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Melatonin vs. phytomelatonin: Therapeutic uses with special reference to polycystic ovarian syndrome (PCOS)

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Melatonin vs. phytomelatonin: Therapeutic uses with special reference to polycystic ovarian syndrome (PCOS)

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Abstract: Melatonin—a tiny tryptophan derivative in the bovine pineal extract. Since then, this wonder molecule is known to regulate a wide variety of physiological and psychological activities of lower and higher vertebrates including the human beings. The exact mechanisms of melatonin actions are poorly understood and explained to date, but the coexistence of endocrine, paracrine, autocrine, and intracrine actions and feedback effects are suggested mostly to be mediated by the specific receptors found in the respective target organs. Melatonin exhibits a remarkable contextual diversity of functions as circadian pacemakers, hypothalamic/pituitary axes to vasomotor effects, immunomodulatory, antioxidative actions, anti-apoptotic effects (direct and indirect), etc. Melatonin with such efficacy and safety may therefore eventually drive its use with other plant extracts containing phytomelatonin in universally effective clinical applications and an adjuvant therapy specially during Polycystic Ovarian Syndrome (PCOS) for treatment in near future and can be proved as a best medicinal tool.

Subjects: Bioscience; Food Science & Technology; Health and Social Care

Keywords: melatonin; polycystic ovarian syndrome; phytomelatonin; LH; FSH; cytokines
1. Introduction
Since decades, the pineal gland was considered as calcified vestige and consequently as Descartes “Seat of the soul.” During the end of 1950, a very rapid progress has been made in uncovering functions of the pineal gland as so for its hormone melatonin. During the present scenario, the functional importance of this hormone in animals including human beings is well established. A.B. Lerner and his associates during 1959 described the chemical structure of melatonin from mammalian pineal extract (Lerner, Case, & Heinzelman, 1959). Following the discovery of structure of melatonin, Wurtman and Waldhauser in 1986 reported pineal as a “neuroendocrine transducer” responsible for converting the received neural signals from sympathetic innervations to a hormonal output i.e. the hormone melatonin (Wurtman & Waldhauser, 1986).

Three years before the discovery of melatonin, Fiske and colleagues 1960 had already described and established the light dependence of the mammalian pineal by their result that its weight was significantly reduced when rats were continuously exposed to light (Fiske, Bryant, & Putnam, 1960). Further it was proposed by Wurtman and Waldhauser regarding light-dependent pineal adjustment and its effect toward the gonadal maturation in many domestic and laboratory animals. Such effect of melatonin from pineal was first of all evidenced with the finding that administration of bovine pineal extract slows gonadal growth in neonatal rats (Kitay & Altschule, 1954). Since the discovery till the present journey, melatonin has been reported to a potent immune regulator in seasonally breeding rodent (Rai & Haldar, 2003). It ameliorates the immunosuppressive effect of synthetic glucocorticoid dexamethasone (Haldar, Rai, & Singh, 2004), immunoprotective (Rai & Haldar, 2006) and immunoproliferative, antiapoptotic (Rai & Haldar, 2011), and antiageing (Rai, Haldar, & Shankar Singh, 2005; Singh, Haldar, & Rai, 2006).

Nowadays the role of pineal in regulation of mammalian reproduction specially among seasonal breeders is very well established (Reiter, 1980, 1981). In human and other laboratory animals/rodents, melatonin has been shown to impact the age of sexual maturation i.e. puberty, the ovulatory cycle, gonadal steroidogenesis, and patterns of reproductive behavior. Pineal gland and its hormone melatonin regulates immune function mediating through endocrine axis (Haldar, Rai, & Tripathi, 2006; Haldar & Rai, 2006; Haldar et al., 2008; Lahiri, Rai, & Haldar, 2006; Rai & Haldar, 2006; Rai, Haldar, & Shankar Singh, 2005; Singh, Haldar, & Rai, 2006).

