicostemmalittorale	Gentianaceae	Mamejava/ white head	--	Swertiamarin (a secoiridoid glycoside)	STZ-diabetic rats	Swertiamarin decreases(↓)blood glucose, ↓HbA1c, TC, TG, LDL, and ↑Hb, plasma insulin	-Antihyperlipidemic, -Antihyperglycemic -Cytoprotective	Dhanavathy 2015
Lactuca sativa	Asteraceae	Lettuce	Leaves/ DCM+ methanol+ water	Lactucaxanthin	STZ-diabetic rats	↓blood glucose	Intestinal α-amylase and α-glucosidase inhibitory activity	Gopal *et al*., 2017
Murraya koenigii	Rutaceae	Curry leaves	--	Koenidine (carbazole alkaloid)	db/db mice and STZ diabetic rats	koenidine ↓blood glucose ↑insulin sensitivity	-Enhancing GLUT4 translocation via AKT-dependent signaling pathway	Patel *et al*., 2016
Mimosa pudica	Mimosaceae	Sleepy plant/ Touch-me-not	Stem/ methanol	Myoinositol	HFD/STZ-type 2 diabetic rats	Myoinositol ↓blood glucose, ↑insulin sensitivity, ↓TC, TG and LDL-c	-Enhancing expression of PPARγ, GLUT4 and insulin receptor (IR) signaling molecules in the adipose tissue	Antony *et al*., 2017
Costus igneus	Costaceae	Spiral flag/ Insulin plant	Leaves/ methanol	Orally active insulin-like protein (ILP)	STZ-induced diabetic Swiss mice	ILP ↓blood glucose and improving oral glucose tolerance	Oral insulin mimetic via increasing cytoplasmic IRS-1 and GLUT-4 translocation	Hardikar *et al*., 2016; Joshi *et al*., 2013
Syzygium cumini	Myrtaceae	Jamun	Seed/ aqueous	Vitalboside A	HFD/STZ-type 2 diabetic rats	↓serum glucose, ↓hyperinsulinemia, dyslipidemia, TNF-α and insulin resistance ↓pancreatic oxidative stress parameters, ↑antioxidant enzyme activities and β-cell functions	-Modulating PPARγ and PPARα -Inhibiting PTP1B	Sharma *et al*., 2012; Thiyagarajan *et al*., 2016
Mitragynaparvifolia	Rubiacea	Kadamb/ Kaim	--	6,17-dihydro-17b-hydroxy isomitraphylline(a indole alkaloid)	Neonatal STZ type 2 diabetic rats	↓ plasma glucose, ↑glucose tolerance, ↑ GLP-1, IL-10 and β-cell proliferation	-Inhibiting DPP IV	Shukla and Srinivasan 2012

Abbreviations: STZ-streptozotocin; HFD-high fat diet; GLUT-glucose transporter; PPAR-peroxisome proliferator-activated receptor; PI3K-phosphatidylinositol 3-kinase; Akt/Rac1-protein kinase B/Ras-related C3 botulinum toxin substrate 1; SREBP-sterol regulatory element-binding transcription factor; HbA1c-glycosylated hemoglobin, NO-nitric oxide, TNF-a-tumor necrosis factor-a; LDL-low density lipoprotein; FFA-free fatty acids; AGE-advanced glycation end products; DCM-dichloromethane; Nrf2-nuclear factor erythroid 2-related factor 2; IRS-insulin receptor substrate,GLP-glucagon like peptide-1; PTP1B-protein tyrosine phosphatase-1B; DPP IV-dipeptidylpeptidase-IV;IL- interleukin

effects of fisetin, tetrahydroxyflavones (polyphenol) isolated from strawberries. Fisetin treatment significantly reduced blood glucose, lipids, HbA1c, nuclear factor (NF)-kB p65 unit (in pancreas) and interleukin (IL)-1β (plasma), serum nitric oxide (NO) along with an elevation in circulating insulin in STZ-induced diabetic rats. Fisetin improves glucose homeostasis through the inhibition of gluconeogenic enzymes in hepatic tissues (Prasath and Subramanian 2014, Prasath *et al*., 2014). The treatment also improved the antioxidant status in pancreas, plasma (Prasath *et al*., 2013) and also in liver (Prasath and Subramanian 2013) of diabetic rats indicating the antioxidant potential of fisetin.

Rosmarinic acid, a polyphenol, modulates the antioxidant status and protects pancreatic tissues from glucolipotoxicity-mediated oxidative stress in HFD/STZ diabetic rats (Govindaraj and Sorimuthu Pillai 2015). It significantly inhibited insulin resistance in skeletal muscle cells by enhancing mitochondrial biogenesis (Jayanthy *et al*., 2017). The effects of morin (2',3,4',5,7-pentahydroxyflavone), an potent natural antioxidant was evaluated in STZ-induced type 1 diabetic rats. Morin significantly reduced the blood glucose and improved the serum insulin levels along with preservation of pancreatic β-cell population. It caused reduction in glucose-6-phosphatase and fructose-1,6-bisphosphatase along with the increase in liver hexokinase and glucose-6-phosphate dehydrogenase activities (Vanitha *et al*., 2014). Similar antidiabetic potential was also demonstrated for zinc-morin, a metal flavonol complex in HFD/STZ type 2 diabetic rats (Sendrayaperumal *et al*., 2014). The antidiabetic effect of morin was partly due to its antioxidant effects against oxidative stress-induced DNA damage in pancreatic β-cells by activating the nuclear factor erythroid 2–related factor 2 (Nrf2) signaling pathway (Vanitha *et al*., 2017).

Embelin, a quinone derivative isolated from *Embelia ribes Burm* (Myrsinaceae) fruit was shown to regulate insulin resistance, alter β-cell dysfunction and modulate key markers involved in insulin sensitivity and glucose transport in type 2 diabetic rats. Embelin improved insulin sensitivity via partial agonistic action of PPAR-γ and glucose uptake through translocation and activation of GLUT4 in adipose tissue via PI3K/pAkt (Akt also known as protein kinase B) signalling pathway (Gandhi *et al*., 2013). The derivatives of embelin such as 6-bromoembelin and vilangin are also reported to be having similar anti-diabetic effects (Stalin *et al*., 2016). Swertiamarin, a secoiridoid glycoside, is reported to possess anti-hyperglycemic, anti-hyperlipidemic, cytoprotective, and immune reactivity and also have a broad spectrum potential of treating diabetes and other diabetic complications (Dhanavathy 2015).

Therapeutic potential of pterostilbene was also demonstrated against pancreatic β-cell apoptosis in diabetes via mediating through Nrf2 (Bhakkiyalakshmi *et al*., 2014, Sireesh *et al*., 2017). Lactucaxanthin, a potential anti-diabetic carotenoid from lettuce (*Lactuca sativa*) has been shown to inhibit α-amylase and α-glucosidase activity *in vitro* and in diabetic rats (Gopal *et al*., 2017). Patel and co-workers have identified and evaluated koenidine as one of the naturally occurring carbazolealkaloids from *Murraya koenigii* as a metabolically stable anti-diabetic compound in db/db type 2 diabetic mice. It showed a considerable reduction in the postprandial blood glucose profile with an improvement in insulin sensitivity (Patel *et al*., 2016). Myoinositol isolated from *Mimosa pudica* Linn. (Mimosaceae) stem methanol extract exhibited anti-diabetic effects which was attributed to enhanced level of PPAR-γ expression in the adipose tissue, upregulation of GLUT4 and insulin receptor signaling molecules (Antony *et al*., 2017).

