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Review

Medicinal plants as a potential source of Phosphodiesterase-5 inhibitors: A review

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ABSTRACT

Ethnopharmacological relevance: The prevalence and distress caused by erectile dysfunction (ED) to both male and female partners are increasing at a steady rate. ED has now become the most treated sexual disorder for men among young and old age groups due to varying physical and psychological factors. The treatment with synthetic Phosphodiesterase-5 (PDE5) inhibitors are cost-effective but due to adverse effects such as priapism, loss of vision, heart attack and syncope, the daily life patterns of these patients are distressed and hence the need for alternative medicaments or sources are of utmost important. Therefore, the exploration of medicinal plants as PDE5 inhibitors will be worthwhile in tackling the problems as many plant extracts and fractions have been long used as aphrodisiacs and sexual stimulants which may be found to be active against PDE5 enzyme.

Aim of the study: To provide a review on the different medicinal herbs traditionally used as natural aphrodisiacs, libido or sexual enhancers which are proven for their PDE5 inhibitory effect.

Materials and methods: Ethnobotanical and scientific information was procured, reviewed and compiled from the literature search of electronic databases and search engines.

Results: A total of 97 medicinal plants exhibiting PDE5 inhibitory effect are reviewed in this paper which is supported by preclinical experimental evidence. Among them, 77 plants have been selected according to their traditional and ethnobotanical uses as aphrodisiacs and the rest are screened according to their effectiveness against predisposing factors responsible for ED and sexual dysfunction such as diabetes and hypertension or due to the presence of phytochemicals having structural similarity towards the identified natural PDE5 inhibitors. In addition, sixteen alkaloids, sixty-one phenolics and eight polycyclic aromatic hydrocarbons have been isolated or identified from active extracts or fractions that are exhibiting PDE5 inhibitory activity. Among them, isoflavones and biflavones are the major active constituents responsible for action, where the presence of prenyl group for isoflavones; and the methoxy group at C-5 position of flavones are considered essential for the inhibitory effect. However, the prenylated flavonol glycoside, Icariin and Icariside II isolated from *Epimedium brevicornum* Maxim (hory goat weed) are the most effective inhibitor, till date from natural sources. Traditional medicines or formulations containing extracts of *Ginkgo biloba* L., *Kaempferia parviflora* Wall. ex Baker, *Clerodendrum colebrookianum* Walp., *Eurycoma longifolia* Jack and *Vitis vinifera* L. are also found to be inhibitors of PDE5 enzyme.

Conclusion: The review suggests and supports the rational use of traditional medicines that can be further studied for the development of potential PDE5 inhibitors. Many traditional medicines are still used in various regions of Africa, Asia and South America that are poorly characterized and experimented. Despite the availability of a vast majority of traditional formulations as aphrodisiacs or sexual stimulants, there exists a need for systemic evaluation on the efficacy as well as the mechanism of action of the herbal constituents for the identification of novel chemical moieties that can be further developed for maximum efficacy.

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Table 1
Different PDE families, their substrate (s) and distribution in the human body.

PDE family	Substrate	Distribution
PDE1	cAMP/ cGMP	Brain, lung. heart, smooth muscle
PDE2	cAMP	Heart, liver, lung, adrenal gland, platelets, endothelial cells
PDE3	cAMP	Smooth muscle, lung, liver, platelets, adipocytes, immunocytes
PDE4	cAMP	Kidney liver, heart, brain, lung, smooth muscle cells, endothelial cells, immunocytes
PDE5	cGMP	Smooth muscle cells, heart, lung, endothelial cells, brain
PDE6	cGMP	Pineal gland, photoreceptors, lung
PDE7	cAMP	Heart, kidney, skeletal muscle, T lymphocytes, pancreas
PDE8	cAMP	Eyes, liver, kidney, ovary, brain, testes, skeletal muscles, lymphocytes, thyroid
PDE9	cGMP	Brain, liver, lung, kidney
PDE10	cAMP/ cGMP	Thyroid, brain, testes
PDE11	cAMP/ cGMP	Prostate, skeletal muscle, liver, pituitary gland, heart

1. Introduction

1.1. History and significance of PDE5 inhibitors

Theophylline, a xanthine alkaloid has been long used as a phosphodiesterase (PDE) inhibitor without any knowledge of its biochemical action. But in 1958, the use of Theophylline as a selective PDE inhibitor was found and led to innumerable pharmacological investigations aside from its adverse effects (Truss et al., 1996). Cyclic adenosine monophosphate (cAMP) was identified as a second messenger signaling in biological processes and PDE was found responsible for its breakdown, thereby paving the way for PDE inhibition. However, both cAMP and cyclic guanosine monophosphate (cGMP) control the regulation of vascular and airway smooth muscles as well as the muscle tone of myocardium (Card et al., 2004; Koitabashi et al., 2010; Truss et al., 1996).

