

Potent natural aphrodisiacs for the management of erectile dysfunction and male sexual debilities

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1. ABSTRACT

The area of natural product research is rapidly progressing from traditional medicine to modern medicine having proper scientific basis of its usage. However, identifying the active constituent or the basis of its mechanism holds the key to synthesis of these drugs in the laboratory. Traditional Indian literature such as *Ayurveda* has listed several plant and animal based resources for treatment of almost every ailment. Erectile dysfunction and male sexual debilities are among the most explored areas in traditional medicine. A number of natural products, mostly

plant based, have been claimed to cure erectile dysfunction and related male sexual debilities. These products often are aphrodisiac and have multi-fold effects on male reproductive system. This review aims at compiling the animal and plant based resources which bear promise of treating loss of libido and erectile dysfunction. A special emphasis is paid to find out scientific basis of their usage. The identification of potential resources could help undertake further studies to establish their possible mechanism of action; opening the doors to proper clinical trials for human use.

2. INTRODUCTION

Infertility is a biological, clinical, personal and social problem and male factors contribute 50% to this subject (1). Men and women have since ages been curious to improve, revive and maintain their sexual efficiency, and ancient literature is witness of use of natural aphrodisiacs for this purpose. The term 'Aphrodisiac' has been derived from Aphrodite, symbol of love and beauty in Greek mythology. Since ancient times a large number of natural (plant and animal) remedies have been used as aphrodisiacs in different cultures and civilizations. Ancient literature and records show the deep interest of human beings for substances to increase libido, potency and sexual pleasure as it takes care of the disorders of sexual desire, ejaculation, orgasm and erectile dysfunction. We find mention of the use of a large number of plant and animal based aphrodisiacs worldwide in different traditional systems such as *Ayurveda*, *Unani*, and *Siddha* of Indian and Chinese (2) as well as in Tibetan, Arabian, Greek and Roman medicinal systems. In Ayurvedic medicinal system of India, a separate section is devoted to cure erectile dysfunction with the help of natural products and it is well known as Vajikaran therapy or Virilification. These materials are being used as aphrodisiacs irrespective of lack of knowledge about their exact mechanism of action. Chinese traditional practitioners are also trying acupuncture for this purpose and there is enough scientific basis to include it in the regimen of conventional medicine (3).

From a very basic biological point of view, the man should be able to achieve erection, penetration and ejaculation for a successful sexual intercourse. This not only ensures reproduction but also ensures personal satisfaction and pleasure. In the modern era of technology and busy life style, disorders related to the problems of erection and infertility are quite common. Therefore, human beings are continuously looking for an ultimate aphrodisiac in search of heightened sexual satisfaction to take care of biological and personal purposes. Despite the availability of well known synthetic aphrodisiacs with their exact mechanism of action, people are interested in finding out a natural substance believing that it could have less or no side effects. Synthetic aphrodisiacs like sildenafil, tadalafil and verdenafil which work through PDE5 inhibition could cure erectile dysfunction and loss of libido; however, a natural aphrodisiac could have additional benefits such as providing nutrition and help recover infertility without any adverse side effects (4). The progress in research work related to natural aphrodisiacs during last decade is the proof about the curiosity and significance of this subject. Though several such substances are known, aphrodisiacs which have undergone rigorous scientific research and could be recommended for human use are only few. The subject is more restricted in its exploration at clinical trial level and is in need of focused investigation for resources and their safe animal and clinical trials.

3. PARAMETERS OF MATING BEHAVIOR TEST

On the basis of available literature and methods used, we have compiled the following parameters for research on

aphrodisiac activity. Research on aphrodisiac plants/animals could use few or all of the following parameters.

Mounting Frequency: the number of mounts attempted before ejaculation.

Intromission Frequency: the number of intromission before ejaculation.

Mounting Latency: the time between the introduction of female to male and first mount.

Intromission Latency: the time period between introduction of the female and the first intromission by male.

Ejaculatory Latency: the time period between the first intromission and ejaculation in a single series.

Post Ejaculatory Interval: the time period taken by male between the first ejaculation and next intromission.

Penile Erection Index (PEI): the product of percent rats exhibiting erection and mean number of erections.

Copulatory Rate: number of mounts + number of intromissions / time period between first mount till ejaculation (5).

Percent Index of Libido: number mated \times 100 / number paired

4. NATURAL APHRODISIACS

4.1. Animal based aphrodisiacs

4.1.1. Ambrein

Ambrein (Figure 1a), a triterpenoid (1-ambra-8, 13, 18 (28) triene, $C_{30}H_{52}O$, M_w 428) is chief constituent of Ambergris, a secretion from the gut of sperm whales (*Physeter catodon*) which is used for different applications including better sexual performance. Taha et al devoted more interest in this subject and demonstrated its effect in stimulation of penile erection and positive orientation towards sexual behavior pattern (6). Animal studies have indicated its stimulatory effects on pituitary and antagonizing effects on various vaso-constricting agents such as noradrenaline, acetylcholine, prostaglandin and oxytocin etc., which ultimately increases libido by altering related hormones and increasing blood flow by relaxing smooth muscles of corpus cavernosum.

4.1.2. Bufo toad

Bufotenine (Figure 1b) or its O-methylated derivative, 5-MeO-DMT (5-Methoxy N, N - dimethyltryptamine), a tryptamine alkaloid, are widely spread in Anuran family (for example toad and frog) as a component of their chemical defense system and act as putative hallucinogen congener of serotonin (8). It is popularly used as an active ingredient in West Indian aphrodisiac "love stone" and Chinese medication "chan su" (9). It shows activity similar to Lysergic acid diethylamide but the mechanism of its action is not yet established. It is however, assumed to act through its effect on central nervous system (7).