The researchers from Pune have recently studied the antidiabetic property of insulin-like protein (ILP) purified from *Costus igneus* belonging to family Costaceae from Western ghats of India. It was demonstrated to be orally active and exhibiting hypoglycaemic effects comparable to insulin given intraperitoneally (i.p.) in STZ-induced diabetic mice. It acts through insulin signaling pathways (Hardikar *et al*., 2016, Joshi *et al*., 2013). *Syzygium cumini* ameliorates insulin resistance and β-cell dysfunction via modulating PPAR, dyslipidemia, oxidative stress, and tumor necrosis factor (TNF)-α in HFD/STZ-induced type 2 diabetic rats (Sharma *et al*., 2012). Bioactivity-based fractionation and purification of *Syzygium cumini* seeds led to the isolation and identification of bifunctional vitalboside A. It was reported to possess antidiabetic and anti-adipogenic activities via inhibition of protein tyrosine phosphatase-1B (PTP1B) and partial agonism to PPAR-γ *in silico*

and *in vitro* (Thiyagarajan *et al*., 2016).

Glucagon like peptide-1 (GLP-1) is known to stimulate insulin secretion, insulin biosynthesis and insulin gene transcription. Shukla and Srinivasan from DIPSAR, New Delhi have shown the inhibitory effects of 16,17-dihydro-17b-hydroxy isomitraphylline, a indole alkaloid isolated from *Mitragyna parvifolia* on DPPIV (an enzyme involved in GLP degradation). It exhibited antidiabetic effects which was associated withreduced plasma glucose concentration, increased glucose tolerance associated with increase in GLP-1, IL-10 levels and β-cell proliferation in neonatal STZ type 2 diabetic rats (Shukla and Srinivasan 2012).

In addition, some of the polyherbal formulations (PHF) likehydroalcoholic extracts of four plants namely *Salacia oblonga, Salacia roxbhurgii, Garcinia indica* and *Lagerstroemia parviflora* (Subhasree *et al*., 2015) and MAC-ST/001 (Yadav *et al*., 2013) were reported to reverse most blood and tissue changes caused by experimental diabetes. Antidiabetic potential of yet another polyherbal formulation, DB14201 has also been demonstrated in experimental models of diabetes (Gopalakrishna Pillai *et al*., 2017).

Antidiabetic Investigations on Synthetic Agents

Akarte and others have shown the antidiabetic effects of vildagliptin, a DPPIV inhibitor which was asscociated with increase in islets blood flow, insulin secretions and inhibition of the excessive NO and peroxynitrite ions formation resulting in protection of pancreatic β cells in diabetic rats (Akarte *et al*., 2012). They have also demonstrated the potent antidiabetic effects of a novel long acting potent, selective DPP-IV inhibitor, PKF-275-055 (1, 3, and 10mg/kg), an analog of vildagliptin in neonatal STZ induced type 2 diabetic rat model (Akarte *et al*., 2012). Another novel long-acting DPPIV inhibitor, ZYDPLA1 was also reported to be effective in preclinical models and has potential to become once-a-week therapy for treatment of type 2 diabetes (Jain *et al*., 2015). Dhanesha and co-workers have recently investigated the effect of combination of glucokinase activator (piragliatin) with GLP-1 receptor agonist exendin-4 in male db/db mice. The chronic treatment with exendin-4, has been shown to improve the antidiabetic efficacy and reverses hepatic steatosis in glucokinase activator treated db/db mice (Dhanesha *et al*., 2013).

The researchers from Hamdard University have recently synthesized and demonstrated the anti-diabetic activity of 2,4-thiazolidinedione based amide derivatives without significant hepatotoxicity *in vitro* and *in vivo* as compared to rosiglitazone and pioglitazone as reference drugs (Naim *et al*., 2017). Recently, the anti-diabetic, anti-oxidant and anti-inflammatory properties of 2-[(4-chlorobenzyl) amino]-4-methyl-1,3-thiazole-5-carboxylic acid (BAC) a new thiazole derivative were also demonstrated in a neonatal STZ diabetic rats (Paudel *et al*., 2017).

Jain and others from Zydus Cadila, Ahmedabad have demonstrated that saroglitazar, a novel dual PPARα/γ agonist exhibits lipid-lowering and insulin-sensitizing effects in different preclinical models of diabetes (Jain *et al*., 2015). Saroglitazar is the first indigenously developed molecule by any Indian pharmaceutical company approved for the treatment of type 2 diabetes by the Drug Controller General of India in June 2013 and is marketed under the trade name Lipaglyn. Saroglitazar has predominant PPAR-α and moderate PPAR-γ activity and its combined receptor activation resulted in significant anti-diabetic and antidyslipidemic effects. Saroglitazar has demonstrated no significant adverse effects like weight gain and edema that are commonly identified with similar molecules like the glitazone class of drugs. The better tolerability and absence of significant side effects could be due to the absence of thiazolidinedione (TZD) ring in saroglitazar molecule.Recent observational study has reported that the use of saroglitazar, for a period of 14 weeks, was associated with significant improvement in both glycaemic and lipid parameters among Indian patients with type 2 diabetes (Chatterjee, Majumder and Ray 2015, Ramakrishnan 2015).

The discovery of potent, selective and orally bioavailable triaryl-sulfonamide based PTP1B inhibitors for the treatment of type 2 diabetes was also reported *in vitro* and *in vivo* (Patel *et al*., 2012). Gowda and co-workers from Connexios Life Sciences Pvt Ltd, Bangalore showed the therapeutic potential of CNX-011-67, a highly selective, potent and orally bioavailable G-protein-coupled receptor 40 (GPR40) agonist in controlling diabetes and other metabolic parameters in Zucker diabetic fatty (ZDF) rats (Gowda *et al*., 2013). CNX-011-67 significantly

stimulated glucose metabolism, enhanced glucose responsiveness and increased insulin secretion in a non-genetic neonatal STZ type 2 diabetic models suggesting its potential for the treatment of type 2 diabetes (Sunil *et al*., 2014). Its beneficial effects in diabetes is also due to its inhibitory action on glucagon secretion from pancreatic islets *in vitro* (Verma *et al*., 2014) and anti-inflammatory effects against inflammation-induced β-cell apoptosis (Verma *et al*., 2014).

AMP activated protein kinase (AMPK) regulates the coordination of anabolic and catabolic processes. It was also reported that CNX-012-570, a direct AMPK activator provided strong glycemic and lipid control along with significant reduction in body weight in diet-induced obese mice and db/db mice models (Anil *et al*., 2014). The investigation from CDRI, Lucknow showed the discovery of biaryl-4-carbonitriles as antihyperglycemic agents that may act through AMP-activated protein kinase (AMPK)-p38 MAPK pathway (Goel *et al*., 2014). Treatment with these compounds improved glucose tolerance, fasting as well as postprandial blood glucose, serum total triglycerides, and increased high-density lipoprotein-cholesterol in different genetic and non-genetic animal models of diabetes.

In addition, antidiabetic effects of some vitamins, minerals and fatty acids have been reported. Vitamin D3 supplementation significantly increased insulin level by regulating altered inositol triphosphate (IP3) and glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor expression in the pancreatic islets of STZ-induced diabetic rat (Jayanarayanan *et al*., 2015). There is recently renewed interest over advantages of zinc supplementation. The scientists from CFTRI, Mysore have provided the scientific evidence that zinc supplementation alleviates severity of hyperglycemia and associated metabolic abnormalities like hypoinsulinemia, insulin resistance, and altered pancreatic morphology in STZ-induced diabetic rats (Barman and Srinivasan 2016). Chromium picolinate has been shown to attenuate hyperglycemia via modulating hepatic glucose metabolism and hyperglycemia-induced oxidative stress in STZ-induced diabetic rats (Sundaram *et al*., 2012, Sundaram *et al*., 2013). Khan and Jena have demonstrated the protective role of sodium butyrate, a short chain fatty acid, a histone deacetylases (HDAC) inhibitor on β-cell proliferation, function and glucose homeostasis through modulation of p38/ERK MAPK and apoptotic pathways in a juvenile STZ diabetic rat (Khan and Jena 2014). Sodium butyrate has also been shown to reduce insulin-resistance, fat accumulation and dyslipidemia and restores glucose homeostasis through HDAC inhibition and histone acetylation in HFD/STZ type-2 diabetic rat (Khan and Jena 2016). Valproic acid, yet another HDAC inhibitor have also yielded similar results as it improves β-cell proliferation, function as well as reduces β-cell apoptosis in juvenile diabetic rats (Khan and Jena 2016).