The PDE enzymes are synthesized from respective membrane-bound or soluble adenylate or guanylate cyclases by their corresponding nucleoside triphosphates. The phosphodiesterase enzymes are a ubiquitous group of hydrolytic enzymes that cleave the 3′-ribose-phosphate bond of cAMP and cGMP (Card et al., 2004). Due to the considerable variations of their isoenzymes and their role in the regulation of cyclic nucleotides, the identification of PDE inhibitors have been narrowed down to selective or partially selective inhibitors. The list of reported families of PDE isoenzymes, their substrates and distribution are given in Table 1 (Keravis and Lugnier, 2012; Ückert and Oelke, 2011). However, only six PDE enzymes have been reported to show any pharmacological significance, they are PDE1, PDE2, PDE3, PDE4, PDE5 and PDE11.

PDE5 isoenzyme inhibitors have been targeted due to its wide range of biological effects as it activates guanyl cyclase (GC) and thereby increasing guanosine monophosphate (GMP) synthesis which in turn, activates certain proteins and results in different pharmacological actions like neuronal plasticity, gene transcription, smooth muscle relaxation, cardiac protection and endothelial permeability. For 80 years, theophylline was used as a non-selective PDE5 inhibitor but many selective inhibitors have been made available in the past 15 years. Zaprinast was an unsuccessful drug candidate (Keravis and Lugnier, 2012) related to the first selective PDE5 inhibitor, Sildenafil marketed by Pfizer Inc. as Viagra ™ for the treatment of male erectile dysfunction (Jiann, 2016). After the identification of Sildenafil, more effective PDE5 inhibitors were developed such as Tadalafil (Cialis ™, Lilly-ICOS), Vardenafil (Levitra ™, Bayer-GSK) and Avanafil (Stendra, Vivus Inc.) (Yafi et al., 2018). The major significance of PDE5 inhibitors is its effectiveness against cardiovascular diseases, pulmonary hypertension, altitude sickness and memory dysfunction (Lee and Kass, 2012; Ückert and Oelke, 2011); improves systolic heart function, cardiac geometry, left ventricle diastolic function, inhibition of breast tumor growth activity, lower urinary tract symptoms and treatment of benign prostatic hyperplasia (Barone et al., 2017; Corinaldesi et al., 2016; Jiann, 2016).

Table 2
List of PDE5 inhibitors, their application and adverse effects.

Marketed PDE5 inhibitors	Applications of PDE5 inhibitors	Adverse effects of PDE5 inhibitors
Sildenafil (Viagra) Vardenafil ODT (Staxyn) Tadalafil (Cialis) Avanafil (Stendra) Vardenafil (Levitra)	Erectile dysfunction Vascular arterial thrombosis Pulmonary hypertension Raynaud disease Peyronie disease Benign Prostatic Hyperplasia (BPH) Pulmonary vascular diseases Cardioprotective Lower urinary tract symptoms (LUTS)	Dyspepsia Myalgia Headache Flushing Cyanopsia Runny nose Angina pectoris Myocardial infarction Arrhythmias Hypertension Priapism Hearing loss Vision loss, NAION

The control of penile erection through the relaxation of corpus cavernosum by the vasodilation effect of nitric oxide (NO) is one of the major uses of PDE5 inhibitors against erectile dysfunction. The effectiveness of PDE5 inhibition therapy for erectile dysfunction is based on the International Index of Erectile Function (IIEF) which denotes 80–85% improvement in erections when performed on male patients having hypertension, postprandial prostatectomy, diabetes mellitus, organic, psychogenic, or mixed causes of ED (Maschi et al., 2008). But reports suggest that the use of PDE5 inhibitors were unable to restore a normal sexual life in 40–50% of the patients where the outcome improved with repeated daily dosing which led to major side effects such as headache, dyspepsia, myalgia, back pain, flushing, cyanopsia, runny nose, angina pectoris, myocardial infarction, arrhythmias, hypertension, priapism, loss of hearing and non-arteritic anterior ischemic optic neuropathy (NAION) that are reported in post-marketing studies (Balhara et al., 2015; Bourin, 2018; Gurney et al., 2011; Moreira et al., 2000; Yafi et al., 2018). Such that the FDA in July 2005 recommended discontinuing any usage of PDE5 inhibitors but in October 2007, FDA requested to include the potential risks to be displayed on the labels for PDE5 inhibitors (Kouvelas et al., 2009). Furthermore, additional reports also suggest the increased expression of PDE5 and PDE9 during aging and in case of Alzheimer's disease, indicating that memory-related disorders can also be treated through the use of PDE5 inhibitors (Puzzo et al., 2008). Despite the overall advancements in PDE5 research, there exists a need for new PDE5 inhibitors with less toxicity and adverse effects where the utilization of medicinal plants as a source for effective targets will be worthwhile as they have provided with competent pharmacophores.

