CHAPTER

24

Herbal aphrodisiac biomolecules in the management of male reproductive and sexual problems: connecting nature with clinics

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24.1 Introduction

As the world approaches toward more and more scientific developments, humanity is becoming acquainted with newer forms of remedies to combat various ailments. In spite of the rich technological aids in diagnostics and therapeutics, recently there has been renewed interest in herbal formulations or products in the management of diseases—a practice that dates back to hundreds of years [1]. According to the World Health Organization (WHO), traditional herbal medicines are naturally occurring, plant-derived substances with minimal or no industrial processing which are used to treat illnesses within local or regional healing practices [2]. Herbal medicines include herbal materials, herbal preparations, and finished herbal products, that contain, as active ingredients, parts of plants, other plant materials or combinations thereof [3]. According to a statistics, almost 80% people worldwide depend on herbal remedies as a primary part of health care [4]. This is probably due to the belief that herbal products pose less side effects, are cheaper in comparison to many modern drugs, and also available locally [1].

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24.2 Traditional herbal medicine

Herbal or folklore medicines have influenced mankind since ancient civilizations, which has resulted in the development of various traditional systems of medicines. Such traditional or folklore systems of medicine have been playing a vital role in the management of diseases, particularly in the geographical region(s) where it developed. Indian subcontinent is well known for traditional systems of medicine that include *Ayurveda*, *Siddha*, and *Unani*. *Ayurveda* or the "science of life," dating back more than 5000 BCE, has its origin in ancient India in the *Vedas—Rigveda* and *Atharvaveda*. *Ayurveda* further evolved between 2500 and 600 BCE with the development of the School of Physicians and the School of Surgeons. During 600 BCE it branched into internal medicine, pediatrics, psychiatry, toxicology, geriatrics, eugenics, and aphrodisiacs [5,6]. *Ayurveda* is also known as the "science of longevity" which provides with the systems for a long and healthy life [7]. It was one of the first of its kind to evolve an integrated approach towards health and disease [8]. *Siddha*, a unique system of medicine has its roots within the ancient civilizations of the Southern India and is one of the oldest systems of medicine in India. The term *Siddha* is derived from *Siddhi*, meaning achievement. It is a psychosomatic system, depending mainly on the drugs of metal and mineral origin. *Siddha* system of traditional medicine mainly focuses on the fields like pediatrics, ophthalmology, and toxicology [6,8]. Aphrodisiacs drugs are also available in *Siddha* system of medicine which includes a well-known herbo-mineral preparation named *Thathu Viruthi Kuligai* used particularly for the management of premature ejaculation [9]. In *Siddha* system, some flowers are also used for their potential aphrodisiac qualities [10]. *Unani* system of medicine originated in Greece and later was introduced in India by the Arabs. This system prefers a single drug or their combinations over compound formulations. Examination of pulse is a vital part of diagnosis in *Unani*, apart from the analyses of tongue, urine and stool. *Unani* system balances humors and assists the natural healing ability of the body involving treatment approaches such as regimental therapy, diet therapy, and pharmacotherapy [6,8,11]. *Unani* medicine also contains a number of natural herbal formulae that comprise of combinations of powerful life enhancing herbs and potent natural aphrodisiacs for improving libido and treating erectile dysfunction (ED), especially associated with diabetes and alcohol [12].

Traditional Chinese medicine (TCM) dates back to over 3000 years. Optimization of human life by the preservation of life sustaining conditions forms the basis of this system. Detecting internal conditions through external manifestations is the key to assessment in TCM [11]. It works to restore the *Qi* (energy) and balance the different components within the body by using a variety of therapies. Some of the treatment approaches of TCM include the use of medicinal herbs and needles (acupuncture), moxibustion, massage, cupping, exercise, dietary therapy, and bone-setting techniques. In case of herbal therapies, poly-herbal formulations are in practice. In TCM, herbal as well as acupuncture therapies have been in use since long to treat ED [13]. In recent times, there is an increasing trend of using the TCMs alongside the conventional medicines [14]. Similarly, traditional Korean medicine that evolved at around 984 BCE provides a rich diversity of natural agents to treat sexual disorders [15,16]. It further gained momentum during the 19th century [17], and involves treatment with herbal medications and various therapies such as acupuncture, moxibustion, cupping therapy, hot pack applications, massage, chiropractic manipulation and infrared irradiations. Diagnosis through this system involves patient observation, palpation, auscultation, and interrogation [15,18]. This system has some similarities with the TCM, however, it has some unique features such as the *Sasang* Constitutional Medicine and runs parallel to conventional Western medicine in healthcare systems [19]. Traditional Korean medicine

provides a rich diversity of natural agents to treat sexual disorders, too [16].

African continent is also noteworthy for its unique traditional systems of medicine. The natural richness of Africa is reflected in its medicine systems, wherein a disease is considered as an imbalance in social relations, human–nature relations or human–ancestral relations. Cause of a disease is believed to have two basic dimensions—a proximal cause, as to how a disease occurs and an ultimate cause, as to why a disease occurs. There are different traditional healers of diverse skills or expertise, and healings range from being plant, animal, or mineral based [14,20]. For instance, traditional herbal remedies particularly based on the roots of *Eriosema* species have been used by the Zulu people of South Africa for centuries for the treatment of ED [21].

24.3 Aphrodisiacs

Since ancient times, humans across diverse cultures have shown keen interest in products which enhance sexual abilities [22,23], pleasure and libido, and treat sexual dysfunctions including ED [24,25]. The word "*aphrodisiac*" is derived from *Aphrodite*, the Greek goddess of love and beauty (Greek Aphrodisiakos meaning "sexual"). An aphrodisiac is defined as an agent, food or drug that provokes sexual desire, maintains libido and increases sexual performance [26,27]. Aphrodisiacs have been primarily divided into three categories on the basis of their actions: those which enhance (1) libido (sexual desire), (2) potency (effective erection), and (3) sexual pleasure [23]. Aphrodisiacs can be of plant, animal or synthetic origin, but those derived from plants are preferred due to less side effects [28]. The use of herbal aphrodisiacs can be traced back to 1700 BCE in Egyptian writings and 300 BCE in TCM, whereas the use of plant preparations by ancient Babylonians to increase sex drive dates back to 6000 years [29]. In *Ayurveda*, herbs having aphrodisiac properties are grouped into a class of drugs known as *Vrishya* or *Vajikarana* [30]. *Vajikarana rasayan* or aphrodisiacs modulate the neuro-endocrine system by acting upon the hypothalamus and limbic systems [31]. In fact, most of the aphrodisiac formulations available commercially contain Asian herbs, of which Indian and Chinese herbs are the most prominent. Some of the herbal sexual stimulants based on the traditional African communities are also available commercially [21]. In modern times, too, some men still prefer the use of traditional medications or herbal products against reproductive and/or sexual disorders due to social or cultural reasons [32].