4.1.3. Spanish fly

Cantharidin (Figure 1c) (3 α , 7 α - dimethylhexahydro-4, 7- epoxyisobenzofuran-1, 3-dione), a compound for sexual stimulation, is derived from emerald

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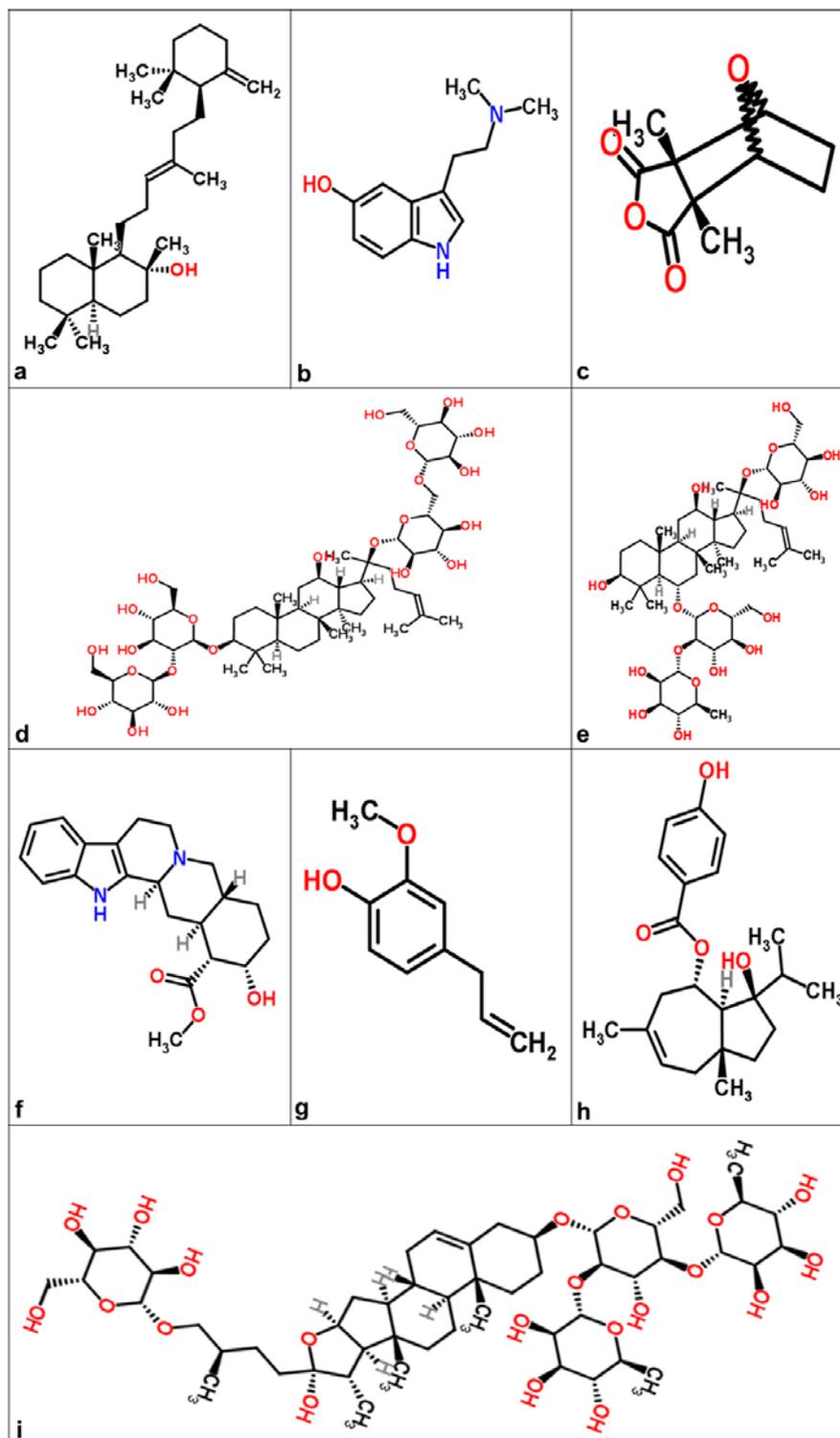


Figure 1. Chemical structures of some of the known active constituents of different animals/plants; a) Ambrein from *Physeter catodon*, b) Bufotenine from Bufo Toad, c) Cantharidin from *Lytta vesicatoria*, d) Ginsenoside Rb1 from Ginseng, e) Ginsenoside Re from Ginseng, f) Yohimbine from *Coryanthe yohimbe*, g) Eugenol from *Syzygium aromaticum*, h) Ferutinin from *Ferula hermonis*, i) Protodioscin from *Tribulus terrestris*.

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– green beetle (*Lytta vesicatoria*) of family Meloidae. Since ancient times cantharidin finds its value for improving sexual vigor but with adverse side effects (10). Cantharides are clinically restricted in human subjects due to their unavoidable side effects like renal toxicity and associated acute tubular necrosis, gastrointestinal hemorrhages and cardiac complications. It is suggested that cantharides act through inhibition of PDE-5, protein phosphatase and activation of β -receptors which ultimately leads to sexual sensation/arousal (7). However, the exact mechanism of action and its clinical efficacy are still the subject of exploration.

4.2 Plant based aphrodisiacs

4.2.1. *Allium tuberosum*

Allium tuberosum (Alliaceae) has been used as a spice, food and medicine since long back (Figure 2a). The ingredients/constituents which have been reported in *Allium tuberosum* are steroidal saponins, alkaloids and sulfur containing compounds etc. Many reports related to aphrodisiac attributes of this plant have been cited in the literature but they are all just opinions rather than scientific observations. In a recent study, butanol extract of *Allium tuberosum* seeds showed good aphrodisiac activity when administered for 40 days at 500 mg/kg BW/day as the sexual behavior in the treated animals improved with a significant reduction in mounting latency, ejaculatory latency, intromission latency and post ejaculatory interval and a significant increase in mounting frequency, intromission frequency and ejaculatory frequency. This Plant is open for further exploration of its aphrodisiac potential with its mechanism of action and side effects, if any (11).