1.2. PDE5 inhibition and erectile dysfunction

Erectile dysfunction or impotence occurs when a man is not able to get or keep an erection firm for sexual intercourse. The reported predisposing factors for causing ED can be both physical and psychological causes such as stress, anxiety, heart disease, diabetes, hypertension, hypercholesterolemia, obesity, diabetes, tobacco use, alcoholism, and sleep disorders (Ajiboye et al., 2018). The preventive measures for ED are to develop healthy lifestyle changes such as management of risk factors, regular medical check-ups, exercise, stress reduction and maintenance of a healthy mental state. However, there are cases of ED that cannot be managed through these lifestyle changes alone and hence require the support of other treatment methods or medications such as PDE5 inhibitors (Raheem et al., 2020). Some of the marketed PDE5 inhibitors that are used against ED are given in Table 2. The mechanism of PDE5 inhibition regarding ED is explained below.

Table 3
Medicinal plants that are reported to inhibit PDE5 enzyme.

Sl. No.	Plant name	Family	Common name	Geographical location	Part used	Type of extract or fraction	Traditional use	Pharmacological properties	Experimental method	Active chemical constituent (s)	Other identified phytochemicals	References
1	*Aframomum melegueta* (K. Schum)	Zingiberaceae	African pepper or Alligator pepper	Western and Northern Africa	Seeds	Alkaloidal fraction	Used for treating body pain, sore throat, diarrhea, catarrh, rheumatism, improves penile rigidity and function.	Hepatoprotective, antimicrobial, anticancer, anti-inflammatory, antidiabetic, haematopoietic activities.	*In vitro* assay by using penile tissue homogenate. IC_{50} = 33.80 μg/mL	Senkirkine, angustifoline, undulatine, myristicin, safrole, lupanine	Gingerol, shogaol, paradol, gingeredione, zerumin A, dihydrogingerenone, (−)-arctigenin, (−)-buplerol	(Adefegha et al., 2017; Toh et al., 2019)
2	Anogeissus leiocarpus (DC.) Guill. & Perr.	Combretaceae	Chew-stick, African birch	Sudan, Senegal, Cameroon, Ethiopia and East Africa	Stem, bark	Aqueous and Dichloromethane extracts	Remedy for leprosy, diarrhea, psoriasis, cough, orodental hygiene, arterial hypertension	Antioxidant, anti-quorum sensing property, antimicrobial, anthelmintic, anti-plasmodial, trypanocidal, hepatoprotective.	The aqueous extract was evaluated by *in vitro* assay by using penile tissue homogenate (IC_{50} = 174.19 μg/mL). The dichloromethane extract inhibits the isolated PDE5 with $IC_{50} = 7.6 \pm 3.5$ μg/mL	NP	Gallic acid, chebulagic acid, chebulinic acid and ellagic acid cathecin, quercetin, isoquercetin, rutin, vitexin, kaempferol.	(Belemnabaab et al., 2013; Oboh et al., 2017b)
3	*Conium maculatum* L.	Apiacea	Poison hemlock	Parts of Africa, Asia and Europe	Aerial parts	Ethanol	Treatment of impotence, spasmodic disorders, nervous excitation, rheumatic pain; used as stomachic and helps to improve sex drive	Analgesic, anti-nociceptive, anti-inflammatory, local anaesthetic, neuromuscular blocker, skeletal muscle activator.	*In vitro* evaluation of Vertigoheel (a low dose combination for treating vertigo) by using PDE5 isolated from human platelets in relation to sildenafil as control	NP	Coniine, N-methyl-coniine, conhydrine, pseudoconhydrine, germacrene D, (Z)-β-ocimene, (E)-β-ocimene, Ergost-5-en-3 β –ol,	(Al-Snafi, 2016; Heinle et al., 2010)
4	*Vaccinium angustifolium* Aiton	Ericaceae	Wild low bush berry	Eastern and central Canada and north eastern parts of America	Berry	Wild blueberry diet	Antioxidant, cardioprotective, blood purifier, treatment of colic	Antioxidant, antidiabetic, hypolipidaemic, vasoconstrictor.	*In vivo* evaluation in spontaneously hypertensive rats with respect to sildenafil	NP	Rutin, quercetin-3-galactoside, quercetin-3-glucoside, quercetin 3-arabinoside, quercetin-3-rhamnoside, epicatechin, catechin	(Harris et al., 2007; Kristo et al., 2013)
5	*Berberis orthobotrys* Bien ex Aitch.	Berberidaceae	Ishkeen/churka	Indigenous to Pakistan and around areas of Gilgit-Baltistan	Roots	Butanol fraction	Treatment for wounds, liver problems, sore throat, leucorrhoea, kidney stone, swelling, and piles	Antifungal, insecticidal, antibacterial, antidiabetic, anti-inflammatory, antioxidant, anti-leishmanial, antitumor and anti-arthritic	*In vitro* evaluation by using isolated PDE5 from bovine aorta (IC_{50} value of 40.4 ± 2.6 μg/mL)	Berberine	Pakistanine, pakistanamine, aromoline, kalashine, chitraline, oxyacanthine, aromoline, β-sitosterol, sesamin	(Alamgeer et al., 2017; 2016; Khan et al., 2016)
6	*Aframomum danielli* (Hook. f.) K. Schum	Zingiberaceae	African cardamom, false cardamom, bastered melegueta	Western and Northern Africa	Seeds	Alkaloidal fraction	Relieving postpartum pain and as flavoring agent, and improve penile rigidity and function.	Anti-browning effects, anti-microbial, listericidal effect, hepatoprotective, anti-oxidant, nephrotoxic, immunosuppressive, genotoxic	*In vitro* assay by using penile tissue homogenate. IC_{50} = 7.24 μg/mL	Gingerdione, Senecionine, Echitamine, Theophylline, Myristicin, 13-Alphahydro rhombifoline, Undulatine, 6-Hydro undulatine	1,8-cineole, β-pinene, α-terpeniol, -(+)- limonene eugenol, phytylplastoquinone	(Adefegha et al., 2017; Adegoke et al., 2016)