24.3.1 Need for aphrodisiacs

Sexuality and reproduction are two important parts of life of a man, consuming a considerable amount of effort and energy. Healthy sexual and reproductive life is one of the indicators of self-esteem and healthy family [33]. Reproductive disorders, especially infertility and the lack of virility have rung alarm in today's society. There has been a decline in human sperm count from 113 million/mL in 1940 to 66 million/mL in 1990, too [34]. Another study encompassing 20 years has recorded deterioration in sperm quality with around 1.5% yearly decline in total sperm count [35]. Globally, around 15% of the couples are affected by infertility, of which 20%–30% are attributed to male factor infertility amounting up to 50% of all infertility cases [36]. With changing lifestyle and environmental disturbances [37] there is a steady decline in the serum androgen levels which affect fertility as well as virility in men [38]. This may further hamper sexual and/or reproductive function(s). Sexual dysfunction is a physiological, psychological and social symptom that occurs in 10%–52% of the males. Apart from the above-mentioned factors, stress plays a significant role in deteriorating sexual health

by interfering with the normal physiology including that of the reproductive system rendering sexual disorders such as hypogonadism [39], ejaculatory dysfunction and ED [40,41]. ED is the inability to achieve or maintain penile erection sufficient to aid satisfactory sexual performance [42]. It is one of the most common sexual dysfunctions experienced by men, partly due to andropausal effects and to some extent due to hormonal or psychological disturbances [26,43]. It may lead to the loss of meaning and value of a man's life as well as a feeling of psychological frustration, social conflict, family disagreement—ultimately affecting a couple's intimacy and sexual harmony [44]. Prolonged stress results in damage to germ cells including increase in the level of cortisol in serum [45] affecting spermatogenesis by generation of reactive oxygen species (ROS) [27,46,47]. Increasing age, lower level of androgens, free radicals, disorders—such as diabetes, atherosclerosis, and unhealthy lifestyle have also been associated with the loss/reduction of fertility in men [48–50]. Aphrodisiacs have been claimed to possess antistress and adaptogenic properties which assist in combating stress, disease and improving physical strength ultimately helping alleviate the anxiety associated with lack of sexual desire and performance [31]. This is why aphrodisiacs pose as an option to mitigate the lack of virility, vitality and/or fertility in men by restoring compromised sexual and reproductive abilities.

24.3.2 Herbal aphrodisiacs

Herbal molecules make up a large share of natural product-based pharmaceuticals [51]. It is estimated that nearly 50% of the drugs approved during the last few decades have their origin in nature/natural products [52]. Herbal aphrodisiacs are either used as single, or mixture of several formulations. Fig. 24.1 shows some of the important plants/plant parts that possess potential aphrodisiac properties.

Clinical significance of such plants as aphrodisiacs in the management of male reproductive and sexual problems is presented in Table 24.1. However, important driving forces

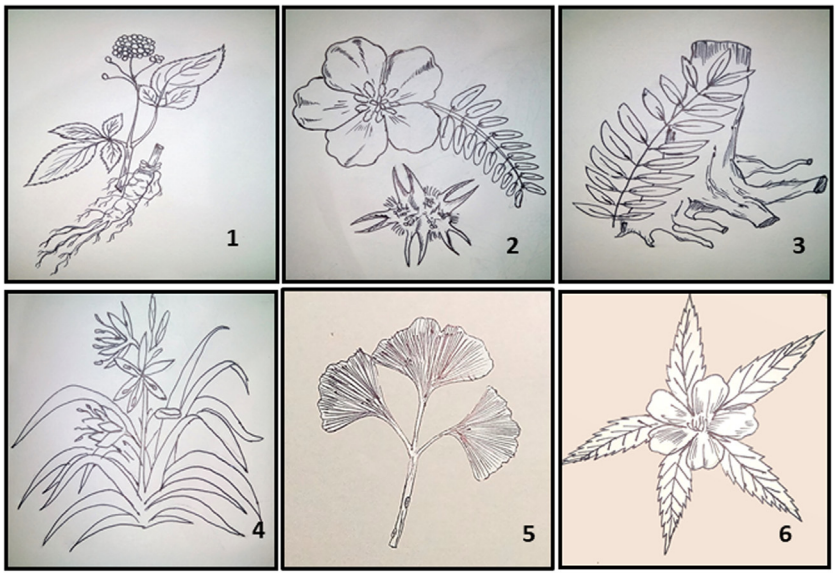

FIGURE 24.1 Important plants/plant parts that possess aphrodisiac properties. (1) *P. ginseng*, (2) *T. terrestris*, (3) *E. longifolia*, (4) *C. borivilianum*, (5) *G. biloba*, and (6) *Turnera diffusa var. aphrodisiaca*.

TABLE 24.1 Clinical significance of herbal aphrodisiacs in male reproductive and sexual health.