Diazepam has been shown to potentiate the antidiabetic, antistress and anxiolytic activities of metformin in type-2 diabetes with co-occurring stress in STZ diabetic animals. The combination significantly attenuated combined diabetes and stress-induced hyperglycemia, hypercorticosteronemia, anxiety-like behavior and insulin resistance compared to monotherapy suggesting that metformin in combination with diazepam may be a better therapeutic option in the management of type 2 diabetes with cooccurring stress condition (Garabadu and Krishnamurthy 2014). The co-administration of curcumin capsules with glyburide may be beneficial to the patients in better glycaemic control. The lipid lowering and antidiabetic properties of the curcumin was shown as a potential future drug molecule (Neerati *et al*., 2014).

Potential of Cell Based Therapy in Diabetes

Islet transplantation is a promising cell therapy for patients with diabetes, but it is currently limited by the reliance upon cadaveric donor tissue (Viswanathan and Sarang 2013). The researchers from Navi Mumbai have studied the human embryonic stem cell (ECS) differentiation into insulin secreting β-cells for diabetes. ESC, when differentiated into pancreatic β ILC (islet-like clusters), have enormous potential for the cell transplantation therapy for type 1 diabetes. The cells were also found to ameliorate hyperglycaemia in STZ-induced diabetic NOD/SCID (non-obese diabetic/severe combined immuno-deficiency) mouse up to 96 days of transplantation (Bose *et al*., 2012). The administration of mesenchymal stem cell (MSCs) in non-irradiated

diabetic Wistar rats reduced hyperglycaemia and was accompanied by increased islet-neogenesis, possibly through trans-differentiation/fusion (Bhansali *et al*., 2015). The investigators from PGIMER, Chandigarh have recently examined the efficacy and safety of autologous bone marrow-derived mesenchymal stem cells (ABM-MSCs) and mononuclear cells (ABM-MNCs) transplantation in type 2 diabetic patients and found that there was sustained reduction in insulin doses and improvement in insulin sensitivity with MSCs and increase in C-peptide response with MNCs (Bhansali *et al*., 2017). Dave and other colleagues have reported that combined therapy of insulin-producing cells and haematopoietic stem cells offers better diabetic control than with only haematopoietic stem cells' infusion for patients with insulin-dependent diabetes (Dave *et al*., 2014, Dave *et al*., 2015).

Pharmacological Investigations in the Area of Diabetic Complications

Long term diabetes leads to various microvascular (e.g. neuropathy, nephropathy) and macrovascular (corondary heart disease, peripheral vascular disease, stroke) complications associated with structural damage and dysfunctions of various organs that account for most of the morbidity and mortality associated with the disease. We have here in focussed on some of the main complications like diabetes-induced neuropathy, nephropathy and cardiac dysfunctions where mainly Indian scientists are working.

Diabetic Neuropathy : Diabetic neuropathies are nerve damaging disorders associated with diabetes mellitus. Diabetic rats demonstrated the mechanical allodynia and thermal hyperalgesia with reduced nerve perfusion and conduction velocity as compared to control. MDL 28170, calpain inhibitor was reported to confer electrophysiological, nociceptive and biochemical improvement against diabetic neuropathic pain (Kharatmal *et al*., 2015). It showed the beneficial effects via modulation of tetrodotoxin-resistant sodium channels (TTX-R $Na^{(+)}$) kinetics and reduction of oxidative stress and neuro-inflammation.The effect of rufinamide,an antiepileptic drug was also reported against diabetic neuropathy as it improves functional and behavioral deficits via blockade of TTX-R $Na^{(+)}$ channels (Kharatmal *et al*., 2015). The researchers from Hyderabad showed that the treatment with A769662, AMPK activator significantly improved mechanical/thermal hyperalgesia threshold and neurological deficits in STZ rat model of diabetic neuropathy. AMPK activation significantly abolished the NF-κB-mediated neuroinflammation, stimulated peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)-directed mitochondrial biogenesis and autophagy induction (Yerra and Kumar 2017). Fisetin, a phytoflavonoid confers neuroprotection against diabetic neuropathy in rats by modulating Nrf2 and NF-kB pathways (Sandireddy *et al*., 2016). The protective effect of EGb 761, a standardized extract of *Ginkgo biloba* was demonstrated on STZ-induced neuropathic pain in rats by inhibiting oxidative and nitrosative stress (Taliyan and Sharma 2012).

Diabetic Nephropathy : Diabetic nephropathy is a common microvascular complication of diabetes and an important cause of chronic kidney disease (Sharma *et al*., 2017). The researchers from IITR (CSIR), Lucknow have recently studied the effect of mixture of flavonoids (baicalin and chrysin) in STZ-induced diabetes and found that it is protective against diabetic tubular injury by modulating receptor of advanced glycation end products (RAGE), oxidative stress and inflammation (Singh *et al*., 2017).

The investigators from Guwahati showed that the treatment with methanolic leaf extract of *Paederia foetida* and some plant derived active principles like diosmin (flavones) and piceatannol (stilbenoid) provided remarkable renoprotection in diabetes by abrogating oxidative stress, NF-kB activation and neuro-inflammation in rat model of diabetic nephropathy (Ahmed *et al*., 2016, Borgohain *et al*., 2017, Borgohain *et al*., 2017). The protective effect of diosgenin, a steroidal saponin, was also demonstrated in diabetes-induced early kidney injury (Kanchan *et al*., 2016). Ellagic acid, a polyphenol present abundantly in fruits and vegetable significantly inhibited AGE accumulation in the diabetic rat kidney and ameliorated AGE-mediated pathogenesis of diabetic nephropathy (Raghu *et al*., 2016). Gallic acid is able to ameliorate renal functions by inhibiting the activation of p38 MAPK in type 2 diabetic rats (Ahad *et al*., 2015). Recently, taraxerol, a pentacyclic triterpenoid, from *Abroma augusta* leaves has been reported to attenuate diabetic nephropathy in HFD/

STZ type 2 diabetic rats (Khanra *et al*., 2017). Sodium valproate was reported to ameliorate diabetes-induced fibrosis and renal damage by the inhibition of HDAC in STZ diabetic rats (Khan *et al*., 2015).

Diabetes-associated Cardiovascular Dysfunctions : The role of protease-activated receptor (PAR) in diabetic cardiomyopathy has recently been evaluated. Treatment with argatroban, a direct thrombin inhibitor attenuates cardiac dysfunctions by reducing fibrosis, inflammation, apoptosis, and PAR expression in heart of HFD/STZ type 2 diabetic rats (Bulani and Sharma 2017). The oral administration of garlic in STZ induced diabetic rats produced cardioprotective effects through activating *sirtuin* (SIRT)3-MnSOD pathway and ameliorating oxidative stress and mitochondrial dysfunction (Sultana *et al*., 2016). The researchers from IICT, Hyderabad also showed that administration of garlic, resveratrol, and metformin in diabetic rat decreased pancreatic β-cell damage and hepatic injury along with restoration of many of the altered metabolic and oxidative stress parameters (Kaur *et al*., 2016). Resveratrol ameliorates cardiac oxidative stress in diabetes through deacetylation of NFkB-p65 and histone 3 (Bagul *et al*., 2015).