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Table 3 (*continued*)

Sl. No.	Plant name	Family	Common name	Geographical location	Part used	Type of extract or fraction	Traditional use	Pharmacological properties	Experimental method	Active chemical constituent (s)	Other identified phytochemicals	References
7	*Clerodendron capitatum* (Willd)	Lamiaceae	Bleeding heart	Sudan, Tropical Africa	Roots	Methanol extract	Remedy for erectile dysfunction, headaches, epilepsy, memory disorders and malaria; also used as a condiment	Seratonergic, hypoglycemic, antilipidaemic, antioxidant, erectogenic, uternine stimulant, antidiarrhoeal, antinociceptive, antimicrobial	*In vitro* evaluation by using purchased PDE5 enzyme, ID_{50} value of 0.161 mg/mL	NP	NP	(Abdelwahab et al., 2012; Idoh et al., 2016)
8	*Cnidoscolus aconitifolius* (Mill.) I. M. Johnst.	Euphorbiaceae	Chaya	Yacatucan peninsula, Mexico	Leaves	Ethyl acetate fraction	Strengthen fingernails, darkening of hair, improves memory and brain function.	Anticonceptive, diabetic, jaundice, kidney pain, kidney stones, back pain, diuretic, vision enhancement, stimulant, laxative, warts, skin diseases, purgative, rheumatism, ulcers.	*In vitro* evaluation by using penile homogenate using sildenafil as standard	Amento flavone, hesperidin, protoca techuic acid, kaempferol, quercetrin, rutin	B-amyrin acetate, α-amyrin acetate, amyrenone	(Abayomi et al., 2014; Ajiboye et al., 2018)
9	*Derris scandens* (Roxb.)	Fabaceae	Jewel Vine	South east Asia, India along the Himalayan ranges and Australia	Leaf and Stem	95% and 50% Ethanol extracts	Treatment of Osteoarthritis, joint pain, diuretic, antidysentery, expectorant, antitussive, rejuvenating agent.	Antidermatophyte, antioxidant, vasorelaxant, anti-inflammatory, antidysentery, antiaging, antibacterial, antimicrobial.	*In vitro,* Leaf (95% Ethanol, IC_{50} = 11.43 μg/mL), Stem (95% Ethanol, IC_{50} = 7.33 μg/mL and 50% Ethanol, IC_{50} = 22.61 μg/mL); with respect to Sildenafil standard	Geni stein, derrisiso flavone A (IC_{50} = 9 μM), lupalbigenin, 4′,5,7-trihydroxybi prenylis oflavone (IC_{50} = 8 μM), scandenin, scandinone, scanderone, osajin[a] (IC_{50} = 4 μM)	Betulinic acid, scandenin, lupeol, β-amyrin, β- sitosterol and β-sitosterol glucopyranoside	(Chaichamnong et al., 2018; Puttarak et al., 2016)
10	*Clerodendrum colebrookianum* Walp.	Lamiaceae	East Indian Glory Bower	India, China, Bangladesh, Malaysia, Myanmar, Sri Lanka, Indonesia and Bhutan	NP	NP	Widely used as anti- hypertensive, blood purifier, antidote, diabetes, gastric disorders	Anti-hypertensive, hypolipidaemic, anti-inflammatory, antipyretic, analgesic, antimicrobial, antioxidant, hepatoprotective, CNS depressant, anthelmintic	*In silico*	Acteoside, martinoside and osmanthuside β6	Colebrin A-E, β-sitosterol	(Arya et al., 2018; Janmoni Kalita, 2012)
11	*Gingko biloba* L.	Ginkgoaceae	Maiden hair	China, Japan and Korea.	Leaves and seeds	Purchased dimeric flavonoids	Used for treatment of asthma, bronchitis, hearing loss, tuberculosis, stomach pain, skin diseases, anxiety, cognitive and	Alzheimer disease, neuroprotective, anti-inflammatory, anti-cancer, hepatoprotective, antioxidant.	*In vitro* evaluation of the dimeric flavonoids using sildenafil and zaprinast standard	Ginkgetin[a], IC_{50} = 0.59 μM; Sequoiflavone, IC_{50} = 19.9 μM; Amento flavone, IC_{50} = 11.7 μM;	Bilibalide, ginkgolide A, ginkgolide B, kaempferol, quercetin, myricetin, apigenin, luteolin, gingketina, gingkolic acid	(Dell'Agli et al., 2006; Kim et al., 2011; Mohanta et al., 2014)