Herbal medicine	Experimental model	Route of administration	Dosage	Calculated human dose[a]	Effects	References
P. ginseng	Human	Oral	350 mg ginseng berry extract per tablet, four tablets daily for 8 wk	–	Improved erection, sexual satisfaction and ejaculation	[53]
	Human microvascular endothelial cells	In vitro	–	–	Increased production of NO	[54]
	Rat	Subcutaneous	–	–	Improved mating behavior, ejaculation frequency	[55]
	Rat	Oral	20, 40, 100, and 150 mg/kg/d for 1–4 wk	194.59, 389.19, 972.97, and 1459.46 mg	Dose and duration dependent increase in intracavernosal pressure	[54]
	Rabbit	In vitro (cavernosal smooth muscle)	10, 20, 50, 100, and 150 mg/mL	–	Improved relaxation of cavernosal smooth muscle, maximum effect at 150 mg/mL dose	[54]
T. terrestris	Human	Oral	1500 mg/d for 12 wk	–	Improved sexual function including penile erection and satisfaction	[56]
	Mouse	Oral	11 mg/kg for 2 wk	53.51 mg	Gonadoprotective; improved semen parameters and testosterone level	[57]
	Rat	Oral	2.5, 5, and 10 mg/kg for 8 wk	24.32, 48.65, and 97.3 mg	Improved body weight, mating behavior and erection	[58]
	Rat	Oral	50 and 100 mg/kg after 2 wk	486.49 and 972.97 mg	Improved mating behavior, erection and serum testosterone level	[59]
E. longifolia	Human	Oral	200 mg for 1 month	–	Improved AMS in LOH patients; improved testosterone level	[60]
	Human	Oral	300 mg daily for 12 wk	–	Improved libido, erection; enhanced semen volume and sperm motility	[61]
	Rat	Oral	50, 100, and 200 mg/kg for 48 d	486.49, 972.97, and 1945.95 mg	Increased plasma testosterone level; improved sperm quality	[62]

(*Continued*)

TABLE 24.1 (Continued)

Herbal medicine	Experimental model	Route of administration	Dosage	Calculated human dose[a]	Effects	References
	Rat	Oral	200, 400, and 800 mg/kg for 10 d	1945.95, 3891.89, and 7783.78 mg	Improved mating performance	[63]
C. borivilianum	Rat	Oral	125 and 250 mg/kg for 54 d	1216.22 and 2432.43 mg	Improved sexual behavior; increased sperm count and motility	[64]
	Rat macrophage cells	Oral	100 mg/kg for 2 wk	972.97 mg	Improved sperm count, seminal fructose concentration and penile erection	[65]
G. biloba	Human	Oral	40–60 mg, twice daily for 4 wk	–	Improved antidepressant induced sexual dysfunction; positive effect on desire, erection, orgasm, and resolution	[66]
	Human	Oral	80 mg, thrice daily for 9 months	–	Improved penile rigidity	[67]
	Rat	Oral	10, 50 and 100 mg/kg for 1, 2, 3, and 4 wk	97.3, 486.49 and 972.97 mg	Improved copulatory behavior; reduced prolactin levels	[68]
	Rat	Oral	50 mg/kg for 2 wk	486.49 mg	Increased NCE, sexual arousal, dopamine level	[69,70]
	Rat	Oral	200 mg/kg for 12 wk	1945.95 mg	Improved antioxidant defense	[71]
Turnera diffusa var. aphrodisiaca	Rat	Oral	0.25, 0.50 and 1.0 mL kg 1 h prior to testing	2432.43, 4864.86, and 9729.73 mg	Improved copulatory performance in sexually sluggish animals	[72]
	Rat	Oral	20, 40 and 80 mg/kg 1 h prior to testing	194.59, 389.19 and 778.38 mg	Improved sexual motivation and behavior in sexually exhausted animals	[73]
	Rat	Oral	10, 20 and 40 mg/kg 1 h prior to testing	97.3, 194.59, and 389.19 mg	Improved copulatory behavior via NO pathway	[74]

[a]*The equivalent human dose has been calculated using "DoseCal," a virtual calculator based on k_m factor for dosage conversion between human and animal species [75]; using the formula: Human equivalent dose (mg/kg) = Dose to be converted/(Human k_m/Animal k_m). The human equivalent dose has been calculated assuming a body weight of 60 kg.*

k_m = Correction factor, calculated by dividing the average body weight (kg) of a species to its body surface area (m^2) [76]. *AMS*, Ageing males' symptoms; *LOH*, late-onset hypogonadism; *NCE*, noncontact erection; *NO*, nitric oxide.

behind the noticeable effects of such aphrodisiacs are the constituent biomolecules—the active principles present in the herbal preparations. Proper identification and scientific validation of such herbal biomolecules may lead to further development of vital drugs against sexual dysfunctions and/or disorders. Hence, it is necessary to understand the phytochemical constituents including the molecular composition of herbal aphrodisiacs that are responsible for improving male sexual and reproductive behavior as well as physiology. In this chapter, important herbal aphrodisiacs that have been validated scientifically are discussed individually in accordance with their effects/actions and the potent phytochemical compounds and/or molecules which manifests the aphrodisiac activities. However, delineating each activity remains difficult due to the interlinking of various associated pathways.

24.3.2.1 *Panax ginseng*

Ginseng, also known as Korean or Asian ginseng [77] has been in use in eastern Asia since last 500 years, although its use in TCM dates back to 3000 years [78]. It is a perennial herb native to Korea and China, and is a part of the Pharmacopoeias of Japan, China, Germany, France, Austria, and the United Kingdom [79]. Apart from aphrodisiac properties, the herb is known for its antioxidant, vaso-stimulatory, antiallergic, antidiabetic, antiinflammatory, anticancer, and cardio-protective potentials [80,81]. The herbal extract has been reported to ameliorate penile erection and sexual satisfaction in human subjects on treatment at a dose 600 mg thrice a day for 12 weeks [82,83]. Treatment with a daily dose of four tablets (each containing 350 mg of standardized Korean ginseng berry extract) for 8 weeks improved all domains of sexual function in subjects with ED [53]. In vivo experiments with ethanolic *P. ginseng* berry extract have shown increased relaxation of cavernosal smooth muscle in rabbits after treated with 10, 20, 50, 100, and 150 mg/mL with maximal effect at 150 mg/kg body weight), and cavernosal pressure in rats on treatment with 20, 40, 100, and 150 mg/kg for 4 weeks. In vitro investigations have revealed the production of nitric oxide (NO) in human microvascular endothelial cells after treatment with 200 μg/mL extract for 30 minutes [54]. Studies have also revealed *P. ginseng*-induced improvement in mating behavior and increase in blood testosterone level of male rats after treatment with 1% and 5% purified extract for 2 months [84]. Subcutaneous application of *P. ginseng* extract at 0.5 mL per 100 g body weight for 5 days also improved mating behavior in rats, as evident from enhanced ejaculatory rates and mating activity [55].