4.2.2. *Alpinia calcarata*

Alpinia calcarata, a member of family Zingiberaceae is a perennial herb that mainly thrives in China and Southeast Asia (Figure 2b). Its rhizome is known to have medicinal properties. This plant was studied for its effect on male sexual competence and fertility by using its hot water extract (HWE) and inhibition in intromission and mounting latencies were reported. Other parameters such as libido and penile erection were found to have no change at lower doses (150 and 250 mg/kg BW) whereas increased level of testosterone and rapid penile erections were reported at a higher dose (500 mg/kg BW) (12). This supports its aphrodisiac activity which could be further explored to understand its mechanism of action.

4.2.3. *Astercantha longifolia*

Astercantha longifolia is a herb of family Acanthaceae and is well known aphrodisiac since long back (Figure 2c). In a recent study, Chauhan et al reported promising results and androgenic properties for ethanolic extract of *A. longifolia*. The ethanolic extract was administered to rats in 100,150 and 200 mg/kg BW/day doses for a period of 28 days resulted in increase in testosterone, fructose and sperm count (validated with histological architecture) as well as increase in weight of secondary sex organs and body weight. 200 mg/kg was reported to be most effective dose for significant

improvement in male sexual behavior and related parameters (13).

4.2.4. *Anacyclus pyrethrum*

Anacyclus pyrethrum DC (Figure 2d), commonly known as 'Akarkara' belongs to family Asteraceae and is a well recognized vitalizer or tonic in *Ayurveda*. The roots of this plant are considered to be aphrodisiac. Lyophilized aqueous extract of this plant was evaluated for its aphrodisiac activity on male albino rats in a 28 days dosing experiment. Improved sexual behavior, orientation behavior, penile erection and associated parameters were observed and 100 mg/kg BW/day was found to be the most effective dose. The extract was also found to be effective in improving sperm count and fructose level concentration in a dose dependent manner. Petroleum ether extract of this plant was also found to improve above mentioned parameters of sexual performance (14). The possible mechanism of action could be via elevation of testosterone level, change in neurotransmitters level and NO based intervention, which is subject to further investigation.

4.2.5. *Bulbus natalensis*

Bulbus natalensis (Baker) (Syn *Bulbine latifolia*) is a member of family Asphodelaceae (Figure 2e). After phytochemical evaluation, this plant was found to have saponins, cardiac glycosides, tannins, alkaloids and anthraquinones. In a study on male rats, the aqueous extract of this plant at doses 25 and 50 mg/kg BW/day was reported to significantly improve mounting frequency, intromission frequency, ejaculatory latency, ejaculatory frequency, LH and testosterone levels, and significantly reduce mounting latency, intromission latency and post ejaculatory interval. Indices of sexual behavior, penile erection and penile reflexes were found significantly improved making this plant a potent future aphrodisiac. The high dose of extract (100 mg/kg BW/day) produced contrasting result as compared to lower doses (25 and 50 mg/kg BW/day). Therefore, the dosage is one critical criterion with this plant as true for few other medicinal plants. The sex stimulating property of this plant is thought to be because of either its alkaloid content which helps in dilation of blood vessels in the reproductive organs or saponin fraction which enhances androgen production or it could be a combined effect of two or some more constituents (15). It is apparent that aphrodisiac potential of this plant should be explored further before it could be approved for use in human trials.

4.2.6. *Butea frondosa*

Butea frondosa, a member of family Papilionaceae (Figure 2f) has been found to be a good aphrodisiac in an experiment on male rats. The aqueous extract of its bark was administered orally (400 mg/kg BW/day) for 28 days and parameters of sexual behavior were studied at day 0, 7, 14, 21 and 28. The extract was found to be effective resulting in significant reduction of mounting latency, intromission latency, ejaculatory latency and post ejaculatory interval and significant improvement in mounting frequency, intromission frequency and ejaculatory frequency in a dose dependent manner in both active and inactive male rats. Its earlier investigated anti-

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Figure 2. Representative pictures of plants/plant-parts having aphrodisiac properties; a) *Allium tuberosum*, b) *Alpinia calcarata*, c) *Astercantha longifolia*, d) *Anacyclus pyrethrum*, e) *Bulbus natalensis*, f) *Butea frondosa*, g) *Chlorophytum borivilianum*, h) *Caesalpinia benthamiana*, i) *Curculigo orchiooides*, j) *Crocus sativus*, k) *Corynanthe yohimbe*, l) *Camellia sinensis*, m) *Dactylorhiza hatagirea*, n) *Eurycoma longifolia*, o) *Ferula hermonis*, p) *Fadogia agrestis*, q) Ginseng r) *Lycium barbarum* s) *Lepidium meyenii*, t) *Microdesmis keayana*, u) *Montanoa tomentosa* v) *Mucuna pruriens* w) *Mondia whitei*, x) *Passiflora incarnate*, y) *Securidaca longepedunculata*, z) *Syzygium aromaticum*, aa) *Tribulus terrestris*, ab) *Turnera diffusa*

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stress property is considered to supplement the stimulation of sexual activity as stimulants/anti-depressants have associated effects such as improving libido, erection, ejaculation time and orgasm. The mechanism by which *B. frondosa* enhances sexual activity is thought to be mediated by increase in testosterone level and change in neurotransmitters level and may involve dopaminergic and adrenergic receptors (16).

4.2.7. *Chlorophytum borivillianum*

Chlorophytum borivillianum commonly known as 'safed musli' is a traditional Indian medicinal plant of family Papilionaceae with diverse therapeutic applications (Figure 2g). It is famous as 'vajikaran' or aphrodisiac in ancient Indian literature. It is well known aphrodisiac agent and revitalizer with good spermatogenic property and is considered to be alternative 'Viagra'. Roots of this plant are used which contain steroidal and triterpenoidal saponins, sapogenins, fructans, magnesium, potassium, calcium along with mucilage, polysaccharides and good amount of simple sugars (17). *C. borovillanum* was found effective in improving sexual behavior parameters in male albino rats in combination with *Asparagus racemosus* and *Curculigo orchoides*. This combination probably works through testosterone like effects or nitric oxide mediated arousal mechanism (18). Animal studies have proven its traditional claim to cure certain forms of sexual complications, such as decreased libido, premature ejaculation, erectile dysfunction and oligozoospermia (19).