Levosimendan, a calcium sensitizer significanlty reduced myocardial damage and improved cardiodysfunctions in STZ-induced diabetic cardiomyopathy via sarco/endoplasmic reticulum Ca^{2+}-ATPase/*sodium-calcium* exchanger (SER CA2a/NCX1) pathway (Akhtar *et al*., 2016). Chrysin, a PPAR-γ agonist improved myocardial injury in diabetic rats through inhibiting AGE-RAGE mediated oxidative stress and inflammation (Rani *et al*., 2016). Genistein ameliorated cardiac inflammation and oxidative stress in STZ-induced diabetic cardiomyopathy in rats (Gupta *et al*., 2015). Esculetin alone and in combination with telmisartan was reported to exert beneficial effects in attenuating insulin resistance, cardiac fibrosis damage and vascular hyper responsiveness in type 2 diabetes rats (Kadakol *et al*., 2015, Kadakol *et al*., 2015). Diabetes also increases the risk of stroke and augments brain damage after ischemia/reperfusion (I/R).3-bromo-7-nitroindazole, selective neuronal nitric oxide synthase (nNOS) inhibitor ameliorated brain I/R injury after middle cerebral artery occlusion in HFD/STZ diabetic rats via inhibition of endoplasmic reticulum stress and apoptosis (Srinivasan and Sharma 2012).

Diabetic Encephalopathy : Apartfrom its deleterious effects on peripheral organs, long term diabetes also leads to central nervous system complications like diabetic encephalopathy and diabetes-associated cognitive decline. The researchers from NIPER, S.A.S. Nagar have reported that NF-κB inhibition using pharmacological inhibitors such as BAY 11-7082 (BAY) and parthenolide ameliorated cognitive deficits in experimental HFD/STZ type 2 diabetic rat models through modulating cAMP response element binding (CREB), neuroinflammation and glutamate/GABA neurotransmitters pathway (Datusalia and Sharma 2016, Khare *et al*., 2017). In addition, derivatives of spices like cinnamaldehyde (a principal component of cinnamon oil) and eugenol (main active principle of cloves) have also been reported to be beneficial in ameliorating neuroinflammation, neurotransmitters homeostasis and oxidative stress in diabetic rat brains (Jawale *et al*., 2016, Prasad *et al*., 2016). The researchers from Pune have recently elucidated dual mode of action of eugenol in combating diabetes as it lowers blood glucose by inhibiting α-glucosidase and prevents AGE formation by binding to ε-amine group on lysine, protecting it from glycation (Singh *et al*., 2016). Apart from its neuroprotective effects, genistein, an isoflavone phytoestrogen has been shown to ameliorate diabetes associated cognitive decline due to its modulatory effects on neuroinflammation, acetylcholinesterase activity and oxidative stress in diabetic mice (Rajput and Sarkar 2017). Researchers from Varanasi have recently provided evidences towards molecular basis of the memory enhancing and antidiabetic role of CDRI-08, a well characterized fraction of *Bacopa monnieri* extract in STZ-induced diabetic mice. It acts via ameliorating alterations in hippocampal oxidative stress and expression of AMPA receptor GluR2 subunit (Pandey *et al*., 2015).

Potential of Nanoformulations for the Treatment of Diabetes : Recently, different nano formulations of herbal and synthetic compounds have been developed mainly aiming at improving their bioavailability and efficacy as deemed to be effective treatment approach for the control of diabetes and diabetic complications.

Oral delivery of insulin may make treatment more

convenient and significantly improve the quality of life of diabetes patients who routinely receive insulin by the subcutaneous route. The oral delivery of insulin remains a challenging task as insulin gets degraded by enzymes in gastrointestinal tract resulting in lack of absorption. Jain and co-workers have demonstrated the novel approach for enhancing the oral absorption and hypoglycemic activity of insulin via encapsulation in folate-(FA) coupled polyethyleneglycol (PEG)ylated polylactide-co-glycolide (PLGA) nanoparticles (FA-PEG-PLGA NPs). This oral nanoformulation of insulin (50 U/kg) exhibited a twofold increase in the oral bioavailability (double hypoglycemia) without any hypoglycemic shock as compared to subcutaneously administered standard insulin solution in STZ diabetic rats (Jain *et al*., 2012). The improved stability and antidiabetic potential of insulin containing folic acid functionalized polymer stabilized multilayered liposomes following oral administration was also reported *in vivo* (Agrawal *et al*., 2014). Sharma and others have explored the surface engineered and ligand anchored nanobioconjugate as an effective therapeutic approach (by incorporating insulin in concanavalin A anchored PEGylated nanoconstructs) for the oral delivery of insulin in experimental diabetic rats (Sharma *et al*., 2015).

In addition, some of the nanoformulations of plant based active principles like quercetin (polyphenol), glycyrrhizin (active constituent of the roots and rhizomes of *Glycyrrhiza glabra*) were also reported to be more efficacious in diabetic rats (Chitkara *et al*., 2012, Rani *et al*., 2017). Self nano emulsifying drug delivery system (SNEDDS) curcumin formulation has been characterized that has prolonged plasma exposure and bioavailability and further enhanced efficacy as compared to plain curcumin in STZ-induced diabetic neuropathy *in vivo* (Joshi *et al*., 2013). The protective effect of selenium nanoparticles (SeNPs) against the progression of type 1 diabetic nephropathy was reported via quenching oxidative stress as well as by activating cytoprotective protein heat shock protein (HSP70) and longevity protein SIRT1 (Kumar *et al*., 2014).

Reproductive Endocrine Pharmacology

Male Reproduction

Studies on Male Contraceptive and Antifertility Effects of Herbal Drugs: The contraceptive efficacy of *Cuminum cyminum* isolated fractions was investigated in male albino rats. The chronic administration of it showed the marked decrease in the spermateogenesis associated with decreased counts in round spermatids, preleptotene spermatocytes, secondary spermatocytes and decline in testosterone levels (Saxena *et al*., 2015).

The ethanolic extract of *Pistia stratiotes* and its active phytoconstituent, saponin were shown as potential male contraceptive. It showed significant anti-spermatogenic activity as evident from reduction in the weight of reproductive organs, sperm count, sperm viability and serum testosterone (Singh *et al*., 2014).

The stem bark methanol extract of *Thevetia peruviana* (Apocynaceae) exhibited antifertility potential in male albino rats and its effects was associated with the reduction in the weight of reproductive organs, decline in different spermatogenic elements, mature Leydig cells and also reduction in sperm density and motility (Gupta *et al*., 2011). The antifertility effects of aqueous extracts of various plants such as *Dalbergia sissoo, Coccinia indica* and *Mimusops elengi* were demonstrated that caused reversible suppression of spermatogenesis and fertility without detectable toxic effects in Parkes strain male mice (Verma and Singh 2014, Verma and Singh 2017). The administration of ethanolic leaf extract of *Citrus limon* (500 and 1,000 mg/kg/day) for 35 days caused suppression of spermatogenesis which may be due to germ cell apoptosis and decreased production of testosterone in Parkes mice (Singh and Singh 2016). The antifertility effects of methanolic bark extract of *Aegle marmelos* (L.) was also demonstrated in male Wistar rats (Agrawal *et al*., 2012). Recent investigations have provided scientific rationale of piperine, an active constituent present in the Piper species of its use for male contraceptive and antifertility effects. Piperine interacts with androgen receptor and androgen binding protein *in vitro*. It exhibits reversible anti-spermatogenic effect of piperine on epididymis and seminal vesicles of rat (Chinta and Periyasamy 2016, Chinta *et al*., 2015).