Roots of this plant contain steroids such as saponins—called ginsenosides or panaxosides, which are believed to be involved in the relaxation of penile smooth muscle. This property is usually taken into consideration to treat patients with ED [85]. Apart from saponins, *P. ginseng* contains flavonoids, polyacetylenes, polysaccharides, and alcohols as notable phytochemical constituents. Saponins or ginseng saponins or the ginsenosides, which are synthesized from 2,3-oxidosqualene [86], are classified into dammarane, ocotillol, and oleanane type oligoglycosides. Ginsenosides are considered as the major active components of *P. ginseng* [87]. The various types of saponins found in the roots of *P. ginseng* include prosapogenins; ginsenosides Ra1, Ra2, Ra3, Rb1, Rb2, Rc, Rd, Re, Re1, Re2, Re3, Re4, Re5, Re6 Rf, Rg1, Rg2, Rg3, Rh1, Ro; notoginsenosides R4, 20-gluco-ginsenoside Rf, koryoginsenoside R1 and R2; protopanaxatriol-type ginsenosides [86,88]. Polysaccharides constitute about 40% of the plant, of which ginsan is one of the most active ones. Alkaloids such as β-carboline alkaloids; glycosides such as isomaltol-α-D-glucopyranoside, ketopropyl-α-D-glucopyranoside and adenosine; phenolic acids such as maltol, phenolic acids such as salicylic acid, vanillic acid and *p*-hydroxycinnamic acid are also present in *P. ginseng* [87].

Using in vitro tissue bath technique, ginsenosides have been found to enhance the acetylcholine-induced relaxations of corpus cavernosa at 250 μg/mL dose in isolated rabbit corpus cavernosum strips [89,90]. Ginseng has also been shown to enhance the formation of citrulline from arginine—implying the synthesis of NO [91]. Ginsenoside Rg1, at a dose of 10 mg/kg body weight has been reported to improve copulatory behavior of male mice [92]. Ginsenoside Re has been shown to increase sperm motility in semen samples of asthenozoospermic men after incubation at 1, 10, and 100 μM for 2 hours in vitro. It has also been found to induce endogenous NO production and cause improvement on NOS activity which in turn, may help in scavenging free radicals in sperm cells [93].

24.3.2.2 *Tribulus terrestris*

T. terrestris or Devil's thorn is a herbaceous perennial plant originally native to the Mediterranean region, but presently distributed across the warm regions of the world. The plant is used as a traditional medicine in India, China, Bulgaria, and South Africa against various ailments including sexual dysfunctions, edema, abdominal distention and cardiovascular diseases [94,95]. Among many males, it has been an all-time herb of choice for enhancing sexual stamina. According to Chinese Pharmacopoeia, fruits of *T. terrestris* are used as kidney tonifying agent, diuretics, cough expectorants, in the management of skin diseases and eyesight problems [96]. In some users, consumption of fruits or aerial parts of the plant has been associated with muscle gain and increase in libido [97]. Dry extract of *T. terrestris* has been reported as a gonadoprotective in experimental mice. Oral treatment with dry extract of *T. terrestris* at a dose 11 mg/kg body weight for 2 weeks has been found to protect against testicular damage induced by cyclophosphamide in mice [57]. In rats, aqueous extract of *T. terrestris* at doses 2.5, 5, and 10 mg/kg body weight administered orally for 8 weeks led to an increase in intracavernous pressure indicating enhanced release of NO from the nerve endings innervating the corpus cavernosum [58]. This suggests the involvement of *T. terrestris* in aiding penile erection. Lyophilized aqueous extract of dried fruits of *T. terrestris* at doses 50 and 100 mg/kg has been found to increase in sexual activity of sexually sluggish male rats by exhibiting improved penile erection, mounting frequency, intromission frequency and serum testosterone level. It was also able to reverse the age induced sexual dysfunction in experimental rats [59]. In another study, administration of *T. terrestris* extract notably increased the levels of serum testosterone and dihydrotestosterone in experimental rodents at doses 2.5, 5, and 10 mg/kg body weight for 8 weeks in rabbits and rats; at 5 mg/kg body weight dose for 8 weeks in castrated rats; and at doses 7.5, 15, and 30 mg/kg body weight in primates. Furthermore, an increment in the release of dehydroepiandrosterone was also noted in primates [98]. A commercially available tablet Tribestan (each containing 250 mg active substance *T. terrestris* herba extractum siccum, standardized to furostanol saponins obtained from the over ground parts of the plant) at two tablets thrice daily for 12 weeks led to enhancement of sexual functions and penile erection [56]. However, detrimental effects of the herb have also been recorded in some exceptional cases. A person was diagnosed with acute interstitial nephritis (also known as acute tubular necrosis)—a case of nephrotoxicity after consuming 2 L *T. terrestris* water for two consecutive days. It resulted into elevated levels of serum aminotransferases, creatinine, urea, and blood pressure [99].

Saponins, flavonoids, lignin, alkaloids, tannins, amides form the important phytochemical constituents of *T. terrestris* [100]. A flavonoid called chrysin has been reported from the fruits of *T. terrestris* [101]. The

presence of furostanol and spirostanol saponins and four sulfated saponins of tigogenin and diosgenin has been reported in the plant, too. Major furostanol saponins present in *T. terrestris* include protodioscin, protogracillin, and prototribestin [102]. These have been reported to be the main components of the aerial parts of *T. terrestris* [103]. Protodioscin comprises about 45% of its total dry weight [58]. Fruits of *T. terrestris* have been reported to contain protodioscin, tribulosaponins A and B, tribulosin and terrestrosin A-K, terrestribisamide, terrestriamide, hecogenin, tribulusamides A and B, harmane, norharmane, tribulusterine, ferulic acid, vanillin, kaempferol, quercetin, and rutin [100,104]. α-Amyrin has also been reported to be a major constituent of the plant [105].