The present review is considered to elucidate the melatonin—a neurohormone with its functional potential as a therapeutic molecule specially implemented for the curing of Polycystic Ovarian Syndrome (PCOS) which is an alarming endocrine/gonadal disorder in present era, noted frequently in female of any age.

The success of reproduction in all mammals depends on the function of the hypothalamus–pituitary–gonadal axis (HPG). In females, gonadotropin-releasing hormone (GnRH), neurons present in the septal area, and hypothalamus send their axons to median eminence. GnRH released, reaches the anterior pituitary where the gonadotrophs are stimulated to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In the peripheral circulation, these hormones stimulate specific cells in the ovary leading to ovulation.

The neuroendocrine regulation of reproductive function is built on neuronal mechanisms affecting peripheral endocrine tissues through the pituitary gland, and endocrine feedback on the hypothalamic pituitary neuroendocrine system. The function of the neuroendocrine hypothalamus is characterized by pulsatility, circadian rhythmicity, and a 24-h sleep–wake cycle. Activation of the hypothalamic–pituitary–ovarian axis (HPO) takes place gradually, with distinct developmental features of gonadotropin pulsatility and diurnal rhythmicity during puberty.

2. Reproductive cycle of human female
During their reproductive years, non-pregnant females normally exhibit cyclical changes in the ovaries and uterus. Each cycle takes about a month and involves both oogenesis and preparation of the uterus to receive a fertilized ovum. Hormones secreted by the hypothalamus, anterior pituitary, and
ovaries control the main events. The ovarian cycle is a series of events in the ovaries that occur during and after the maturation of an oocyte. The uterine (menstrual) cycle is a concurrent series of changes in the endometrium of the uterus to prepare it for the arrival of a fertilized ovum that will develop there until birth. Decline in the level of ovarian hormones as a result of lack of fertilization causes the stratum functionalis of the endometrium to slough off. The general term, female reproductive cycle, encompasses the ovarian and uterine cycles.

A large population of women with PCOS have increased levels of LH (van Santbrink, Hop, & Fauser, 1997) and normal/decreased levels of FSH (Fauser et al., 1991), resulting in the discussed classical hormonal hallmark of an increased LH/FSH ratio. The prevalence of an increased LH/FSH ratio is partly related to BMI, and it is more prevalent in PCOS of normal weight and less common with increasing BMI. The increase in LH is explained by an increased pulse frequency of the hypothalamic gonadotropin-releasing hormone (GnRH), which may favor the production of the \( \beta \)-subunit of LH over the \( \beta \)-subunit of FSH, and/or by increased pituitary sensitivity to GnRH stimulation. The increase in LH causes the ovaries to favor the production of androgens from the theca cells carrying LH receptors. A trade-off relation between reproduction and immune function of melatonin has been postulated and confirmed experimentally in many other seasonal breeding rodents and avian species (Lahiri et al., 2006; Rai & Haldar, 2006). Experimental evidences suggest that melatonin mediates its actions through activation of G-protein coupled receptors (GPCRs) which have been cloned and classified as MT1 and MT2 (Lahiri et al., 2006).

3. Pathogenesis of PCOS
The pathogenesis of PCOS is multifactorial syndrome and is not understood properly. Multiple causative mechanisms are being proposed, these involve interactions between certain genes and environmental factors (Norman, Dewailly, Legro, & Hickey, 2007). The pathophysiology of PCOS is subject of many hypothesis and speculations. An experiment carried by our research group explains that melatonin administration in a letrozole-induced polycystic rat which reverses the normal ovarian histology with the gonadal hormone (Rai, Basheer, Ghosh, Acharya, & Hajam, 2015. Unpublished data, Manuscript No: 15–903, OMICS). It is reported that the melatonin can function as both a pro and anti-inflammatory agent and its action may change throughout the year. There is a bidirectional communication between the melatonin and the pro and anti-inflammatory agent which is regulated via circadian clock and could explain a mechanism of physiological and pathological functions (Turkowska, Majewski, Rai, & Skwarlo Sonta, 2013). However, it is recently published that the development of inflammation could be driven more by the clock system than by melatonin itself.