4.2.8. *Caesalpinia benthiana*

Caesalpinia benthiana (Fabaceae) (Figure 2h) was earlier investigated for its antibacterial and antioxidant properties (20) and later in the same year its aphrodisiac, vasoactive and antioxidant properties were demonstrated in male rats. After oral administration of aqueous extract of *C. benthiana* (50mg/Kg BW), mounting behavior test and mating performance tests were conducted and found satisfactory to explore it as an aphrodisiac. The enhanced sexual activity is considered to act through nitric oxide production which leads to vaso-relaxation (21).

4.2.9. *Curculigo orchoides*

Curculigo orchoides also known as 'kali musli' belongs to family Amarylladaceae (Figure 2i) and is a well known aphrodisiac since ancient times and has a reputation in Indian traditional medicinal system especially in *Ayurveda* and in Chinese medicine. Ethanolic extract of rhizome (100 mg/kg BW/day) showed remarkable improvement in parameters of mating performance, sexual behavior and penile erection index in male rats. *C. orchoides* probably works through increase in the level of testosterone or some neurotransmitters; however, the mechanism of action is yet to be established. It has spermatogenic potential and increases weight of reproductive organs due to its anabolic effect (22). It improves sperm count in heat exposed rats as compared to heat exposed positive control group (23). It has potential aphrodisiac properties and requires more exploration for its mechanisms of action.

4.2.10. *Crocus sativus*

Crocus sativus belongs to family Iridaceae (Figure 2j) and its dried stigma known as saffron (kesar) is

used for medicinal purposes since ages and is famous as strong aphrodisiac among common man. *Crocus sativus* thrives in Mediterranean and especially cultivated in Iran. Saffron contains crocin, picrocrocin and safranal as its major constituents. In recent years, Iranian scientists have shown their interest in exploration of its aphrodisiac potential and reported positive effects of its use. Phytochemical constituents of this plant 'safranal' and 'crocin' were assessed for their aphrodisiac activity in male rats, and 'crocin' was reported as effective constituent especially at doses 160 and 320 mg/kg BW; however, safranal did not show its effect for the same parameters (24). The effect of saffron was also proven in erectile dysfunction (ED) patients by testing them on parameters of Nocturnal Penile Tumescence (NPT) and International Index of Erectile Function (IIEF) (25). A very recent study on 346 ED patients did not support its effect against ED and left the field open for further testing and exploration of Saffron (26).

4.2.11. *Coryanthe yohimbe*

Yohimbine (Figure 1f) is obtained from the bark of *Coryanthe yohimbe*, a member of family Rubiaceae (Figure 2k). It has been a source of aphrodisiacs since long back. Yohimbine history is old and in last three decades several studies has been conducted to establish yohimbine as a star aphrodisiac. Yohimbine hydrochloride was found effective in decreasing latency time and increasing mounts as compared to vehicle in aged male rats (27). It is an alpha 2-adrenoceptor blocker and used against erectile impotence as evidenced by increased mounts and increased ejaculation in mating test with rats as well as increased copulatory behavior in sexually inactive rats (28). Meta - analysis of few studies has supported yohimbine as an aphrodisiac with fewer side effects in human subjects (29).

4.2.12. *Camellia sinensis*

Camellia sinensis which is commonly known as 'tea' belongs to family Theaceae (Figure 2l) and is claimed to be a potent herbal aphrodisiac especially by Sri Lankan herbal practitioners. Black tea brew of *C. sinensis* is a good sexual stimulant and delays premature ejaculation, shortens mounting and intromission latencies and elevates the serum testosterone level as tested during sexual behavior experiments. *C. sinensis* is non-toxic and probably works through suppression of anxiety and increase in testosterone level (30).

4.2.13. *Dactylorhiza hatagirea*

Dactylorhiza hatagirea is a plant of family Orchidaceae and its bulbous roots are used as sexual stimulant as well as nutritive and restorative tonic (Figure 2m). Aqueous extract of its roots was evaluated for sexual behavior parameters and spermatogenesis in male rats. Induced steroidogenesis (especially T) and significant anabolic effect was correlated with increased body and reproductive organs weight. The treated groups were found to have decreased post ejaculatory interval and considered to involve nitric oxide based mechanism. Significant reduction in mount latency, intromission latency and post ejaculatory latency was observed during sexual behavior study such that overall effect was comparable to

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testosterone treatment (5). Such plants are great hope as natural aphrodisiacs and may replace artificial testosterone treatment in near future.

4.2.14. *Eurycoma longifolia*

Eurycoma longifolia locally called 'Tongkat Ali' is a shrub of family Simaroubaceae (Figure 2n) and is commonly found in the forests of Southeast Asia. Over the years this plant has been reported as a potent aphrodisiac. *Eurycoma* has been found to be a potent herb in activating orientation effects in sexually experienced male rats towards receptive females (31). The root powder of this plant is effective in improving sexual performance in sluggish rats after oral administration of acute (250, 500, 1000 mg/kg BW/day) and sub-acute (500 mg/kg BW/day) doses (32). Animal studies have shown that it promotes the growth of accessory reproductive gland e.g. prostate and seminal vesicle as compared to control and is effective in improving sexual performance (33). The effect of *Eurycoma* was also evaluated in old and retired breeder rats while they were assessed for sexual arousal. The aphrodisiac effect was evaluated on the basis of yawning and stretching as these are evolutionary conserved markers of sexual arousal. Yawning and stretching parameters were found positive at a dose of 800 mg/kg BW/day (34). In studies on this plant, different parameters of sexual behavior provided enough support to its use this as an aphrodisiac. However, its further investigation and exploration through clinical trials is required to reach full-proof conclusion.