As discussed above, *T. terrestris* is used as an aphrodisiac for its ability to enhance reproductive physiology and sexual behavior in the users. Based on animal and human studies, the biological activity of *T. terrestris* has been attributed mainly to protodioscin, protogracillin, and prototribestin [58,106]. Protodioscin, commercially available in the form of Libilov when administered orally at a dose of three tablets twice a day for 2 months have been able to increase both sperm numbers and quality in moderately idiopathic oligozoospermic men. It also effectively restored and/or enhanced libido, erection, ejaculation and orgasm during sexual intercourse in about 80% of the patients [107]. It is believed that erection and libido are induced by the conversion of protodioscin to dehydroepiandrosterone [108]. Protodioscin is also believed to improve hormonal levels and sperm parameters [109]. It is also a major constituent of commercial product Tribestan [103].

24.3.2.3 *Eurycoma longifolia*

Commonly known as jack or tongkatali, *E. longifolia* is indigenous to the South-East Asian countries such as Indonesia, Malaysia, and Vietnam. It is also found in Cambodia, Thailand, and Myanmar. Roots of this evergreen plant are of medicinal importance [110,111]. The plant is well known for its antimalarial, antidiabetic, antimicrobial, antipyretic, and aphrodisiac potentials [110]. This herb is also considered as a symbol of a "man's ego and strength [63]. Root extracts of *E. longifolia* has gained popularity for its unique virility enhancing property [110]. Clinical studies have revealed that intake of 200 mg of standardized aqueous extract of *E. longifolia* daily for 1 month is able to increase serum testosterone levels in men suffering from late-onset hypogonadism (LOH) thereby improving the ageing males" symptoms (AMS). The study also paved the way for its use to boost routine testosterone therapy in patients who are in need [60]. *E. longifolia* is suggested to be one of the safe and useful herbal aphrodisiacs by virtue of its capacity to increase muscle strength and serum testosterone level in aged men [112]. It is believed to enhance male sexual parameters—such as desire, steroidogenesis, adenosine triphosphate production by inducing oxidative phosphorylation [113], and improve mating performance in castrated male rats when treated at doses 200, 400, and 800 mg/kg body weight [63].

Important bioactive components of *E. longifolia* include quassinoids—such as eurycomanone, eurycomanol, hydroxyklaineanone, eurycolactone, eurycomalactone, eurycomadilactone, laurycolactone, longilactone, and hydroxyglaucarubol; β-carboline alkaloids; canthin-6-one alkaloids; triterpene-type tirucallane; eurycomaoside; 13α(21)-epoxyeurycomanone; 13α, 21-dihydroeurycomanone [62,110,112,114–116]. Squalene derivatives occurring in the herb include teurilene, eurylene 14-deacetyleurylene, and longilene peroxide [112], whereas quassinoid diterpenoidsareeurycomalide A, eurycomalide B, 13β,21-dihydroxyeurycomanol, and 5α,14β,15β-trihydroxyklaineanone [117]. Quassinoid glycoside eurycomanol-2-O-β-D-glycopyranoside was also reported from the plant [118]. Eurycomanone fractions isolated from the root of the plant at a dose 25 mg/kg, body

weight have been associated with enhancement in spermatogenesis and testosterone level in rats [119]. It may facilitate steroidogenesis and spermatogenesis, and is believed to act as a sexual enhancer [62].

24.3.2.4 *Chlorophytum borivilianum*

Musli forms an integral component of the traditional medicinal systems in India including *Ayurveda* and *Unani*. The genus *Chlorophytum* is distributed in tropical and subtropical forests throughout the world [120]. It is an annual herb, and the root tubers are of medicinal value [121]. The plant is a well-known aphrodisiac and considered by some as a herbal alternative to synthetic Viagra [121,122]. In recent years this plant has been exploited commercially. Traditionally, root tubers of this plant are used for the management of ED and oligozoospermia. The extract of this herb is believed to enhance sexual parameters including libido in experimental animals [65,120]. Treatment with *C. borivilianum* extract capsules at a dose 500 mg twice daily for 12 weeks brought about a desired effect by improving serum testosterone level, semen volume, sperm count, motility, and morphology in patients [121]. Sperm parameters along with libido were found to improve in male rats treated orally with *C. borivilianum* extract at doses 125 and 250 mg/kg body weight for 54 days [64]. In mice, aqueous extract of *C. borivilianum* has been found to improve sperm parameters as well as penile erection in vivo and inducible NO release by mouse macrophage cell lines. Male rats when treated with *C. borivilianum* extract at 100 mg/kg body weight for 2 weeks improved sperm count, seminal fructose concentration and penile erection index. Mouse macrophage cells RAW264 treated with the extract at a dose 10 mg/mL for 24 hours showed enhanced release of NO [123]. Studies on rats have shown that enhancement in sexual behavior such as arousal, sexual vigor, and libido apart from sperm count after administration of aqueous root extract of *C. borivilianum* at doses 125 and 250 mg/kg body weight [124]. When administered orally at 500 mg twice daily for 12 weeks, the aqueous root extract resulted in improvement in semen volume and sperm count in male volunteers, too. Presence of stigmasterol and saponins in the herb has been attributed towards the stimulation of spermatogenesis [121]. *C. borivilianum* has also been reported to be rich (2%–17%) in steroidal saponins [125]. Steroidal saponins borivilianosides (A-H) have been isolated from the roots of the plant [126,127].