4. Free radical generation and tissue damage—antioxidative effect of melatonin
Melatonin has an antioxidative effect (Reiter, Calva, Karbownik, Qi, & Tan, 2000). The first mechanism of this effect is to function as a free-radical scavenging antioxidant that removes hydroxy radicals (HO) (Tan, Chen, Poeggeler, Manchester, & Reiter, 1993), peroxyl radicals (Pieri, Marra, Moroni, Recchioni, & Marcheselli, 1994), and in addition extremely highly toxic peroxynitrite (Cuzzocrea et al., 1997). Melatonin also inhibits lipid peroxidation and blocks the production of isoprostanes (Zhang et al., 2006). The second mechanism of action is to activate endogenous enzymes that scavenge free radicals. Administration of melatonin to pregnant rats increased the activities of superoxide dismutase (SOD) or glutathione peroxidase in fetal brain tissues (Okatani, Wakatsuki, & Kaneda, 2000). Melatonin has its own antioxidative effect and also intensifies the activity of endogenous antioxidative enzymes, which together exerts a powerful antioxidative effect. Considering that melatonin is secreted during the night-time and passes through the blood–brain barrier, it may play a preventive role against oxidation disorders of cerebral nerve cells during nocturnal sleep. A clinical study performed by the Anti-Aging Medical Research Center, Doshisha University, demonstrated that when the quality of sleep was upgraded by the use of comfortable bedding, oxidative stress disorders as evaluated by an indicator of urinary 8-hydroxydeoxyguanosine (8-OHdG) were improved (Yonei, Takahashi, Shionoiri, & Inada, 2007). This may be explained by the exertion of an antioxidative effect resulting from increased melatonin secretion.
The antioxidative property of melatonin has attracted the pinealogists and the novel finding in this regard has really opened a new horizon of research correlating the involvement of melatonin in regulation of various immunological, gerontological, metabolic, and reproductive physiology.

5. Genetic factors
There is evidence of a genetic component based on the existence of familial clustering (Diamanti-Kandarakis, Kandarakis, & Legro, 2006) and twin studies have displayed a twofold increased concordance of PCOS in genetically identical twins compared with non-identical twins (Vink, Sadrzadeh, Lambalk, & Boomsma, 2006). In spite of numerous association studies (mainly focusing on genes associated with the synthesis and metabolism of androgens and insulin), the way in which PCOS is inherited remains unclear (Balen, 2010). Recent efforts, using modern mapping techniques, have made some progress to identify promising candidate genes.

6. Environmental factors
Environmental factors such as prenatal exposure to androgens and weight gain have been main contributing factors. The genetic factors give a high susceptibility to PCOS and that the syndrome will develop only in the added presence of a specific environment, most likely with exposure during fetal life or early childhood. Excess fetal exposure to maternal androgens is thought to contribute to inducing the PCOS in fetus.

In humans, higher testosterone levels, which were elevated to male levels, have been found in the umbilical vein in female infants born to mothers with PCOS. However, the only prospective study of the relationship between prenatal androgen exposure and the development of PCOS during the human female adolescence did not confirm any association between these variables (Hickey et al., 2009).

7. Obesity
Obesity has a considerable effect on the manifestation of PCOS (Norman et al., 1995) and family studies have implied that weight gain may promote the PCOS phenotype in a predisposed population (Legro, Bentley-Lewis, Driscoll, Wang, & Dunaif, 2002). Weight gain is usually associated with a worsening of symptoms, while weight loss usually ameliorates the symptoms and the endocrine/reproductive and metabolic disturbances (Clark, Thornley, Tomlinson, Galletley, & Norman, 1998).