Studies on Male Aphrodiasic, Fertility and Chemoprotective Effects of Herbal Drugs : The root extracts of *Salvia haematodes* (5, 50 and 300 mg/kg, orally for 30 days) and *Asparagus*

adscendens (100, 200, and 300 mg/kg orally for 30 days) significantly increased anabolic, reproductive function and sexual behavioral performance in male rats in dose dependent manner, providing the scientific rationale for their traditional use as an aphrodisiac for sexual disorders (Bansode *et al*., 2014, Bansode *et al*., 2015).

The aphrodisiac and spermatogenic potential of alkaloid enriched fraction of *Hygrophila spinosa T. ander* were also shown in rats. Its treatment led to the increased serum testosterone level resulting in higher number of spermatozoa in testicular lumen as well as increased libido (Vyas and Raval 2016). The alkylamide-rich ethanol solution extract *Anacyclus pyrethrum* showed the aphrodisiac, androgenic and spermatogenic potential which may improve male fertility by enhancing spermatogenesis (Sharma *et al*., 2013). Interestingly, the biphasic effect of aqueous extract of *Syzygium aromaticum* flower buds on reproductive physiology of male mice has been demonstrated. Lower dose of *S. aromaticum* (15 mg/kg) is androgenic in nature and increases the serum level of testosterone and sperm function and morphology while higher doses (30 mg and 60 mg) adversely affect these parameters (Mishra and Singh 2016). The oral administration of herbo-mineral ayurvedic formulation Afrodet Plus(®) resulted in significant increase in daily sperm production in the testis along with increase in epididymal sperm count and progressive motility without producing any treatment-related adverse effects in male rats (Dhumal *et al*., 2013). *Trigonella foenum-graecum* increased testosterone levels up to 46% in 90% of the study population and sperm counts and sperm morphology improved in 85.4% and 14.6% of the study population, respectively (Maheshwari *et al*., 2017).

The protective effects of *Commelina benghalensis* L. and *Cissusquadran gularis* L. were demonstrated against quinalphos-induced male reproductive toxicity in mice. Quinalphos, an organothiophosphate pesticide causes the disruption of endocrine system by inducing oxidative stress, reduction in level of testicular cholesterol leading to decreased testosterone levels and viable sperm count. Treatments significantly reduced the oxidative stress and prevented inhibition of steroidogenesis thereby preventing male infertility (Kokilavani *et al*., 2014). Sharma and co-workers demonstrated that the treatment with ethanolic extract of *Tribulus terrestris* and resveratrol elicit protective effects against cypermethrin-induced reproductive toxicity in male Wistar rats. They ameliorated testicular damage by reducing oxidative stress and by enhancing the level of sex hormones (Sharma *et al*., 2013, Sharma *et al*., 2014). The investigators from IVRI, Izatnagar investigated the ameliorative effect of curcumin on imidacloprid-induced male reproductive toxicity in Wistar rats. Imidacloprid, a systemic insecticide treatment resulted in significant decrease in total epididymal sperm count, sperm motility, live sperm count, and increase in sperm abnormalities along with decreased testosterone concentration in testis and plasma which was restored by co-administration with curcumin (Lonare *et al*., 2016). The experimental findings established the potential of *Eugenia jambolana* extract as a therapeutically better antioxidant and protective against the adverse effects of anticancer drug cisplatin on testicular function as compared to N-acetylcystein-treated rats (Anand *et al*., 2015). Significant alterations in serum luteinizing hormone (LH), follicular stimulating hormone (FSH) and testosterone were observed in cisplatin group which were effectively reversed by *E. jambolana* extract supplementation. Singh and co-workers have recently reported that IN0523 (Urs-12-ene-3α,24β-diol) a plant based derivative of boswellic acid protects against cisplatin-induced urogenital toxicity via inhibiting the oxidative stress/redox status imbalance (Singh *et al*., 2017).

Investigators have also studied the protective effects of various plants against diabetes-induced reproductive organs' damage and dysfunctions. *Mallotusrox burghianus* methanolic extract protects against diabetes-induced oxidative damage of testis. The main compounds of this plant like phenols (bergenin) and terpenes (betulinic acid) and their antioxidant and antidiabetic activities might be responsible for its protection of testes in alloxan-induced diabetic rat model (Roy *et al*., 2015). Ethanolic seed extract of *Mucuna pruriens* (Linn.) improved male sexual behavior, libido and potency, sperm parameters and hormone (FSH, LH and testosterone) levels in STZ-induced diabetic male rats (Suresh and Prakash 2012). The corrective role of ethyl acetate fraction of hydro-methanolic extract of seed of *Eugenia jambolana* on testicular impairment was shown in STZ-induced diabetic male rat (Ghosh

et al., 2014). The protective effects of *Eugenia jambolana* is due to its antiapoptotic efficacy on testicular germ cell associated with significant recovery in the glycated haemoglobin, serum testosterone, sperm viability, hypo-osmotic swelling and nuclear chromatin decondensation (Ghosh *et al*., 2016). *Caralluma fimbriata* (200mg/kg, for 90 days) prevented all abnormalities of reproductive system induced by the high-fat diet (Gujjala *et al*., 2016). Fluoride exposure is reported to aggravate the testicular damage and sperm quality in diabetic mice. The administration of ginseng and banaba extracts alone and in combination reversed fluoride-induced toxicity on sperm density, motility, viability and morphology and the testicular biochemical parameters (Sm and Mahaboob Basha 2017).

Studies on Effects of Synthetic Drugs on Male Reproduction : The reversible dose-dependent adverse effects of antibiotic salinomycin on male reproductive system of mice were reported. Salinomycin decreased motility and spermatozoa count with increased number of abnormal spermatozoa leading to infertility. The testosterone and LH levels were decreased in testis but increased in serum at higher doses (Ojo *et al*., 2013). The combination of ampicillin and sulphasalazine has been shown to produce synergistic and reversible anti-fertility effects in male rats. A decrease in the parameters related to fertility of males such as sperm count, sperm motility, fertility ratio, serum testosterone level, glycogen and protein content in sexual organs was observed (Gupta *et al*., 2013). High dose of metronidazole (500 mg/kg body weight/day for 28 days) induced reversible deleterious effects on the male reproduction and fertility associated with significant reductions in the weights of the testis and epididymis but without significant changes in serum testosterone levels in male mice (Kumari and Singh 2013). Enrofloxacin treatment significantly decreased testicular weight, total sperm count and viability associated with dose dependent decrease in testosterone level, testicular antioxidant enzymes and increase of lipid peroxidation. Selenium supplementation partially restored oxidative stress and sperm damage without affecting the plasma concentrations of enrofloxacin (Rungsung *et al*., 2016).

Recently, the authors have demonstrated the protective effects of zinc against lead-induced testicular and epididymal toxicity in Wistar rats. Zinc significantly restored the spermatogenesis and steroidogenesis (Anjum *et al*., 2017). The protective role of zinc supplementation was shown against diabetes-induced testicular and epididymal damages in rat via improving the levels of Nrf2, SOD1, and glutathione peroxidase 5 (GPX5) (Maremanda *et al*., 2016). Zinc also protects against cyclophosphamide-induced testicular damage and restores testosterone levels in rat via modulating metallothionein, tesmin and Nrf2 associated antioxidant pathways (Maremanda *et al*., 2014). The protective effects of troxerutin (100 mg/kg) against nickel-induced testicular toxicity was also demonstrated in male Wistar rats via inhibiting testicular oxidative stress (Elangovan *et al*., 2016).