24.3.2.5 *Ginkgo biloba*

Ginkgo or maiden hair is one of the oldest plant species, living for almost 270 million years—and hence known as "living fossil." The tree has the ability to resist a wide range of environmental stress, and has been believed to be of medicinal value since ancient times. It is distributed throughout China, Korea, Japan, Europe, and the United States [128,129]. Well known for its memory boosting and cardioprotective properties, it also enhances sexual activity such as erection. Leaf extracts of *G. biloba* at a dose 80 mg thrice daily for 9 months has been reported to improve erection and help regain penile rigidity in patients suffering from arteriogenic ED (insufficient arterial blood supply to the penile tissues) [67,130–132]. At the same dose when used together with tadalafil twice a week for 3 years *G. biloba* has shown beneficial effects in improving ED [133]. Leaf extracts (particularly 4% and 10% extracts) have shown neuroprotective effects including improvement of erectile function in rats at a dose 5 mL/kg body weight for 4 weeks [134]. It improved copulatory behavior in experimental rats at a dose 50 mg/kg body weight after 2, 3, and 4 weeks in vivo [68]. The same dose when administered in rats for 2 weeks led to the enhancement of sexual arousal and noncontact erection (NCE—erection as a response to audio, visual,

olfactory or chemosensory sexual stimuli), too [69,70]. The standardized leaf extract, EGb 761 at a dose 1 mg/mL has been reported to enhance testosterone production in rats both in vivo and in vitro (in Leydig cells) [68]. Moreover, *G. biloba* extract when administered at daily doses 25, 50, and 100 mg/kg body weight for 3 months, was found to increase the mean weight of cauda epididymis and prostate in mice, and provided protection against cisplatin-induced testicular atrophy, cellular disorganization and degeneration [135,136]. In addition, at 200 mg/kg body weight for 12 weeks, *G. biloba* extract helped increase the production of antioxidant enzymes such as superoxide dismutase, catalase, NO and thiols in rats, which in turn, played a crucial role in ameliorating oxidative stress in testicular tissues [71]. In spite of its benefits, certain side effects of *G. biloba* have also been reported. It has been associated with carcinogenesis in mice, while some of its extracts were reported to be neurotoxic. It may also increase the risk of bleeding and interfere with other medications [137].

The phytochemical constituents of *G. biloba* include flavonol, flavone glycosides and terpenoids, catechin, 6-hydroxykinuretic acid, protocatechuic acid, shikimic acid, and vanillic acid. The extracts used as medicinal agents usually contain 24% flavone and 6% terpenoids, the latter comprising of gingkolides A, B, C, and J, and bilobalide [134,138,139]. Kaempferol, one of the constituents of *G. biloba* can prevent dopamine degradation by inhibiting the monoamine oxidase B (MAO-B). Activity of dopamine in the medial preoptic area (MPOA), a potent area of brain which regulates male sexual behavior and physiology, is important for enhancement of sexual response [68].

24.3.2.6 *Turnera diffusa var. aphrodisiaca*

Damiana is a shrub distributed mainly throughout Mexico, the Caribbean, Central and South Americas. The leaves are mainly known for medicinal values, and possess antioxidant and aphrodisiac properties, which reportedly enhanced sexual activity in sluggish male rats in vivo. *T. diffusa* leaf extract at doses 0.25, 0.50, 1.0 mL/kg when administered orally in sexually potent and sexually sluggish male rats resulted in improvement of copulatory performance. However, the extract had no impact on the copulatory behavior of sexually potent rats. At a dose 1 mL/kg body weight administered 2 hours, *T. diffusa* extract has been able to increase the percentage of rats achieving ejaculation, while reducing ejaculation latencies. However, it was accompanied by a decrease in mounting and intromission [72]. Higher numbers of mounts and intromissions were noted in mice treated with 10 mg *T. diffusa* in 0.3 mL peanut oil administered for 2 weeks [140,141]. The herb has also been reported to improve sexual motivation and behavior in sexually exhausted male rats. *T. diffusa* leaf extract when administered orally at doses 20, 40, and 80 mg/kg body weight not only improved the sexual behavior but also reduced the post-ejaculatory interval after 1 hour of application [73]. Furthermore, when treated with 10, 20, and 40 mg/kg body weight of the herbal extract, an improved sexual behavior was noted in rats as expressed by short ejaculation latency [74].

The phytochemicals present in the plant include terpenoids, flavones, flavonone, flavonoid O-glycosides, flavonoid C-glycosides, phenolic glycoside, maltol glycoside, apigenin 7-glucoside, Z-echinacin, pinocembrin (a flavanone) and acacetin (a flavone). Biomolecules such as pinocembrin and acacetin may possess the ability to inhibit aromatase activity. Pinocembrin and acacetin are believed to possess the ability to inhibit aromatase activity and induce steroidogenesis [142]. This may be one of the probable reasons behind the enhancement of steroid hormones, particularly testosterone levels by damiana [142]. Leaf extract of the plant also contains cyanogenic glucoside damianine; flavonoids gonzalitozine and apigenin; caffeine; acacetin; 5-OH,4′-dimethoxyflavone;