The ovarian cycle in primates, is regulated by a complex interplay between the gonads and the gonadotropes of anterior pituitary along with GnRH pulse generator in the medial basal hypothalamus. During the follicular phase, LH and FSH are released in low-amplitude, circhoral pulses, reflecting negative feedback effects of estrogens on pulse amplitude but not frequency. Estrogen triggers positive feedback resulting in rise of GnRH, LH, and FSH, eliciting increases in pulse frequency and/or amplitude. Inhibin-B in addition to ovarian steroids is secreted by the granulosa cells during the follicular phase, and inhibin-A is secreted by the corpus luteum during the luteal phase, possibly exerting a superficial negative feedback on FSH release; however, the precise role of inhibin in primate ovarian cycles is not yet clear (Randolph, 2008; Zeleznik & Pohl, 2006). Interestingly, FSH concentration is elevated during the luteal phase in squirrel monkeys, suggesting that development of antral follicles may occur during this period, and possibly permitting the extremely short follicular phase of these species (Yeoman et al., 2000). A variety of experimental approaches have suggested that positive feedback by estrogens at the pituitary alone is sufficient to generate preovulatory LH surges, although GnRH plays an obligate permissive role. Nonetheless, other studies have indicated that hypothalamic release of GnRH increases in response to sustained elevations of estrogens. Negative feedback by estrogens, likewise, may be mediated primarily at the level of the pituitary; however, estrogens reduce pulse amplitude (but not pulse frequency) of GnRH as well as on LH, indicating that the negative feedback effects of estrogens (Figure 1) are mediated in part at the hypothalamus (Mizuno & Terasawa, 2005).
8. Synthesis and distribution

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine which is synthesized from an essential amino acid, tryptophan via serotonin. Melatonin is a unique, small (low molecular weight), lipophilic indole amine and is ubiquitously present. It exhibits pleiotropic biological activities in species from bacteria to mammals (Hardeland et al., 2011). This indole amine is primarily in neural tissues whose ontogeny reflects a phototransductive phylogeny, i.e. the retina and the epithalamic pineal gland. This pattern of tissue localization offers a key to understanding melatonin’s primary role during the course of mammalian evolution as a chemical signal encoding environmental light condition (photoperiods). In animals, melatonin is secreted from the pineal gland during the night. It acts as a hormone, functioning as a circadian mediator for time information over the course of each day, and is also able to eliminate free radicals (reactive oxygen species). Melatonin also exists in higher plants (edible plants), and is inadvertently obtained from daily meals (Hattori et al., 1995; Oba, Nakamura, Sahashi, Hattori, & Nagata, 2008). This substance was isolated by chance from the pineal gland, an endocrine organ, and is therefore named a hormone. (Lerner, Case, & Takahashi, 1958).

It has been regarded as a specific hormone of the pineal gland, but is actually produced in the retina, brain (cerebral cortex, raphe nuclei, striate body, etc.), gastrointestinal tract (stomach, small intestine, etc.), testes, ovaries, spinal cord, lymphocytes, lens, cochlea, and skin. Melatonin is widely distributed not only in both vertebrate and invertebrate animals but also in plants such as rice, barley, and wheat (Oba et al., 2008; Paredes, Korkmaz, Manchester, Tan, & Reiter, 2009).

The generation and release of melatonin occurs almost entirely during the dark phase of the 24-h day/night cycle. The mechanisms driving nocturnal MEL synthesis have been studied in considerable detail in numerous vertebrate species. A key feature of the secretion pattern of MEL is its plasticity under different photo periods. Thus, long duration profiles of elevated MEL are associated with short day lengths and vice versa (Goldman, 2001).