4.2.15. *Ferula hermonis*

Ferula hermonis is a small shrub of family Apiaceae (Figure 2o) and is very famous in natives of Lebanon, Syria and Jordan. In an animal trial, an interesting stimulatory effect on sexual behavior and libido in male rats was observed with methanol extract of this plant, and a relatively low effect with water extract. However; investigators reported a significant reduction in sexual vigor (decrease in MR) and sexual performance (Decrease in IR and increase in IL) with petroleum ether and ethyl acetate extract as compared to control (35). Its active constituents, ferutinin, teferdin and teferin were tested in male rats for their influence on sexual behavior parameters. Only acutely administered (2.5 mg/kg BW/day) ferutinin (Figure 1h) reduced mounting and intromission latencies in sexually potent rats. Repetition of the same experiment in sexually sluggish/impotent rats showed same results with 'ferutinin' while 'teferdin' exhibited reduction in ejaculation latency. 'Ferutinin' and 'teferdin' also increased the level of testosterone in a significant manner (36).

4.2.16. *Fadogia agrestis*

Fadogia agrestis is a shrub that belongs to family Rubiaceae (Figure 2p) and can be seen in Nigerian region and is claimed to be an aphrodisiac helpful in management of erectile dysfunction. Identification of phytochemical constituents reported the presence of alkaloids and saponins as major and anthraquinone and flavonoids as minor constituents. Aqueous extract of *Fadogia agrestis* at doses 18 mg/Kg, 50 mg/Kg and 100 mg/Kg BW/Day were tested in male rats for sexual behavior parameters and testosterone

level. At all doses significant change in sexual behavior parameters was noted as there was increase in mounting frequency and intromission frequency, and reduction in mounting latency and intromission latency along with prolonged ejaculatory latency. Serum testosterone level was found to increase in a dose dependent manner. Therefore, this plant finds place in the list of potent aphrodisiacs available for further animal and clinical trials (37).

4.2.17. Ginseng

Ginseng is basically the root which belongs to genus *Panax* and family Araliaceae (Figure 2q) and its two well known forms are *Panax quinquefolium* (American ginseng) and *Panax ginseng* (Asian /Korean/Chinese ginseng) (38). On the basis of roots processed, two forms of ginseng, viz. white ginseng and red ginseng are commercially available. Due to its popularity, some other plants similar in properties are called as local ginseng or native ginseng of that particular region. For example, *Withania Somnifera* is also called as Indian ginseng and *Trichopus zeylanicus* is popularly called as ginseng of Kerala in South India. Ginseng contains ginsenosides namely Rb1 (Figure 1d) and Re (Figure 1e) (derived from *P. ginseng*) and trilinolein which is a triacyl glycerol with linolenic acid (39). Various animal studies have elicited that ginsenosides and trilinolein are effective in nitric oxide mediated vasorelaxation (40, 41, 42). A clinical study on 90 patients confirmed that Korean red ginseng is effective in enhancing libido, penile erection and sexual performance (43). Ginsenosides act through i-NOS mediated nitric oxide release in endothelial cells along with its direct effect on the same via increased Ca^{2+} ion concentration (44).

4.2.18. *Lycium barbarum*

Lycium barbarum is a Chinese medicinal plant that belongs to family Solanaceae (Figure 2r) and has earned reputation throughout Asia and is commercially described as "Red Diamonds". This plant has been a traditional remedy for male sexual dysfunction. Polysaccharide is an important phytochemical constituent of this plant which is thought to be responsible for its medicinal properties. *L. barbarum* polysaccharides were tested on rat testis damaged artificially by exposure to high temperature (43°C) and DNA damage induced by H_2O_2 in mouse testicular cells; reporting significant improvement as compared to negative control of the related group. The fraction stimulated significant weight increase in testis and epididymis of rats along with better superoxide dismutase activity and improved gonadal hormone levels. The polysaccharide fraction was also found effective against DNA damage in a dose dependent manner in mouse testicular cells. Apart from the above, this fraction also improved sexual performance and well-coordinated secretion and increased the level of sexual hormones in hemi castrated male rats (45). The scientific evidence presented above makes this plant a good choice for further investigation.

4.2.19. *Lepidium meyenii*

Lepidium meyenii, famous as 'Maca' is a member of family Brassicaceae and the root of this herb is used in

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Andean folklore medicine to cure male sexual dysfunction (Figure 2s). It thrives especially in South America and is called as 'Peruvian' or 'Andean ginseng'. Due to its long history and its supposed traditional use as aphrodisiac backed by its proven effect in animal and clinical trials; 'Maca' products are very popular and commercially available under different trade names viz., Royal Maca, Maca 750, Maca magic, Maca Andina, Vimaca, Eregma power, MACA (46). There are many supportive animal studies data which claim 'Maca' to be potent aphrodisiac. Tremendous activity of 'Maca' is due to its unique composition / combination of essential amino acids, fatty acids, vitamins and minerals like iodine, iron, calcium, manganese, magnesium etc. along with alkaloids, steroids, glucosinolates, isothiocyanates and macamides. In a recent double blind clinical trial, 50 men suffering from mild erectile dysfunction were treated with 2400 mg Maca dry extract per individual, along with a placebo group. After 12 weeks of treatment, Maca as well as placebo treated patients were reported to have significant increase in International Index of Erectile Function-5 (IIEF-5) and psychological performance related satisfaction score (SAT-P) score, but it was more in Maca treated group than that of placebo. However, physical and social performance related satisfaction score SAT-P was significant only in Maca group (47). The mechanism by which it plays its role as aphrodisiac has been subject of exploration for many investigators. A study demonstrated that Maca extract does not interact with androgen receptor and it has no direct androgenic activity (48). The hypothesis that Maca acts by modulation of hypothalamic-pituitary axis through regulation of hormone secretion and balance was also found to be not true up to large extent as Maca was found to have no impact on gonadal hormone levels viz. FSH, LH, testosterone, estradiol and prolactin (49). Therefore, exact path of its mechanism is yet to be established before it could be considered for human fertility programme.