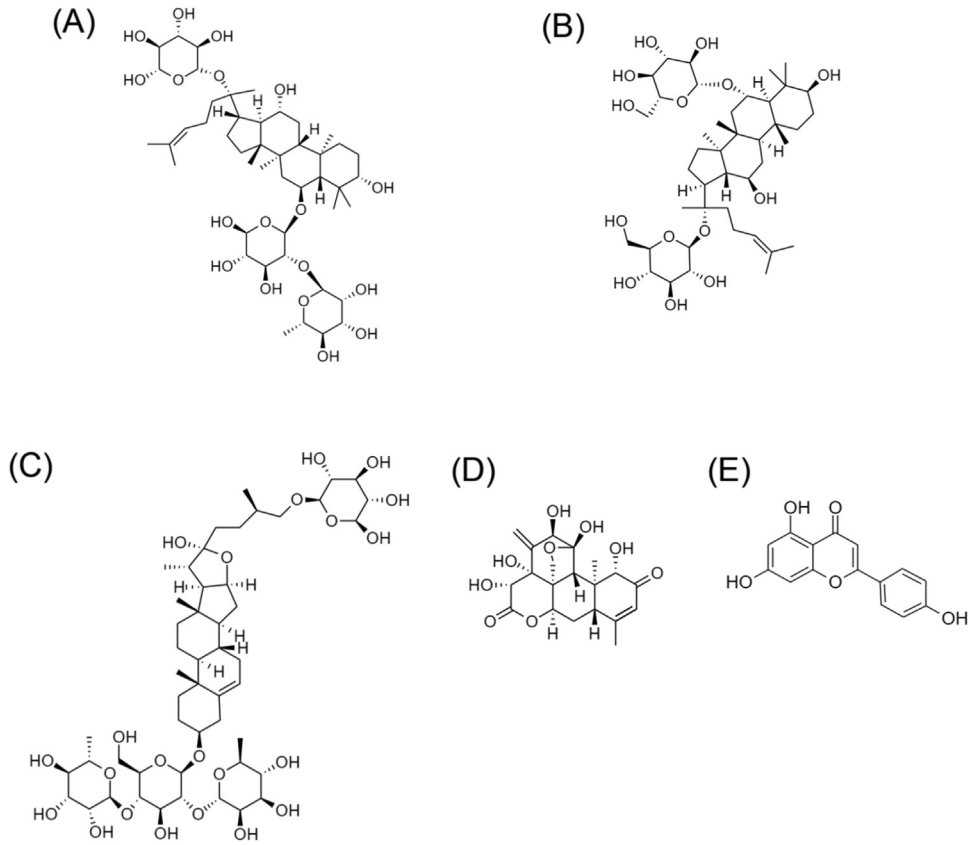

FIGURE 24.2 Herbal aphrodisiac molecules with potential for clinical application in male reproductive and sexual health. Ginsenoside Re and Rg1 isolated from *P. ginseng* may improve sperm parameters, erection, and copulatory behavior. Protodioscin, a saponin present in *T. terrestris* can increase testosterone production, libido, and hence erectile function. Isolated from *E. longifolia*, eurycomanone (a quassinoid) fraction may also stimulate the production of testosterone whereas *apigenin*, a flavone occurring in *Turnera diffusa var. aphrodisiaca* may act as an anxiolytic agent thereby enhancing sexual functions.

and luteolinglycoside [73], which may be associated with some of its aphrodisiac properties. 5,7,4′-trihydroxy flavone, that is, apigenin, isolated from *T. diffusa* extract has been found to be an effective anxiolytic agent at a dose 2 mg/kg in experimental rats when tested 45 minutes after administration in vitro [143].

Some of the important herbal aphrodisiac biomolecules with potential for clinical application are presented in Fig. 24.2.

24.4 Potential mechanism of action of aphrodisiac biomolecules

There can be various pathways through which herbal molecules and compounds may affect the sexual and reproductive functions. Some of the effective ways include increment in hormonal levels or modulation of neurotransmitters. In men, sex drive is primarily attributed to the activity of testosterone. Higher blood testosterone levels result in maximal penile

reception [144]. Some of the herbs as mentioned in the previous section boost the process of steroidogenesis mainly by increasing serum testosterone level. Steroidogenic properties of these herbal aphrodisiacs have been attributed to the presence of flavonoids. Chrysin, a natural flavonoid occurring in plants including *T. terrestris* has been reported to enhance steroidogenesis in mouse Leydig cells [145]. In presence of cyclic adenosine monophosphate (cAMP), chrysin can induce the expression of steroidogenic acute regulatory (StAR) protein, which controls mitochondrial cholesterol transfer and affects testosterone production. It was also found to upregulate the expression of StAR promoter and StAR mRNA [145], which are considered crucial for the production of testosterone by Leydig cells [146]. In fact, StAR is the regulatory factor for the rate-limiting step in testosterone biosynthesis [147]. Apigenin, another natural flavonoid molecule occurring in aphrodisiac herbs such as *T. diffusa*, can modulate the process of steroidogenesis, too [147]. Investigations on mouse Leydig tumor cells MA-10 have shown apigenin to induce steroidogenesis by increasing the sensitivity of Leydig cells to cAMP stimulation. Interaction of apigenin with cAMP enhanced the expression of StAR protein resulting in improved steroidogenesis [147]. Other bioactive flavonoids of *T. diffusa* such as pinocembrin and acacetin may also play a role in the elevation of serum testosterone levels by inhibiting aromatase activity [142]. The polysaccharide biomolecules of *P. ginseng* can upregulate the expression of androgen receptor mRNA thereby maintaining healthy blood testosterone levels [84,148]. Squalene, another phytoconstituent, whose derivatives have been reported in aphrodisiac herbs including *E. longifolia* [112], has been reported to increase serum testosterone level in rats [149]. These findings suggest probable mechanisms of action of herbal flavonoid biomolecules, particularly chrysin and apigenin in the process of steroidogenesis. Eurycomanone, an important bioactive quassinoid isolated from *E. longifolia* can enhance testosterone biosynthesis at 0.1, 1, and 10 μM concentrations 2 hours postadministration by inhibiting the aromatase conversion of testosterone to estrogen. At high concentration, it may also involve phosphodiesterase inhibition, too [119]. Stigmasterol, another component biomolecule of aphrodisiac herbs including *C. borivilianum* [121], is structurally related to testosterone [33,120].

Saponins, isolated from a number of aphrodisiac herbs including *P. ginseng*, *T. terrestris*, and *C. borivilianum* have been shown to possess androgenic properties [150]. Saponins have the ability to activate neurotransmitters including NO thereby assisting the relaxation of penile smooth muscles [151]. Ginsenoside Rg1, a purified bioactive ingredient of *P. ginseng* has been reported to improve copulatory behavior of male mice when treated intraperitoneally at doses 5 and 10 mg/kg body weight for 20 d. This may be attributed to its actions at both testosterone levels and signal transduction pathway in corpus cavernosum. It not only increases the testosterone level (which is reported to play a central role in penile erection) but also helps to boost up NO release and cGMP accumulation in corpus cavernosum both in vivo in mice model and in vitro in rabbit model at doses 0.5 and 5 μM. The NO/cGMP cell-signaling system activation is the prime driver of erectile functions [84,92]. Polyphenols such as quercetin occurring naturally in herbs including *T. terrestris*, has been shown to improve erection in experimental rats by enhancing intracavernous pressure [152], and are presented as potential candidates for the treatment of ED. Quassinoids, another group of herbal compounds also improve sexual functions by modulating the neurotransmitters. Isolated from aphrodisiac herb *E. longifolia*, eurycomanone has been reported to induce testosterone synthesis and modulate brain neurotransmitters such as dopamine [153]. Testosterone helps in NO synthesis in the MPOA of the hypothalamus thereby