Light information received by the retina passes primarily through the retinohypothalamic pathway and is transmitted to the Suprachiasmatic nucleus (SCN), where a circadian clock (for most organisms and plants, a body that oscillates over a 24 ± 4-h cycle; for human beings, about a 25-h cycle) exists, thus enabling synchronization of the phases of the circadian clock with the light/dark cycle (over a 24-h cycle) of the outside world. The time information at the SCN passes through a new nerve to reach the superior cervical ganglion and is then transmitted to the pineal gland. This pathway is actually activated during the night without light stimuli, as the nervous activities of the superior cervical ganglion are inhibited by light stimulation. Noradrenaline is secreted by nerve terminals derived from the superior cervical ganglion and stimulates the pineal cells, primarily via β-receptors,
thereby accelerating the synthesis of cAMP, the second messenger, to activate arylalkylamine N-acetyltransferase activity (AANAT), and a rate-limiting enzyme of melatonin synthesis. During the daytime, AANAT is only weakly activated. Melatonin levels in the pineal gland and blood show a circadian variation, being high during the night-time and low during the daytime. In human beings, melatonin secretion is highest at the age of 1 to 3 years, starts to decrease from puberty onward, and reduces to 1/10 of the peak value at age 70 years or older (Hattori, Suzuki, & Somei, 2006; Figure 2).

The circadian rhythm of melatonin secretion is noted not only in blood but also in almost every type of bodily fluid, including cerebrospinal fluid, saliva, aqueous humor of the anterior chamber, follicular fluid, and breast milk. Melatonin receptors are distributed over a variety of tissues and organs, and accordingly, the time information based on melatonin concentration is transmitted to tissues throughout the entire body. The presence of melatonin receptors has so far been confirmed in the brain (including the SCN), spinal cord, pituitary gland, retina, spleen, thymus, adrenal gland, liver, kidney, heart, lungs, testes, ovaries, blood vessels, lymphocytes, and osteoblasts (Ikegami et al., 2009; Ishii, Tanaka, Kobayashi, Kato, & Sakuma, 2009). It is therefore assumed that in addition to the melatonin-related synchronization of the circadian clock at the SCN, synchronization with sleep phase may occur at the entire body level, bringing better rest to the body.

Melatonin (N-acetyl-5-methoxytryptamine) also known as “chemical expression of darkness” is an indoleamine produced by pineal gland and is secreted in a circadian manner during the night (Masana & Dubocovich, 2001). It is indisputable that melatonin has been potentially implicated as a therapeutic agent in several conditions. In mammals, melatonin can affect the reproductive function through activation of receptor sites within the hypothalamic–pituitary–gonadal axis (Malpaux, Migaud, Tricoire, & Chemineau, 2001). Melatonin is found inside ovarian follicles (Ronnberg, Kauppila, Leppaluoto, Martikainen, & Vakkuri, 1990), thus proving its direct action in ovarian function. It has also been proposed that preovulatory follicles contain high amount of melatonin which was indirectly linked to the 17 b-estradiol (E2) and progesterone (P4) synthesis (Tamura et al., 2009). Melatonin is a neurohormone and highly conserved molecule, and is produced in all vertebrate species. It is the chief secretory product of the pineal gland and a powerful free radical scavenger and antioxidant (Reiter et al., 2000).

9. Importance of melatonin in reproduction
Melatonin has variable effects dependent on the menstrual phase. It is also well known that shift-workers are more likely than daytime workers to experience circadian disruption and longer menstrual cycles, more menorrhagia and dysmenorrhea (Attarchi et al., 2013; Grajewski, Nguyen, Whelan, Cole, & Hein, 2003). These results are corroborated by a very large cohort study, which also