4.2.20. *Microdesmis keayana*

Microdesmis Keayana, a plant from Pandaceae family (Figure 2t), has history of its use for erectile dysfunction, but the responsible phytochemicals for this action are subject to exploration now – a - days. The isolated and identified major alkaloids from roots of *M. Keayana* were 'Keayanidine B' and 'Keanine' (50). Later the same group evaluated its aqueous extract and alkaloids for parameters of sexual behavior in male rats and observed better sex stimulating action (51). ROS scavenging and vasorelaxation property through e-NOS pathway is considered to be its mechanism of aphrodisiac action (52).

4.2.21. *Montanoa tomentosa*

Montanoa tomentosa (chihupati) of family Asteraceae (Figure 2u) has been used as an aphrodisiac in ethno-medicine and is a candidate plant for exploration as aphrodisiac. The claim of its aphrodisiac action was found authentic as the aqueous crude extract of *M. tomentosa* is effective in sexual arousal and stimulation of mounting behavior in animals compromised by anesthesia in genital area as well as in non-copulating males (53). In another study, this plant was evaluated for its pro-sexual and pro-

ejaculatory activities and was found helpful in inducing ejaculatory motor pattern and sexual potency in spinal male rats (54).

4.2.22. *Mucuna pruriens*

Mucuna pruriens Linn. a member of family Papilionaceae has been a treatment for male sexual debilities since ancient times (Figure 2v) (55). This plant is a rich source of alkaloids such as prurienine, prurieninine, prurienidine as well as triterpenes, sterols and amino acids. A sexual behavior study was performed to validate traditional claims for its aphrodisiac activity and rats were administered ethanolic extract of *M. pruriens* a 150,200,250 mg/kg BW/day dose for 45 days. 200mg/kg was reported to have with significant activity in improving sexual behavior correlated with significantly increased mounting frequency, intromission frequency and ejaculatory latency and reduced mounting latency and intromission latency as compared to controls. *M. pruriens* also improved sperm count and motility along with increased testicular and epididymal weight (56). Later, effect of *M. pruriens* was observed in diabetic rats on sexual behavior parameters. Ethanolic extract of seeds at dose 200 mg/kg BW/day was found significant in improving sexual behavior, libido and potency along with spermatogenic potential. This plant has bright scope to be considered as potent aphrodisiac after animal and clinical trials (57).

4.2.23. *Mondia whitei*

Mondia whitei is an aromatic woody climber belonging to family Periplocaceae (Figure 2w). In an animal experiment, Lampiao et al found *M. whitei* to be effective in stimulating a significant increase in serum and testicular testosterone levels, testicular protein and sperm density in cauda epididymis in rats. *M. whitei* has been found to reduce alpha-adrenergically stimulated contraction in corpus cavernosum tissue in guinea pig and has the property of inducing and maintaining penile erection as it relaxes cavernous smooth muscles. The cavernosum smooth muscle relaxation does not work through nitric oxide mechanism as a non-specific nitric oxide synthase inhibitor NG-nitro-L-arginine methyl ester (L-NAME) did not affect the relaxation. It is also helpful in improving total sperm motility and can solve the problem of asthenozoospermia as well (58, 59). *M. whitei* aqueous extract at 400 mg/kg BW/day dose for 8 days of treatment was found effective in inducing serum and testicular testosterone level, testicular protein and sperm density in cauda epididymis (60). A sexual behavior study conducted in male wistar rats reported decrease in mounting latency and hexane extract was found more efficient than aqueous extract (61). This plant has enough animal data for its trial in human subjects.

4.2.24. *Passiflora incarnata*

Passiflora incarnata Linn. the member of family Passifloraceae (Figure 2x), is well known for its sedative, adaptogenic, analgesic and anxiolytic activity and enough ancient literature is available for supporting medicinal properties. Later aphrodisiac feature was explored and a study reported that Benzoflavone (BZF) moiety isolated

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from *P. incarnata* is effective in protection of fertility activities against THC (Δ 9-tetrahydrocannabinol) induced reduction in libido, sperm count and mating performance parameters. Of the two trial doses (10 mg/kg BW and 20 mg/kg BW), 20 mg/kg BW was found to be the appropriate dose. BZF is strongest aromatase enzyme inhibitor and it prevents the metabolic breakdown of testosterone into estradiol; thus making available the free plasma testosterone which in turn stimulates gonadotropins (LH and FSH), resulting ultimately in improved spermatogenesis, libido and other fertility parameters. BZF moiety of *P. incarnata* is also capable of reversing addictive drug induced suppression in sexuality. It is thought to act through neuro-steroidal mechanism (62). Methanolic extract of leaves was evaluated for its aphrodisiac behavior in male rats at doses 75, 100 and 150 mg/kg and 100 mg/kg was found to show maximum activity levels (63). *P. incarnata* could be a good future aphrodisiac after human trials in a systematic manner.

4.2.25. *Securidaca longepedunculata*

Securidaca longepedunculata is a herb that belongs to family Polygalaceae (Figure 2y). This plant was investigated for its aphrodisiac activity by an in vitro study evaluating its effect on the relaxation of corpus cavernosum smooth muscle. Chloroform extract of root bark exhibited maximum concentration activity at 13 mg/ml dose and induced almost 67 % relaxation as compared to Viagra which was used as a positive control for this experiment (64). Later, among the fractions of this plant, 2-hydroxy-1, 7-dimethoxy xanthone was found potent to relax cavernosum smooth muscle cell in a specific in vitro assay (65).