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Table 3 (*continued*)

Sl. No.	Plant name	Family	Common name	Geographical location	Part used	Type of extract or fraction	Traditional use	Pharmacological properties	Experimental method	Active chemical constituent (s)	Other identified phytochemicals	References
							sexual dysfunctions.			Sciadopitysin, IC_{50} = 3.24 μM; Bilobetin, IC_{50} = 1.52 μM		
12	*Hunteria umbellata* (K. Schum) Hallier	Apocyanaceae	Osu, Erin, Nkpokiri	West and west-central Africa, Nigeria	Seeds	Aqueous extract	Treatment of yaws, stomachic, ulcers, dysmenorrhea, sexual dysfunction, diabetes mellitus, fever, leprosy.	Oxytocic effect, analgesic, antibacterial, hypoglycemic, antihyperlipidaemic, cardioprotective, anti-inflammatory, anti-oxidant,	*In vitro* evaluation using penile homogenate with IC_{50} value of 537.72 and 539.72 μg/mL	NP	Erinidine, ursolic acid, oleanolic acid, squalene	(Oboh et al., 2018b; 2017b)
13	*Cylicodiscus gabunensis* Harms	Mimosaceae	Okan, Denya	Nigeria, Ghana, Cameroon, parts of West and Central Africa	Stem bark	Lyophilized aqueous extract of bark.	Treat male impotence, stomach ache, malaria, headache, psoriasis, gastrointestinal disorders, rheumatism, also used as antiemetic	Antimicrobial, anti-diarrhoeal, antiplasmodial, antibacterial, antiplasmodial.	*In vitro;* IC_{50} of 611.35 μg/mL and 204.4 μg/mL using penile tissue homogenate	NP	Coumestoside C and D, β-amyrin-n-nonyl ether, cylicodiscic acid, gabunoside	(Molkulaires and Cylicodiscus, 1991; Oboh et al., 2018b, 2018a)
14	*Kaempferia parviflora* Wall. ex Baker	Zingiberaceae	Kra-chi-dam or Thai ginseng	Thailand, Malaysia, Sumatra	Rhizome	Ethanol extract	Treatment of peptic, duodenal ulcers, colic disorders, allergy, fungal infections and impotence.	Antiallergenic, antimutagenic, anti-inflammatory, antidepressant, antimicrobial, anticholinesterase, antiobesity, cardioprotective, anticancer.	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. IC_{50} = 12.24 ± 0.99 μg/mL	5,7-dimethoxy flavone[a], IC_{50} of 10.64 ± 2.09 μM; 5,7,4′-trimeth oxyflavone, IC_{50} of 37.38 ± 1.15 μM; 3,5,7-trime-thoxyflavone, IC_{50} of 16.32 ± 1.93 μM; 3,5,7,3′,4′-pentameth oxyflavone, IC_{50} of 30.41 ± 0.81 μM	5-hydroxy-7-methoxyflavone, 5-hydroxy-3,7-dimethoxyflavone, 5,3′-dihydroxy-3,7,4′-trimethoxyflavone	(Azuma et al., 2008; Saokaew et al., 2017; Temkitthawon et al., 2011)
15	*Acorus calamus* L.	Acoraceae	Sweet flag	China, India	Root	Ethanol extract	Used as anti swelling agent, aphrodisiac, sedative, treatment of constipation, fever, asthma, brohchitis, stomachic, headache and weak digestion.	Antimicrobial, antioxidant, insecticidal, hypotensive, hypolipidaemic, anticonvulsant, immunomodulator, antibacterial, nephroprotective, spasmolytic, neuroprotective.	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 0.87 ± 2.49%	NP	α- and β-asarone, acorenone, calamenone, acoradin, shyobunone, asaronaldehyde, calamusenone, preisocalamenediol, cryptoacorone.	(Balakumbahan et al., 2010; Chandra and Prasad, 2017; Temkitthawon et al., 2011)
16	*Barleria strigosa* Willd.	Acanthaceae	Bristly Blue Baleria,	Thailand, India	Whole plant	Ethanol extract	Used against influenza, nose bleeds, as antipyretic,	Cytotoxic, antimicrobial, antioxidant	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil	NP	Verbascoside, isoverbascoside, decaffeoyl verbascoside, parvifloroside A and B.	(Prapalert et al., 2017; Temkitthawon et al., 2011)

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Table 3 (*continued*)