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**Figure 2. Pathway of melatonin synthesis in the human pineal gland.**
found that duration of shift-work was modestly associated with menstrual cycle irregularity (Lawson et al., 2011). A Japanese study found that melatonin levels varied significantly between night- and day-shift workers, while LH and FSH levels did not, suggesting that the menstrual irregularity associated with shift work could be explained by melatonin fluctuations (Miyauchi, Nanjo, & Otsuka, 1992). These findings are in line with central effects on the hypothalamic pituitary axis, being capable of modifying the release of gonadotropins and GnRH (Boczek-Leszczyn & Juszczak, 2007). In fact, in very high doses, when combined with progesterone, melatonin has the ability to suppress ovulation in humans, possibly by interfering with LH release (Voordouw et al., 1992). This may represent an evolutionary remnant with inhibition of ovulation during darker months designed to prevent the birth of offspring when resources are less abundant. Interestingly, melatonin receptors have been found on granulosa cells, indicating that this may be an additional site of melatonin activity (Boczek-Leszczyn & Juszczak, 2007; Itoh, Ishizuka, Kuribayashi, Amemiya, & Sumi, 1999; Salhab et al., 2013). Indeed, when given systemically in cats, melatonin appears to accumulate preferentially in the ovaries compared with other organs (Wurtman, Axelrod, & Potter, 1964) and higher concentrations of melatonin are found in preovulatory follicular fluid than in serum (Brzezinski, Seibel, Lynch, Deng, & Wurtman, 1987; Ronnberg et al., 1990). A human found that larger preovulatory follicles had higher concentrations of follicular fluid melatonin than smaller immature follicles study (Nakamura, Tamura, Takayama, & Kato, 2003). This is the only study that has addressed follicular fluid differences within the same patient, and indicates that follicular fluid from mature follicles have higher antioxidant capacity than smaller follicles, implying a role for melatonin in oocyte maturation. However, it is as yet unclear whether this is a cause or consequence. Adding further credence to the role of melatonin in reproduction, melatonin requirements appear to increase during pregnancy (Carlomagno, Nordio, Chiu, & Unfer, 2011), and researchers have begun to assess its role as a potential therapy in pre-eclampsia and neonatal neurological morbidity (Nakamura et al., 2003).

10. Cytokines and ovarian function
Cytokines are small proteins that act locally through specific cell surface receptors to coordinate interactions of the immune system and surrounding tissues. Macrophages secrete a diverse repertoire of cytokines including IL-1, IL-2, IL-6, IL-10, IL-12, interferon-α (INF-α), tumor necrosis factor-α (TNF-α), and granulocyte macrophage colony-stimulating factors. These cytokines have been identified in the ovaries of many species and are known to impact many aspects of ovarian function (Brannstrom & Norman, 1993; Bukulmez & Arici, 2000; Terranova & Rice, 1997) including follicle growth and differentiation, cell apoptosis, ovulation, and corpus luteum formation and regression (Paria, Reese, Das, & Dey, 2002; Saito, 2000; Schäfer-Somi, 2003). Interactions between the endocrine and cytokine system play an important role in the regulation of follicular development and atresia (Chaouat, Dubanchet, & Ledée, 2007; Moffett & Loke, 2006).

Each cytokine binds to a specific cell-surface receptor. Subsequent cascades of intracellular signaling then alter cell functions. This may include the up regulation and/or down regulation of several genes and their transcription factors, in turn resulting in the production of other cytokines, an increase in the number of surface receptors for other molecules, or the suppression of their own effect by feedback inhibition. Cytokines are produced locally in the ovulatory follicle, and the role of these factors in the different components of the ovulation process: follicle rupture and remodeling, leukocyte infiltration, angiogenesis, ovarian steroidogenesis, and oocyte maturation.

The cytokine IL-6, described originally as a T-cell-derived factor that specifically induces differentiation of B lymphocytes into active antibody-producing plasma cells (Hirano et al., 1985), has recently been shown to exert modulatory influence over ovarian function. Specifically, IL-6 is capable of directly influencing FSH-stimulated progesterone production by granulosa cells in vitro. Moreover, IL-6 is produced by the granulosa cell, suggesting a potential role for this cytokine in the autocrine and/or paracrine regulation of ovarian function (Figure 3).
11. Phytomelatonin

Melatonin was initially considered as a signaling molecule in animals but later on it was recognized as an ancient molecule. Its presence is traced to primitive photosynthetic bacteria, red and green algae, fungi, and plants. The primary function of this molecule is free radical scavenger and antioxidant to protect organisms from environmental and internal oxidative stress. The other functions were during the course of evolution (Tan, Hardeland, Manchester, Galano, & Reiter, 2014). Melatonin was found for the first time in plants two decades ago (Hattori et al., 1995).