The supplementation of testosterone mitigated lead-induced suppressed reproduction in male rats. Testosterone treatment significantly increased epididymal sperm count, motile spermatozoa, viable spermatozoa and also the activity levels of testicular 3β- and 17β-hydroxysteroid dehydrogenases (HSD) as compared to lead-exposed group (Anjum and Reddy 2014). The significance of estrogen in testicular activities and to find out the mechanism by which it regulates spermatogenesis in mice has been studied. The tamoxifen, a selective estrogen receptor inhibited the estrogenic effect which is responsible for the increased expression of NOS and NO formation in testicular cells leading to germ cell apoptosis and impaired spermatogenesis (Verma and Krishna 2017). Letrozole, a selective aromatase inhibitor/estradiol synthesis inhibitor suppressed spermatogenesis by reducing insulin sensitivity and glucose transport in the testis, but significantly increased testosterone level by promoting gonadotrophin release due to decreased estradiol (Verma and Krishna 2017). The presence of β-endorphin, a naturally occurring opioid peptide, and its receptor (μ-opioid receptor, μOR) has been reported in rat testes. Mukherjee and Haldar demonstrated the functional role and significance of photoperiodic regulation of μOR in testicular steroidogenesis using naltrexone, a μOR antagonist. Its administration significantly increased the steroidogenic markers and plasma testosterone concentration in goldern Syrian hamster (Mukherjee and Haldar 2015).

Prostate Gland : The protective effect of bark of different species of Prunus was evaluated against testosterone-induced benign prostatic hyperplasia (BPH). *P. domestica* showed the most encouraging effect on prostate associated with remarkable anti-inflammatory and antioxidant activities. It restored the serum and prostate testosterone level in a similar manner as by finasteride suggesting its action through inhibition of 5α-reductase enzyme (Jena *et al*., 2016). *Boerhaavia diffusa* (100 mg/kg, for 28 days) showed significant inhibition of prostate growth, improved symptoms of prostatic hyperplasia but did not change the serum testosterone level (Vyas *et al*., 2013). Dietary zinc deficiency (2-4 weeks) affected the prostate structure and enhanced NO as well as acid phosphatase activities and impaired HSD activities indicating its prominent role in maintaining the prostate integrity (Joshi *et al*., 2014).

Female Reproductive System

Pharmacological Studies of Herbal Drugs on Female Reproduction : Abortifacient potential of methanolic extract of *Anthocephalus cadamba* stem bark was demonstrated in mice. The administration of extract in pregnant mice reduced the number of live fetus, weight and survival ratio of the fetus, number of corpora lutea (CL), progesterone, estradiol and LH whereas the number of dead fetus, number of mice that aborted, percentage vaginal opening and post-implantation loss increased significantly (Shaikh *et al*., 2015). Methanolic extract of *Thevetia peruviana* leaves containing quercetin 0.0326% and kaempferol 0.138% exhibited a significant antifertility potential by decreasing the progesterone level (Samanta *et al*., 2016). The n-butanol fraction of the ethanolic extract of tubers of *Pueraria tuberosa* exhibited significant antifertility activity in various laboratory animals. The researchers from IICB, Kolkata have recently identified puerarin as the major constituent of *P. tuberosa* and further showed that the oral administration of puerarin post-coitus resulted in complete implantation failure. It is reported as selectiveoestrogen receptor modulator that adversely modulates the endometrial expression of oestrogen receptor-α and β resulting in anti-implantation (Saha *et al*., 2012). This group recently developed poly lactic-co-glycolic acid-encapsulated nano-puerarin and further studied the molecular pathway underlying its anti-implantation effects (Saraswat *et al*., 2016). The administration of ethanol extract of *P. oleracea* L. (Portulacea) blocked ovulation by inhibiting cyclooxygenase activity, altered estrous cycle with a prolonged diestrous, increased the uterine muscle weight and ovary weight suggesting its anti-ovulation effect in rats (Londonkar and Nayaka 2013).

The methanolic extract of *Artemisia vulgaris* leaves was found to have strong anti-implantation activity and estrogenic activity (Shaik *et al*., 2014). Methanolic extract of *Drynaria quercifolia* has shown higher efficacy for both abortifacient and anti-implantation performance and also effected hormone release level (Das *et al*., 2014). The hydroalcoholic leaves extract of *Michelia champaca* administered orally at dose levels (100 and 200 mg/kg body weight) exhibited the antifertility activity as evidenced by significant anti-implantation activityin female Wistar rats and estrogenic/anti-estrogenic activity in ovariectomized female rats (Taprial *et al*., 2013).

The efficacy of novel fenugreek seed extract (*Trigonellafoenum-graecum*, Furocyst) was studied on premenopausal women diagnosed with polycystic ovarian syndrome (PCOS). It significantly ameliorated the symptoms of PCOS associated with decrease in both ovarian volume and the number of ovarian cysts, significant increases in LH and FSH levels (Swaroop *et al*., 2015). A study demonstrated that oral administration of high-concentration ashwagandha root extract (HCARE) supplementation may improve sexual function in healthy women (Dongre *et al*., 2015). The use of dydrogesterone in women with recurrent abortions has been shown to improve pregnancy outcome, such as a reduction in abortions and improved gestational age and baby weight at delivery which were not,however, modulated by T-helper(Th)1 and Th2 cytokine production (Kumar *et al*., 2014).

Pharmacological Studies of Synthetic Agents on Female Reproduction : PCOS is a major cause of anovulatory infertility in women in their reproductive age. PCO-mice showed reduced ovarian LH receptor expression, circulating estradiol and progesterone level which was restored by GnRH-agonist resulting in ovulation in PCO-mice and showed more beneficial effect over the use of GnRH-antagonist (Singh *et al*., 2016). Pandey and co-workers have observed that the administration of buserelin acetate or hCG on day

12 post-ovulation leads to accessory corpus luteum (CL) formation, improves luteal profile and consequently increases conception rate in buffaloes (Pandey *et al*., 2013). Oxytocin injections are illegally used for milk let down in cattle thereby causing oral exposure to human population. It has been shown that oral exposure to hormone oxytocin in female Wistar pups lead to anomalies in ovary associated with increased ovarian weight, γ globulin, total number of follicles, and number of CLs indicating higher ovulation (Mishra *et al*., 2013). The treatment with resistin to the vespertilionid bat, *Scotophilus heathi* caused increase in and rostenedione due to stimulatory effects on 3β-HSD, but decrease in estradiol level due to inhibitory effect on aromatase suggesting that obese women through increased resistin synthesis may cause development of non-ovulatory antral follicles through insulin receptor signaling cascade (Singh *et al*., 2014).

A controlled release delivery system helps to overcome the problem of short life of the leutinizing hormone releasing hormone (LHRH) in blood and avoids use of multiple injections to enhance reproductive efficacy. Chitosan nanoconjugates had a 13 per cent higher and chitosan gold preparation had a 9 percent higher fertilization rate as compared to plain LHRH in female fish (Rather *et al*., 2013). The recent study reported that the delivery of chitosan nanoconjugated salmon LHRH increased the expression level of Sox9 transcripts (a primary factor in regulation of gonadal development) in gonads and steroid hormonal levels in blood of male and female walking catfish (Bhat *et al*., 2016). A recent clinical report suggests that both the combined hormonal vaginal ring (that releases 15 µg of *ethinylestradiol* and 120 µg of the 25 etonogestrel per day) with combined hormonal pills (containing 30 μgm of EE and 150 μgm of levonorgestrel) are very effective short-term treatments for heavy menstrual bleeding in reproductive age group (Dahiya *et al*., 2016).

The researchers from NII, New Delhi reported the contraceptive efficacy of *Escherichia coli*-expressed recombinant porcine zona pellucida proteins. Immunization of female mice with these recombinant proteins elicited high antibody titers as well as T-cell responses. Immune sera recognized mouse oocyte also inhibited *in vitro* fertilization. Immunized mice showed significant decrease in fertility indicating the usefulness of contraceptive vaccine (Gupta *et al*., 2013). In addition, the second generation anti-epileptic drugs like topiramate and gabapentin adversely affected the reproductive functions in young non-epileptic female rats as ascertained by disturbed hormonal levels and estrous cyclicity as well as alterations in GABAergic system and GnRH neuronal-glial plasticity (Kumar and Kaur 2014).