4.2.26. *Syzygium aromaticum*

Syzygium aromaticum (family Myrtaceae) is the dried flower bud, popularly known as clove (Figure 2z), finds use as a spice in cuisine and in traditional system of Indian and Chinese medicine. Essential oil extracted from clove having eugenol (Figure 1g) as the chief constituent is used for different purposes particularly as medicine. It has antibacterial, antioxidant, antifungal, antiviral, antitumor and insecticidal properties which makes it important among medicinal plants domain. 50% ethanolic extract of *Syzygium aromaticum* along with 50% *Myristica fragrans* is effective in stimulating sexual behavior in male mice (66). Evaluation of 50% ethanolic extract of clove for sexual behavior parameters and libido test showed promising results for all the associated parameters against control with no adverse side effects (67). *S. aromaticum*, therefore, could be a good option to explore as aphrodisiac and may be a candidate for human trials.

4.2.27. *Tribulus terrestris*

Tribulus terrestris (family Zygophyllaceae) (Figure 2aa) has been used in traditional system of medicine for treatment of various diseases particularly sexual dysfunctions in men. Efficacy of its extract, protodioscin (PTN) (Figure 1i), in the sexual behavior study on normal and castrated adult SD rats claimed it to be a potent aphrodisiac. The study suggested that it works probably through androgen enhancement and nitric oxide

release from nerve endings of corpus cavernosum tissue (68, 69). Another study on male rats reported increased androgen receptor and NADPH-d positive neurons which were probably due to its androgen enhancing properties (70). In contrast to the above, another study on human subjects reported that *T. terrestris* is not involved in either direct or indirect androgen enhancing properties. This plant therefore needs to be further explored further for its aphrodisiac properties and possible mechanism of action.

4.2.28. *Turnera diffusa*

Turnera diffusa is an aromatic plant of family Turneraceae (Figure 2ab) and thrives in Mexico, Central America, some regions of South America and West Indies. Caffeine, arbutine, luteolin, apigenin, damianine, acacetin, sodium gluconate, gonzalitozin and flavonoids are the principle constituents found in the active extract of *T. diffusa*. A study more than a decade back established it as an aphrodisiac and supported its traditional reputation as a sexual stimulant when its fluid extract used alone or in combination with a shrub *Pfaffia paniculata* improved the sexual performance of the sexually sluggish or impotent animals (71). Aqueous extract of *T. diffusa* was found effective in recovery of sexual desire/motivation in sexually exhausted rats. Experiments on sexual behavior exhibited improved sexual performance in sexually exhausted male rats (72). Probably its flavonoid content affects the libido and sexual performance via their effects on central nervous systems; however, the exact mechanism of action is yet to be established.

5. DISCUSSION

Medicinal plants are the invaluable wealth provided by the nature to animals and human beings. The era of medicine began with the identification of medicinal properties of plants and animals. It was only after exploring these natural sources that we could synthesize chemical entities in the laboratory to help produce the medicinal compounds at a much faster rate. A number of drugs have been synthesized in the laboratory taking clue from natural resources and the latter are still the most important drug repositories. It is surprising that we have explored only 1% of the natural medicinal resources available to us. Most of the medicinal plants which find mention in the ancient literature are still being used; however, their use is restricted to certain areas of the world depending upon their initial use. This knowledge is not widespread due to lack of appropriate scientific research supporting their claimed medicinal properties. Therefore, on the basis of the ancient literature, traditional practitioners and experience based claims, scientists are now looking to explore our entire ancient medicinal database. As detailed above, the laboratory research has often supported the said claims.

In this review, we explored the existing literature on medicinal plant and animal based resources to provide an update on their use to cure male erectile dysfunction and related sexual debilities. Although many synthetic aphrodisiacs in the form of PDE-5 inhibitors are available; however, identification of a natural aphrodisiac is always desirable given no or little side effects of natural resources.

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Table 1. Potent aphrodisiac plants to cure erectile dysfunction

Aphrodisiac Plant	Family	Parts Used	Major Constituent	Experimental Model	Possible mode of action
<i>Allium tuberosum</i>	Alliaceae	Seeds	Steroidal saponin and Alkaloids	Rat	---
<i>Alpinia calcarata</i>	Zingiberaceae	Rhizome	---	Rat	Testosterone production
<i>Astercantha longifolia</i>	Acanthaceae	Seeds	---	Rat	Testosterone and fructose production, stimulation of accessory reproductive glands
<i>Anacyclus pyrethrum</i>	Asteraceae	Roots	---	Rat	Testosterone production? Nitric oxide induction?
<i>Bulbus natalensis</i>	Asphodelaceae	Stem	Glycosides, Tannins, Anthraquinones, Alkaloids and Saponins	Rat	GnRH-LH signaling? testosterone production? vasorelaxation?
<i>Butea frondosa</i>	Papilionaceae	Bark	---	Rat	Testosterone production
<i>Chlorophytum borivilianum</i>	Liliaceae	Roots	Saponins and Sapogenins	Rat	Testosterone production?, nitric oxide release?
<i>Caesalpinia benthamiana</i>	Fabaceae	Roots	---		Vasorelaxation, nitric oxide release
<i>Curculigo orchioides</i>	Amaryllidaceae	Rhizome	---	Rat	Testosterone production? nitric oxide induction?
<i>Crocus sativus</i>	Iridaceae	Stigma	Crocin	Rat, Human	---
<i>Corynanthe yohimbe</i>	Rubiaceae	Bark	Yohimbine	Rat, Human	CNS and PNS activation, alpha 2-adrenoceptor antagonism
<i>Camellia sinensis</i>	Theaceae	Leaves and leaf buds	---	Rat	Suppressed anxiety? testosterone production?
<i>Dactylorhiza hatagirea</i>	Orchidaceae	Roots	---	Rat	Testosterone production, nitric oxide induction?
<i>Eurycoma longifolia</i>	Simaroubaceae	Roots	Quassinoids, Squalene derivative	Rat	Stimulation of accessory reproductive glands
<i>Ferula hermonis</i>	Apiaceae	Whole plant	Ferutin and Teferdin	Rat	Testosterone production
<i>Fadogia agrestis</i>	Rubiaceae	Stem	Alkaloids, Saponins and flavonoids	Rat	Testosterone production
Ginseng	Araliaceae	Roots	Ginsenoside and Trilinolein	Rat, Human	Nitric oxide release, testosterone production, inhibition of prolactin
<i>Lycium barbarum</i>	Solanaceae	Fruits	Polysaccharides	Rat, Mouse	ROS Scavenging, gonadal hormone production
<i>Lepidium meyenii</i>	Brassicaceae	Roots	---	Rat, Human	Testosterone production, stimulation of accessory reproductive glands, nitric oxide production
<i>Microdesmis keyana</i>	Pandaceae	Roots	Keayanidine and Keayanine	Rat	ROS Scavenging, nitric oxide production, vasorelaxation?
<i>Montanoa tomentosa</i>	Asteraceae	Leaves	---	Rat	---
<i>Mucuna pruriens</i>	Papilionaceae	Seeds	Prurienine, Prurienidine, Triterpenes and Sterols	Rat, Human	GnRH signaling
<i>Mondia whitei</i>	Periplocaceae	Roots	Glucosides and Alkaloids	Rat, Guinea pig	Testosterone production, corpus cavernosum relaxation
<i>Passiflora incarnata</i>	Passifloraceae	Whole plant	Benzoflavone	Mouse, Rat	Stimulation via anxiolytic property, Aromatase inhibition, testosterone production, neurosteroidal regulation
<i>Securidaca longepedunculata</i>	Polygalaceae	Root Bark	Xanthones	Rabbit	Corpus cavernosum relaxation
<i>Syzygium aromaticum</i>	Myrtaceae	Bud	Eugenol	Rat	---
<i>Tribulus terrestris</i>	Zygophillaceae	Whole Plant	Protodioscin	Human, Rat, Mouse	Androgen enhancement?, nitric oxide release?
<i>Turnera diffusa</i>	Turneraceae	Leaves	Caffeine, Arbutine, apigenin, damianine, gluconate and flavonoids	Rat	Vasorelaxation, nitric oxide release?