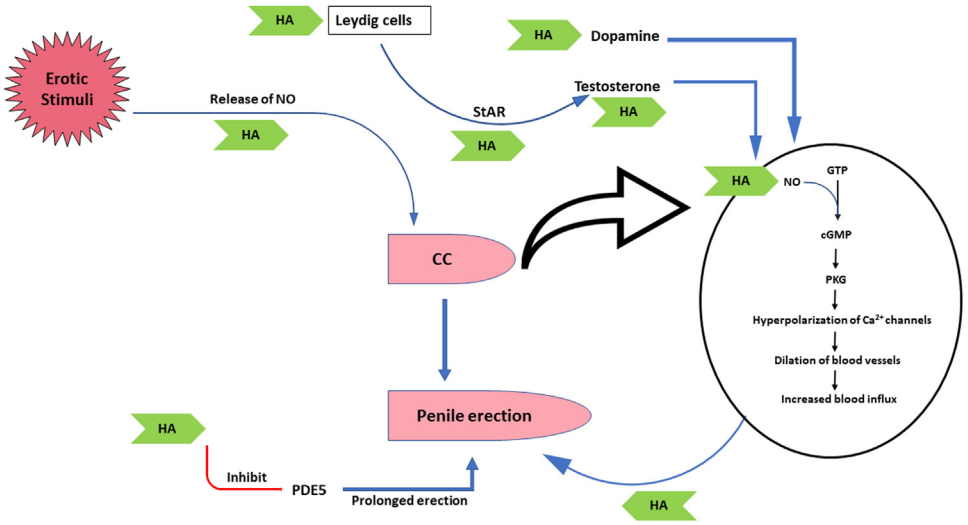

FIGURE 24.3 Potential mechanism of action of aphrodisiac biomolecules in male reproductive and sexual health.

increasing the release of dopamine as well as sexual motivation [154]. An increased release of dopamine (a neurotransmitter associated with sexual motivation and desire) in the MPOA during precopulatory activities of experimental rats indicated its role in maintaining sexual motivation [155].

ROS can contribute to infertility/subfertility in the male by inducing alterations in the sperm cell including DNA. Antioxidant capacity also decreases as a result of oxidative stress [156]. Another probable pathway by which herbal aphrodisiacs combat sexual disorders is by ameliorating oxidative stress. Supplementation of *G. biloba* extracts containing bioactive ingredients such as ginkgolides and bilobalides may improve the health of reproductively compromised men through reduction of oxidative stress [71,157]. This may be attributed to the buffering action of these biomolecules against oxidative stress, along with their role in lowering the expression of a transcription factor NF-κB, which is a potent mediator of oxidative stress-induced inflammation [71,136]. The probable mechanisms of action of herbal aphrodisiac biomolecules have been illustrated in Fig. 24.3.

24.5 Conclusion

Herbal products have received medicinal importance since ancient times. Traditional systems of medicine across various regions including Asian as well as the Indian subcontinent continue to depend on herbs in promoting men's health. In some men, reproductive health issues not only create mental, physical and social barriers but also provoke a sense of dilemma about adopting modern treatment options. Herbal aphrodisiacs remain one of the methods of choice for such men. These are commonly used as extracts which contain a cocktail of different molecules and compounds, and as a result, the active principles which manifest the beneficial effects remain unknown in many cases. If investigated thoroughly, these biomolecules may prove vital drug candidates and further yield potent medicines for possible incorporation into the workup algorithm of clinicians in the management of men's health issues.

Libilov, a commercially available form of protodioscin when administered at a daily dose of six tablets for 2 months have been found to increase testosterone production, followed by

increase in libido and restoration of erectile functions in moderately idiopathic oligozoospermic men [107]. A commercially available tablet Tribestan (herbal biomolecule protodioscin being one of its major components) at two tablets thrice daily for 12 weeks led to enhancement of sexual functions and penile erection [56,103]. An in vitro study conducted among semen samples from asthenozoospermic men has shown progressive improvement in sperm motility and induction of endogenous NO production 2 hours after administration of ginsenoside Re at a dose range 10–100 μM [93]. Apart from these, there are other biomolecules which also possess potent aphrodisiac activity but lack well documented experimentation. Apigenin may act as an anxiolytic agent as has been shown in experimental rats in vitro [143]. Eurycomanone, a quassinoid fraction has been found to stimulate testosterone level in rats [119]. Ginsenoside Rg1, at a dose can improve copulatory behavior of male mice [92], whereas kaempferol may also play a role in the enhancement of sexual response preventing dopamine degradation [68]. Stigmasterol and saponins, particularly borivilianosides A–H may potentially stimulate spermatogenesis, too [121,125]. Ginkgolides and bilobalide may possess aphrodisiac activity, too, but as of now these biomolecules lack clinical studies to prove their efficacy. Chrysin, apigenin, pinocembrin, acacetin, squalene, and quercetin are some other herbal biomolecules which may also be worthy of experimentations. Therefore, more investigations are necessary to reveal the exact activity and mechanism of action of such biomolecules both in animals and humans in order to validate the claims. For their potential incorporation into the clinical management of male reproductive and/or sexual disorders such as ED or male infertility in future, these herbal aphrodisiac biomolecules have to pass through stringent confirmatory studies including proper assessment of their safety and regulatory issues together with any side effect and associated toxicity for safe human administration. Such quality control and efficacy testing of herbal aphrodisiac biomolecules as potential drug candidates must further undergo pre-clinical experimentation, dose escalation studies, and mandatory phase 1, 2, and 3 clinical trials [158]. Therefore future research should focus on the molecular aspects of herbal aphrodisiacs using reverse pharmacology approach particularly for validating the efficacy of the age-old traditional practices of herbal medical practitioners for potential translation in the clinical setting as efficient drugs for the management of male reproductive and sexual disorders.

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