Sl. No.	Plant name	Family	Common name	Geographical location	Part used	Type of extract or fraction	Traditional use	Pharmacological properties	Experimental method	Active chemical constituent (s)	Other identified phytochemicals	References
							restorative and as antidote, aphrodisiac		standard. Percentage PDE5 inhibitory effect = 2.13 ± 5.75%			
17	*Berchemia floribunda* Wall.	Rhamnaceae	Japanese Supple-jack	China, India, Nepal, Bhutan	Stem bark	Ethanol extract	Jaundice, strains, dysmenorrhoea, aphrodisiac, rheumatoid arthritis, gall stones, stomachic	Cytotoxic, hepatoprotective	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 7.33 ± 0.59%	NP	Berchemiaside A and B, eriodictyol, aromadendrin, avicularin, maesopsin, physcion, chrysophanol	(Temkitthawon et al., 2011; Y. F. Wang et al., 2006)
18	*Betula alnoides* Buch.-Ham. ex G. Don	Betulaceae	Khamlang suea khrong, Bhurjapatra, Saur tree	Thailand, India, Myanmar, Southern China	Stem	Ethanol extract	Tonic, stomachic, promotes longevity, carminative and aphrodisiac. Treatment of post natal and joint pain, bleeding, and sprains	Anti-inflammatory, hypolipidaemic, antioxidant, antimicrobial, α-glucosidase inhibitory effect, anti-HIV-I integrase activity and neuroprotective	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 36.40 ± 8.07%	NP	Betulinic acid, betulin, lupeol, oleanolic acid, ursolic acid, lupeol	(Chaniad et al., 2019; Temkitthawon et al., 2011, 2008)
19	*Boesenbergia rotunda* (L.) Mansf.	Zingeberaceae	Chinese keys or fingerroot	Southeast Asia, India, Southern China	Rhizome	Ethanol extract	Larvicidal, pupicidal promotes appetite, carminative, aphrodisiac, diuretic. Treatment of rheumatism, gout, flatulence, dyspepsia, dental problems	Anti-inflammatory, antioxidant, antimicrobial, aphrodisiac, antiparasidal, antiulcer, anti-mutagenic, anticancer, antifungal, antiviral	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard Percentage PDE5 inhibitory effect = 40.86 ± 3.94%	NP	Boesenbergin A, rubranine, pinostrobin boesenbergin B, panduratin A, (±)-panduratin B1 and B2, pinostrobin pinocembrin alpinetin	(Eng-Chong et al., 2012; Temkitthawon et al., 2011)
20	*Butea superba* Roxb	Fabaceae	Red Kwao Krua	Thailand, Vietnam, India	Root bark	Ethanol extract	Rejuvenator, improve sexual performance, treatment of erectile dysfunction, and boosts sperm count	Erectile dysfunction, androgenic, anti-estrogenic, anti-proliferative	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard Percentage PDE5 inhibitory effect = 7.88 ± 5.59%. Another study suggests 87% of patients responded positively to *B. superb* extract with respect to sildenafil for treating erectile dysfunction in a clinical setup.	NP	3, 7, 3′-Trihydroxy-4′-methoxyflavone, 3, 3′-dihydroxy-4′-methoxyflavone-7-O-β-D-glucopyranoside	(Cortés-González et al., 2010; Temkitthawon et al., 2011)
21	*Caesalpinia sappan* L.	Caesalpiniaceae	Patag or Sappan wood	South East Asia	Stem and leaf	Ethanol extract	Aphrodisiac, emmenagogue, demulcent and antibacterial agent.	Anti inflammatory, antioxidant, anti cancer, immunosuppressant,	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil	NP	Brazilin, sappanchalcone, protosappanin A and B, caesalpin J, P, ombuin, episappanol, brazilide A, neosappanone A,	(Pawar et al., 2008; Temkitthawon et al., 2011)

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Table 3 (*continued*)