The PDE-5 inhibitors though effective, sometimes cause mild to severe side effects such as headache, flushing, dyspepsia and blurred vision (73). Normal reproductive health and fertility is a subject of well co-ordinated neural, hormonal, vascular and psychological system (74). A major problem in cure of erectile dysfunction and male sexual debilities is their complex nature as they work in coordination with other organs such that malfunctioning of

one affects the other, making it difficult to diagnose the exact system in crisis. The existing knowledge about natural aphrodisiacs is not good enough to reach the level of human trial in spite of promising results in animal trials. The human system is far complex than animal models in several aspects and more trials preferably on human subjects would yield strength to such findings. The treatment for human beings differs according to the kind of

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problem, severity level, age group, ethnicity and other existing disease/disorders such as diabetes, hypertension and cardiovascular problems etc. (75). Only a few plants have been properly investigated, while most others need proper investigation to understand their efficacy and mechanism of action. This could help us establish them as aphrodisiacs beyond a patterned study of mating behavior /sexual performance. To further characterize and understand the aphrodisiacs, the type of extract is most important. For example, in case of *Ferula hermonis*, only methanolic extract was active, and petroleum and ethyl extract showed opposite effect on sexual activity. Apart from efficacy and mechanism, other parameters such as plant part, dose, duration of therapy etc. also need to be standardized.

Aphrodisiacs apart from increasing libido and sexual performance could also help treat male infertility. Male infertility in a significant number of cases is not related to sperm count or motility. Significant proportions of infertile male individuals display normal semen parameters and are classified as normozoospermic infertile men. The sperm count in these individuals is sometimes higher than normal fertile counterparts. However, there are other unidentified parameters which render them infertile. One of several such possible parameters could be related to lack of erection good enough for sperm deposition deep into the vagina enabling the sperm reach and fertilize the ovum. The failure to achieve erection during sexual intercourse could lead to psychological impotence resulting in infertility. Such cases could otherwise have normal fertility parameters and their sperm do well in assisted reproductive techniques. Use of aphrodisiacs in such cases could help the patients get rid of anxiety and fears of sexual intercourse, enabling them achieve fatherhood. Use of natural aphrodisiacs could be further advantageous as most of the plants are good sources of anti-oxidants. The antioxidant could help fight damage caused by reactive oxygen species enabling improve the sperm quality, thereby increasing the chances of fertilization several folds.

Most of the aphrodisiac plants improve sexual efficiency but different botanicals differ in their specific mode of action to small or large extent. They are considered to act through different mechanisms such as NO and cGMP signaling along with NOS expression (i/eNOS), increase in LH and FSH secretion and decrease in prolactin level, increase in testosterone level, co-ordination of central, sympathetic and parasympathetic nervous system which ultimately leads to improved sexual performance by increasing libido and penile erection (Table 1). Sometimes psychological/behavioral therapy can supplement the effect of aphrodisiac to reduce anxiety, depression and stress, guilt and fear of sexual failure that affects sexual behavior and function. We have reviewed the literature regarding plant and animal based aphrodisiacs. We have a large repertoire of plant based resources for management of male sexual debilities but most of them need further investigation to understand their phytochemistry, pharmacognosy, pharmacokinetics and targets of their active constituents. It is only after thorough understanding

of these parameters that we could recommend them for human use.

6. CONCLUSION

Male sexual dysfunction and related sexual debilities arise as a result of various physiological, psychological and clinical factors. Aphrodisiac plants are in demand to cure erectile dysfunction and have the promise to replace very costly and less safe synthetic aphrodisiacs. The most important issue at present is investigation of more aphrodisiac plants followed by isolation and identification of their active constituents. More precise and properly oriented animal and clinical trials are needed to evaluate aphrodisiac activity related parameters along with safety studies. A better approach with inclusion of pharmacology, pharmacokinetics and pharmacodynamics is required to avoid any controversy about activity and efficacy of these resources. Further research on active constituents, possible modes of action, and pathways involved could help us identify promising natural aphrodisiacs which could be a milestone in the management of male sexual dysfunction.

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