Pharmacological Studies on Thyroid and Parathyroid Glands

The researchers from JIPMER, Pondicherry have shown that the extract of *Costus pictus* (insulin plant) has therapeutic potential in restoring thyroid hormone levels and in preventing the biochemical complications due to thyroid hormone insufficiency in animal model of experimental hypothyroidism (Ashwini *et al*., 2017). Betulinic acid, a naturally occurring pentacyclic triterpenoid is reported to possess therapeutic potential in chemically induced hypothyroidism model in rats (Afzal *et al*., 2014).

The anti-thyroid effects of various natural compounds such as rutin, naringin and hesperidin in L-thyroxine (T4)-induced hyperthyroidism have been demonstrated in rats. L-T4 administration significantly enhanced the serum concentrations of thyroxine and triiodothyronine, hepatic 5'-deiodinase I (5'DI) activity, serum lactate dehydrogenase (LDH) and serum glutamic-pyruvic transaminase (SGPT) along with an increase in malondialdehyde (MDA) content in hepatic tissues and depletion of cellular antioxidants. However, on administration of these test flavonoids, these effects were more or less normalized possibly via mediating through their antioxidant actions (Panda and Kar 2014). A gitogenin-type steroidal saponin and 5,7,4'-trihydroxy-6,3'dimethoxy-flavone5-O-α-l-rhamnopyranoside isolated from the leaves of *Malvastrum coromandelianum* and *Annona squamosa* leaves, respectively are reported to have similar anti-thyroid and antioxidant potential as compared to standard antithyroid drug, propylthiouracil in rat model of thyrotoxicosis (Panda and Kar 2015, Panda and Kar 2016).

It is reported that catechin, a tea flavonoid has potent antithyroid activity as evidenced from decreasedactivities of thyroid peroxidase and thyroidal 5'DI, serum T3 and T4 levels coupled with significant

elevation of serum thyroid stimulating hormone (TSH) in rats (Chandra and De 2013). Radioactive iodine (I) (RAI) is used widely for the treatment of hyperthyroidism either as a first-line treatment or following relapse after antithyroid drug treatment. The recent pilot study suggested that a short course of lithium is safe and could be beneficial for hyperthyroid patients considered for RAI therapy as it increased the RAI retention in thyroid, and thus had the potential to increase the effect of RAI therapy (Chouhan *et al*., 2016).

Teriparatide (parathyroid hormone 1-34 [PTH (1-34]), an amide of PTH), is widely available for the use in osteoporosis but is also reported to be effective in the treatment of hypoparathyroidism (Upreti *et al*., 2017). The oral human parathyroid hormone 1-34 (PTH 1-34) loaded pegylated chitosan and further biocompatible and mucoadhesive thiolated chitosan (TCS) nanoformulation as an alternative patient compliant route in treating osteoporosis have been evaluated both *in vitro* and *in vivo* (Narayanan *et al*., 2013, Narayanan *et al*., 2014). A novel flavonoid C-glucoside isolated from *Ulmus wallichiana* protects against glucocorticoid -induced bone loss by promoting osteoblast survival through p53 inhibition and activation of AKT pathways as compared to human PTH (Khan *et al*., 2013).

Pharmacological Studies on Adrenal Gland

The administration of *Andrographis paniculata* extract and pure andrographolide exhibited protective effects against chronic stress-triggered pathologies in rats. The treatment significantly ameliorated footshock stress-induced alterations in body weight, gastric ulcer, adrenal and spleen weights, plasma cortisol levels, and cytokines in blood and brain (Thakur *et al*., 2014). The aqueous extract of *Cinnamomum tamala Nees* and *Eberm* possesses significant anxiolytic, antidepressant, and anti-stress effects by normalizing the plasma levels of corticosterone, glucose, cholesterol, and triglyceride levels in rats (Upadhyay *et al*., 2016). The gastro-protective and anti-stress efficacies of monomethyl fumarate and a *fumaria indica* extract were demonstrated in chronically stressed rats and shown to act as regulators or modulators of monoamine, corticosterone, and cytokine homeostasis (Shakya *et al*., 2016). The researchers from IIT (BHU), Lucknow reported that *Asparagus racemosus* attenuated anxiety-like behavior on different paradigms (open-field test, hole-board, and elevated plus maze tests) in rats via enhancing amygdalar serotonin and norepinephrine levels (Garabadu and Krishnamurthy 2014).

It is reported that anovulation that results from psychological stress is due to increase in cortisol level (Kala and Nivsarkar 2016). It is reported that catecholamines can also modulate ovarian steroidogenic activity in catfish, *Heteropneustes fossilis* (Joy *et al*., 2014). Catecholamines stress hormones like epinephrine and norepinephrine regulate energy homeostasis by regulating iron homeostasis in cells (Tapryal *et al*., 2015). Excess aldosterone is reported to result in decreased glucose uptake and oxidation in skeletal muscle in adult male rat, thus increasing the incidence of type2 diabetes (Selvaraj *et al*., 2013). Vitamin C is reported to inhibit etomidate-induced adrenal suppression in patients undergoing cardiac surgery (Das *et al*., 2016). The potential role of ondansetron (a 5HT3 receptor antagonist) was shown in reversing chronic unpredictable stress-induced depressive behavior, which is possibly mediated by its modulating effects on the HPA-axis and serotonergic system in mice (Gupta *et al*., 2014).

Pharmacological Studies on Pineal Gland and Role of Melatonin

Melatonin, also known as *N*-acetyl-5-methoxy tryptamine, is a hormone that is produced by the pineal gland and regulates sleep and wakefulness. In addition to its role in chronobiology, multiple pharmacological effects of melatonin have been reported in mammals. The protective effect of melatonin against metabolic and reproductive disturbances in PCOS was demonstrated in rats. Melatonin (2 mg/kg) treatment resulted in significant decrease in serum total testosterone and fasting insulin levels (Pai and Majumdar, 2014). Supplementation of melatonin in rat reduced ovariectomy-induced oxidative stress. Melatonin is reported as more potent and safe alternative to estrogen replacement therapy in alleviating postmenopausal increases in oxidative stress and hepatic and renal dysfunction (Baxi *et al*., 2013). Melatonin pretreatment in carp ameliorates ovaprim actions on the process of oocyte maturation by the enhancing the formation of maturation-

promoting factor (MPF) and alleviates oxidative stress in pre-ovulatory follicles by stimulating different antioxidants (Moniruzzaman *et al*., 2016). The protective effect of melatonin was reported against dexamethasone-induced testicular toxicity and germ cell apoptosis and immunosuppression in golden Syrian hamsters and this contributes to enhanced survival of male hamster (Mukherjee *et al*., 2015, Vishwas *et al*., 2013).