Sl. No.	Plant name	Family	Common name	Geographical location	Part used	Type of extract or fraction	Traditional use	Pharmacological properties	Experimental method	Active chemical constituent (s)	Other identified phytochemicals	References
							Also used to treat. Fever, delirium, ulcers.	antidiabetic, antimicrobial, anti proliferative, acaricidal, antibacterial cardiovascular diseases related to endothelial dysfunction, hepatoprotective	standard. IC_{50} value of 45.95 ± 3.62 μg/mL (stem) and 25.87 ± 6.49 μg/mL (leaf)		protosappanin E−2, tetraacetylbrazilin	
22	*Drosera burmannii* Vahl	Droseraceae	Sundew plant	Sri Lanka, China, India, West Africa, Australia.	Ariel part	Ethanol extract	Used in Ayurvedic preparation called as Swarnabhasma, which is useful against memory loss, infertility, asthma, eyesight, diabetes, fatigue.	Anticancer, antioxidant, anti inflammatory, antitumor, hepatoprotective.	*In vitro;* using PDE5 NP isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 4.52 ± 0.40%.		Plumbagin, hydroplumbagin glucoside, rossoliside, kaempferol, myricetin, quercetin	(Ghate et al., 2016; 2015; Temkitthawon et al., 2011)
23	*Elephantopus scaber* L.	Asteraceae	Prickly leaved elephant foot or elephant's foot	Eastern Asia, tropical Africa, India, Southeast Asia, Northern Australia, South America.	Whole plant	Ethanol extract	Treatment for gonorrhoea, diarrhea, filariasis. leucorrhoea, spermatorrhea, menorrhea and headache. Used as astringent and diuretic agent	Antitumor, antibacterial, antifungal, antidiabetic, hepatoprotective, antioxidant, anti inflammatory, analgesic, anti platelet activity.	*In vitro;* using PDE5 NP isolated from mouse lung tissue and sildenafil standard Percentage PDE5 inhibitory effect = 4.12 ± 0.75%		Deoxyelephantopin, isodeoxyelephantopin, elescaberin, scabertopin, tricin, luteolin, lupeol, betulinic acid, epifriedelanol	(Hiradeve and Rangari, 2014; Temkitthawon et al., 2011)
24	*Hiptage benghalensis* (L.) Kurz	Malpighiales	Hiptage	India, Phillippines, Southeast Asia	Stem	Ethanol extract	Wound healing, ulcer, inflammation, leprosy, rheumatism, asthma, astringent, cardiotonic, antiinflammatory, pruritis.	Antidiarrhoeal, hemostatic, antiinflammatory, antioxidant, anti viral, antidiabetic, anti allergic, larvicidal, anthelmintic	*In vitro;* using PDE5 NP isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 32.31 ± 3.77%		Kaempferol, quercetin, mangiferin, friedelin, epifriedelinol, hiptagin	(Meena et al., 2014; Temkitthawon et al., 2011, 2008)
25	*Leea indica* (Burm. f.) Merr.	Vitaceae	Bandicoot berry	India, Australia, China, Malaysia, pacific islands	Root	Ethanol extract	Used for treating fever, diarrhea, bone fracture, sexual disorders, ulcer, skin disorders, rheumatism, asthma. Also used as sudorific, aphrodisiac and anti-inflammatory agent	Antibacterial, antifungal, antiviral, antioxidant, cytotoxic, thrombolytic, anti-diarrhoeal, hepatoprotective, sedative, hypolipidaemic, anxiolytic, analgesic, hypoglycemic, larvicidal and anti-malarial	*In vitro;* using PDE5 NP isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 31.36 ± 7.47%		Gallic acid, methyl gallate, myricetin-3-*O*-rhamnoside, epigallocatechin-3-*O*-gallate, quercetin-3-*O*-rhamnoside, 3-hydroxyphloridzin, phloridzin,	(Singh et al., 2019; Temkitthawon et al., 2011)
26	*Mucuna collettii* Lace	Leguminosae	Black kwao Krua	Thailand	Stem	Ethanol extract	Remedy for male rejuvenation, promotion of sexual potency	Anti-mutagenic, anti proliferative.	*In vitro;* using PDE5 NP isolated from mouse lung tissue and sildenafil standard. Percentage PDE5		Miroestrol, diadzin, ginistein, coumestrol, ginistin, puerarin, kwakhurin, mirificin	(Cherdshewasart et al., 2008; Temkitthawon et al., 2011)

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Sl. No.	Plant name	Family	Common name	Geographical location	Part used	Type of extract or fraction	Traditional use	Pharmacological properties	Experimental method	Active chemical constituent (s)	Other identified phytochemicals	References
									inhibitory effect = 1.13 ± 5.06%			
27	*Myxopyrum smilacifolium* Blume	Oleaceae	Chathurakkodi, Chathuravalli, chathuramulla	India, Thailand, Myanmar, Vietnam, Bangladesh	Root	Ethanol extract	Treatment of rheumatism, cough, sexual disorders, otopathy and cephalagia, used as anodyne, febrifuge.	Adaptogenic, antioxidant, cytotoxic	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 0.46 ± 0.69%	NP	Myxopyroside, 6-O-Acetyl-7-O-(E/Z)-*p*-methoxycinnamoylmyxopyroside	(Rajalakshmi and Mohan, 2016; Temkitthawon et al., 2011)
28	*Polygala chinensis* L.	Polygalaceae	Field Milkwort	India, China, hailand, malaysia, Java, Sumatra	Whole plant	Ethanol extract	Treating snake bites, bronchitis, cough, used as expectorant, tonic, anti- inflammatory and aphrodisiac	Anticancer, anti-inflammatory, free radical scavenging activity.	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 3.85 ± 9.35%	NP	Chinensin, 1,5-anhydro-D-mannitol, squalene, loeic acid, myristin	(Gurav et al., 2007; Temkitthawon et al., 2011)
29	*Piper sarmentosum* Roxb.	Piperaceae	Wild betel	Vietnam, India, China.	Root	Ethanol extract	Anti-inflammatory, aphrodisiac, carminative, relieve cough and muscle pain, headaches, as expectorant, against pleurisy, rheumatic pain.	Anticancer, hypoglycemic, anti-tuberculosis, antioxidant, anti-malarial, antibacterial, anti-protozoal, antihypertensive	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 4.19 ± 6.70%	NP	Pellitorine, guineensine, brachystamide B, sarmentine, brachyamide B, sarmentosine, sesamin	(Rukachaisirikul et al., 2004; Temkitthawon et al., 2011)
30	*Securidaca inappendiculata* Hassk	Polygonaceae	Chan yi Teng	Southern China, India, Vietnam, Malaysia	Stem	Ethanol extract	Cures fractures, used as sexual stimulant and to treat rheumatoid arthritis	Antirheumatic, anti-inflammatory, analgesic and immunodepressive	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 9.50 ± 7.27%	NP	Securiphenoside B, securiterpenoside E-F, securioside C, D, E, securioside E	(Temkitthawon et al., 2011; Zuo et al., 2014)
31	*Tacca chantrieri* André	Taccaceae	White bat plant	Thailand, Malaysia, Southern China	Root	Ethanol extract	Sexual stimulant, relieves pain, stomachic, antidote for food poisoning, treatment of enteritis, hepatitis, gastric ulcers and burns	Cytotoxic, microtubule stabilizing activity, NF-κB activation and PPAR transcriptional activity, analgesic, anti-inflammatory, antipyretic, hypotensive	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 0.49 ± 7.75%	NP	Chantriolide A-E and taccasteroides	(Kittipong et al., 2010; Temkitthawon et al., 2011)
32	*Tinospora crispa (L.)* Miers ex Hook.f. & Thomson	Menispermaceae	Bitter grape	South East Asia, Africa including Thailand, Malaysia, Indonesia	Stem	Ethanol extract	Used as aphrodisiac, antipyretic, and in the treatment of internal inflammation, alcohol intoxication, treat diabetes,	Anti-inflammatory, immunomodulatory, cytotoxic, antioxidant, anti-nociceptive, anti-malarial, hypoglycemic, anti-filarial, cardioprotective.	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 2.54 ± 7.88%	NP	Genkwanin, genkwanin 7-glucoside, cycloeucalenol, tinocrispol A, borapetols B, tinoscorside A, magnoflorine, N-acetylanonaine, lysicamine	(Ahmad et al., 2016; Temkitthawon et al., 2011)