Melatonin regulates the germination, growth, and reproduction of plants and promotes the ripening of fruit (Tan et al., 2012). A study carried out by Sun et al., 2015 reported that melatonin upregulates the ethylene signal transduction system genes and enhances the ethylene biosynthesis. Melatonin protects the plants from biotic (Lee, Byeon, & Back, 2014) and abiotic (Zhang et al., 2015) stressors. Several reports exist suggesting presence of melatonin in different plants which has opened a new horizon in the field of plant-derived melatonin (phytomelatonin) (Reiter et al., 2007).

India is very rich in biodiversity especially in medicinal plants. The state of Chhattisgarh is known to have a rich wealth of medicinal plants, but most of them have remained unexplored. The state of Chhattisgarh being placed in Deccan bio-geographical area, houses an important part of that rich and unique biological diversity. What is more conspicuous is that the state is significantly rich in endemism with respect to many plants having medicinal importance.

In plants, there are present a number of phytochemicals which possess antioxidant properties. These chemicals may be flavonoids, terpenoids, polyphenols, pigments, lignins, saponins, carotenoids, etc. Medicinal plants are valued for their unique complement of bioactive molecules. They have been used from times immemorial to prevent and treat various diseases.

In a number of plant species melatonin has been detected. It is both synthesized as well as taken by the plants from the soil. It carries out a number functions in plant like antioxidant, growth promoter, regulation of plant reproductive physiology, and defense against apoptosis induced under harsh environmental conditions. The presence of melatonin in plants seems to be universal but there is an absence of information on its occurrence in plants outside the angiosperms. The main reason for this is the inefficient detection methods. But in recent past, some methodologies have been designed in order to get results about melatonin content in plants. The first preliminary indications about the presence of melatonin in plants were provided by Tassel and O’Neill (1993), Tassel, Roberts, and O’Neill (1995), and Kolar et al. (1995) but the first publications in this regard were
independently provided by Dubbels et al. (1995) and Hattori et al. (1995). Melatonin has been seen to be involved in a number of physiological aspects in plants, where it acts as a circadian regulator, cytoprotector, and growth promoter. It also acts in rhizogenesis, cellular expansion, and stress-protection.

Murch, KrishnaRaj, and Saxena (2000) carried out the first study about the melatonin in plant St John's wort. Plants are also able to absorb melatonin from soil or the medium in which they grow (Table 1).

12. Traditional medicinal herbs in treatment of ovarian/endocrine dysfunction/PCOS
Lifestyle change is first-line treatment in an evidence-based approach in the management of the majority of PCOS women who are overweight (Moran, Pasquali, Teede, Hoeger, & Norman, 2009). Furthermore, prevention of excess weight gain should be emphasized in all women with PCOS of both normal and increased body weight. As little as 5% to 10% weight loss has significant clinical benefits improving psychological outcomes (Galletly, Clark, Tomlinson, & Blaney, 1996), reproductive features (menstrual cyclicity, ovulation and fertility) (Clark, Thornley, Tomlinson, Galletly, & Norman, 1998; Huber-Buchholz, Carey, & Norman, 1999), and metabolic features (insulin resistance and risk factors for CVD and DM2). A number of plants, Glycyrrhiza glabra (Decio et al., 2004), Panax ginseng (Sok et al., 2005), Mentha spicata (Grant, 2010), Linum usitatissimum (Nowak & Snyder, 2007), Aloe barbedensis (Maharjan & Nagar, 2010), Cinnamomum zeylanicum (Wang & Anderson, 2007), Vitex agnus-castus (Westphal, Polan, & Trant, 2006), Matricaria chamomilla, (Zafari, Minea, Amirzargar, & Ahangarpour, 2010), Silybum marianum (Taher, Atia, & Amin, 2010), Labisia pumila (Mannerås et al., 2010), have been utilized in treating the various complications which are associated with PCOS.