Melatonin has been shown to have neuroprotective effects in some experimental models of neurodegenerative and neurological disorders like Huntington's disease, cerebral ischemia, peripheral neuropathy and epilepsy (Areti *et al*., 2017, Bhattacharya *et al*., 2014, Chakraborty *et al*., 2014, Rao *et al*., 2016, Vishnoi *et al*., 2016, Waseem *et al*., 2017). Agomelatine, a synthetic melatonin protects against pentylenetetrazole (PTZ)-induced kindling in mice and kindling-associated oxidative stress, depression, and impairment of spatial memory (Azim *et al*., 2017). Recently, the protective role of nanocapsulated melatonin was studied in cerebral I/R of aged brain in rats. It exhibited significantly higher potential to rescue neuronal cells and mitochondria during I/R insult and also restored the activities of antioxidative enzymes and matrix metalloproteinases (Sarkar *et al*., 2017). The protective effects of melatonin are also reported against other experimental disease models viz. isoproterenol-induced myocardial injury, ulcerative colitis and associated colon carcinogenesis (Mukherjee *et al*., 2012, Trivedi and Jena 2013, Trivedi *et al*., 2016). Diabetes-associated neurobehavioural and neurochemical changes were reported to improve by two week administration of melatonin (3 mg/kg and 10mg/kg) alone or in combination with nicotinamide by inhibiting oxidative stress-PARP pathway (Jangra *et al*., 2013). In HFD fed mice, low dose of melatonin is found to abrogate lipotoxicity-mediated stellate cell activation and hepatic fibrosis progression (Das *et al*., 2017). Melatonin also confers protective effects in chemotherapy-induced mitochondrial damage in liver of rats, by reducing oxidative stress (Madhu *et al*., 2015). One week melatonin (50 mg/kg/d, i.p.) treatment is also reported to antagonize the memory impairment due to the adverse effects of propoxur poisoning (Mehta *et al*., 2014). Melatonin has also been shown to be protective against microwave radiations-induced testicular toxicity in rats (Meena *et al*., 2014) and also ^{60}Co γ-irradiation-mediated testicular, hematopoietic, immunological and gastrointestinal injuries in C57BL/6 male mice (Khan *et al*., 2015, Khan *et al*., 2017).

Endocrine Disruptors, Toxic Chemicals and Heavy Metals

Endocrine disruptors are chemicals that can interfere with endocrine (or hormone) systems at certain doses. These disruptions can cause cancerous tumors, birth defects, and other developmental disorders. Phthalates are commonly used as plasticizers in a variety of products and are reported as endocrine-disrupting chemicals. Long-term exposure (45 days) of phthalates between pre-pubertal to adult stage significantly affected male fertility by altering both structural and functional integrity of Sertoli cells in testes. Its treatment significantly reduced serum testosterone levels, indicating anti-androgenic nature of the test phthalates (Kumar *et al*., 2015). Lactational exposure of phthalate was also reported to cause long-term disruption in testicular architecture by altering tight junctional and apoptotic protein expression in Sertoli cells of first filial generation pubertal Wistar rats (Sekaran *et al*., 2015).

Bisphenol A (BPA) is a well-known endocrine disruptor which represents a major toxicological and public health concern due to its widespread exposure to humans. Tiwari and co-workers have shown that oral administration of bisphenol A (BPA, 10 μg, 5mg and 50mg/kgbw for 6 days) exhibited weak germ cell mutagenic and genotoxic activity that affects male reproductive functions that may be due to oxidative stress (Tiwari and Vanage 2013, Tiwari and Vanage 2017). Deltamethrin is a synthetic pyrethroid insecticide that shows significant harmful effects on testes, liver and kidney. Deltamethrin showed the dose-dependent toxic effects associated with significant histological alteration in the testis, reduction in sperm count, sperm motility, serum testosterone, FSH and LH (Sharma *et al*., 2014). The exposure of tributyltin (TBT), a common environmental contaminant and endocrine disruptor hinders intracellular cholesterol transport resulting in abnormal sex steroid biosynthesis and subsequent spermatogenic defects in hamsters (Kanimozhi *et al*., 2014).

The exposure of two endocrine disrupting pesticides viz., Mancozeb and imidacloprid on reproductive behaviors and secondary sexual

characters in a seasonally breeding wildlife bird, red munia has been studied. Their exposure causes impairment of the lactotropic as well as hypothalamic-pituitary-testicular (HPT) axes that was accompanied with increased plasma prolactin and decreased LH, FSH and testosterone levels (Pandey *et al.*, 2017). BDE-209, a congener of polybrominated diphenyl ethers (PBDEs), a class of brominated flame retardants is having structural similarity with thyroid hormones and acts as an endocrine disruptor by interfering with thyroid homeostasis. Exposure of BDE-209 to adult mice is also reported to cause impaired testicular steroidogenesis due to down-regulated expression of steroidogenic factor 1 (SF-1) and suppression of spermatogenesis (Sarkar *et al.*, 2016). The effects of triptolide on reproduction of wild female rodent pest species, *Bandicota bengalensis* revealed that it affected the histomorphology of uterus by causing a decrease in lumen and columnar cell height and number of uterine glands and ovary by increasing the number of atretic follicles and decreasing the number of developing follicles (Dhar and Singla 2014).

Excess iodine when administered above its tolerable ranges (100 and 500 times more than recommended doses) for prolonged duration acts on thyroid itself developing a state of biochemical hypothyroidism (as evident by low T3) that induces oxidative stress in testis and reduces circulating testosterone level resulting in structural and functional changes of male gonads (Chakraborty *et al*., 2016). Where as in females, iodine in excess exerts biphasic mode of action depending on the dose (100 and 500 times) in female reproductive physiology and both the doses used in this study affected fertility equally in adult rats (Mahapatra and Chandra 2017). Effect of exposure hexavalent chromium (CrVI), an environmental pollutant was investigated in a rat model. Pregnant Wistar rats were exposed to 50/100/200ppm CrVI through drinking water during embryonic days 9-14. On 120 postnatal days, testes showed increased level of CrIII in sertoli cells and germ cells, serum and testicular interstitial fluid associated with decreased testosterone, seminiferous tubules atrophy and disruption of sertoli cells tight junctions (Kumar *et al*., 2017). Mother rats exposed to CrVI showed reduced reproductive outcome, while the offsprings showed higher accumulation of Cr in ovary, altered steroid, and peptide hormones (Samuel *et al*., 2014).

Titanium di-oxide (TiO_2) or its nanoparticle has a potential effect on reproduction and fertility due to its accumulation in testicular cells. Intravenous administration of TiO_2 nanoparticles induces oxidative stress, which in turn produce cytotoxic and genotoxic changes in sperms along with decrease in the testosterone activity (Meena *et al*., 2015). Arsenic has a detrimental effect on reproductive system. The higher doses of arsenic(V) (more than 50 ppm) were shown to elicit testicular toxicity and impair semen quality by inducing oxidative stress in the testicular microenvironment (Guvvala *et al*., 2016). Short term copper (Cu) administration has been found to exert deleterious effect on intracellular organelles of rat ovarian cells *in vivo*. *In vitro* administration of Cu in porcine ovarian granulosa cells releases insulin-like growth factor (IGF-I), steroid hormone progesterone, and induces expression of peptides related to proliferation and apoptosis (Roychoudhury *et al*., 2016). Environmental toxicants such as lead or cadmium and phthalate esters have deteriorating effect on male reproductive system. Recent study showed that lead or cadmium or phthalates might independently contribute to decline in semen quality which include sperm motility, sperm count and sperm DNA damage as well as it affects the level of male sex hormone (Pant *et al*., 2014). Cadmium chloride also significantly affected the ovarian steroidogenesis and inhibited the secretion of gonadotropin-induced 17β-estradiol in female common carp *Cyprinus carpio* (Das and Mukherjee 2013). Changes in lifestyle lead to insulin resistance in females ultimately predisposing them towards infertility. Cadmium (Cd), also an environmental endocrine disruptor, is reported for detrimental effects on granulosa cells, thus leading to ovarian dysfunction. The combined effect of insulin resistance with 32 μM cadmium in granulosa cells demonstrated significant decreases in expression of steroidogenic acute regulatory protein (StAR), CYP11A1, CYP19A1, 17β-HSD, 3β-HSD, FSH-R and LH-R. There was a decrease observed in progesterone and estradiol concentrations as compared to control (Belani *et al*., 2014, Belani *et al*., 2016).

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