13. Conclusion
N-Acetyl-methoxytryptamine (Melatonin) synthesized from serotonin primarily in pineal gland and is released in a circadian manner being high during the dark phase of light-dark cycle. In mammalian species, melatonin affects reproductive function partially by activating receptor sites within the

| S. No | Plant          | Family       | Reference                        |
|-------|----------------|--------------|----------------------------------|
| 1     | Allium cepa L. | Amaryllidaceae| Hattori et al. (1995)            |
| 2     | Allium sativum L. | Amaryllidaceae | Badria (2002)                   |
| 3     | Asparagus officinalis L. | Asparagaceae | Hattori et al. (1995)            |
| 4     | Ananas comosus L. | Bromeliaceae | Hattori et al. (1995)            |
| 5     | Avena sativa   | Poaceae      | Hattori et al. (1995)            |
| 6     | Zea mays L.    | Poaceae      | Hattori et al. (1995) (Badria 2002) |
| 7     | Triticum aestivum L. | Poaceae | Hernández-Ruiz, Cano, and Arnao (2005) |
| 8     | Zingiber officinlae Rosco | Zingiberaceae | Hattori et al. (1995), Pape and Luning (2006) |
| 9     | Prunus cerasus  | Rosaceae     | Burkhardt, Tan, Manchester, Hordeland, and Reiter (2001) |
| 10    | Nicotiana tabacum | Solanaceae  | Dubbels et al. (1995)            |
| 11    | Lupinus albus  | Fabaceae     | Hernández-Ruiz, Cano, and Arnao (2004) |
| 12    | Chenopodium rubrum | Amaranthaceae | Kolar et al. (1997)          |
| 13    | Basella alba L. | Basellaceae  | Hattori et al. (1995)            |
| 14    | Brassica rapa L. | Brassicaceae | Hattori et al. (1995)            |
| 15    | Cucumis sativus L. | Cucurbitaceae | Hattori et al. (1995)            |
| 16    | Olea europaea L. | Oleaceae     | de la Puerta et al. (2007)      |
| 17    | Malus domestica Borkh | Rosaceae  | Hattori et al. (1995)            |
| 18    | Papaver somniferum L. | Papaveraceae | Manchester et al. (2000)        |
| 19    | Beta vulgaris L. | Amaranthaceae| Dubbels et al. (1995)            |
hypothalamic–pituitary–gonadal (HPG) axis. The effect of melatonin on ovarian function varies with tissue structure, cell type, and whether the species is seasonal or a non-seasonal breeder. The present review is aimed to summarize in brief the role of melatonin in regulation of reproduction during the polycystic ovarian condition. Knowingly, melatonin is per se neither anti gonadotropic nor progadotropic, but changing the duration of nocturnal melatonin provides message signal to the hypothalamic pituitary gonadal axis about the information of calendar year. The reproductive axis uses the melatonin rhythm to adjust ovarian physiology accordingly. Polycystic ovary syndrome is the common endocrine disorder of unknown etiology. During PCOS, GnRH declines the optimum concentration and melatonin having an inverse relation with the hypothalamic GnRH (a decapetide) released in a pulsatile fashion from neurosecrectory cell of hypothalamus to regulate the production and release of FSH and LH from anterior pituitary. Present review also summarizes about the edible plants listed for the presence of melatonin. Such plant extracts in combination with melatonin may be used during PCOS pathogenesis under the new pharmacological strategies to explore a novel therapeutic molecule.

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**Competing interests**
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