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Sl. No.	Plant name	Family	Common name	Geographical location	Part used	Type of extract or fraction	Traditional use	Pharmacological properties	Experimental method	Active chemical constituent (s)	Other identified phytochemicals	References
							hypertensionand backache.					
33	*Talinum paniculatum* (Jacq.) Gaertn.	Portulacaceae	Som Java, Fameflower or Jewels of Opar	Thailand	Rhizome	Ethanol extract	Used for treating dysmennorhoea, skin diseases, gastrointestinal disturbances, general weakness and reproductive disorders and as an aphrodisiac	Estrogenic, antibacterial, anti fungal, anti mycobial, cytotoxic, anti nociceptive, and edematogenic activity	*In vitro*; using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 1.16 ± 4.19%	NP	Dotriacontane, tritriacontane and pentatriacontane. heneicosanoic acid, the ester nonacosyl nonacosanoate, urea, 3-O-β-D-glucosyl-β-sitosterol	(Temkitthawon et al., 2011; Thanamool et al., 2013)
34	*Ventilago denticulata* Willd.	Rhamnaceae	Bor-kalia	India, South east Asia	Stem	Ethanol extract	Treatment of wounds, eye disease, stomach ulcer, tonic, dyspepsia, fever and sprains, sexual performance enhancer	Antioxidant, anti fungal, cytotoxic, anti-inflammatory, anthelmintic, antibacterial	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 36.43 ± 7.25%	NP	Friedelin, ventinone A, B, lupeol, β-sitosterol	(Devhadrao et al., 2019; Temkitthawon et al., 2011)
35	*Acacia auriculaeformis* A. Cunn.	Fabaceae	Ear-pod wattle, Darwin black wattle and tan wattle	Australia, India, new Guinea, Indonesia	Leaf	Ethanol extract	Used to treat aches, sore eyes, diabetes, rheumatism, skin diseases and allergy	Antioxidant, antifungal, anti microbial, antimalarial, cestocidal, antifilarial, larvicidal, pesticidal, CNS depressant, spermicidal, hepatoprotective, antidiabetic	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. IC_{50} value of 12.72 ± 2.27 μg/mL	NP	3,4′,7,8-tetrahydroxy flavanone, 4′,7,8-trihydroxyflavanone, teracacidin, proacaciaside-I, II, auriculoside, acaciamine	(Sharma et al., 2016; Temkitthawon et al., 2011)
36	*Acacia concinna* (Willd.) DC.	Fabaceae	Shikakai or fruit for the hair	India, South east Asia	Leaf	Ethanol extract	Control dandruff, promotes hair growth, strengthening hair roots, hair cleansing agent, cure malarial fever, purgative, treat jaundice, constipation, skin problems, astringent.	Anti-bacterial, anthelmintic	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 28.70 ± 3.19%	NP	Acacigenin B, Oxalic, tartaric, citric, succinic and asorbic acids; calycotomine, nicotine; rutin, calycotomine, nicotine	(Temkitthawon et al., 2011; Todkar et al., 2010)
37	*Acacia pennata* (L.) Willd. subsp. insuavis (Lace) I.C. Nielsen	Mimosaceae	Climbing acacia, climbing wattle, feather acacia, narrow leaved soap pod	India, China, Myanmar, Bangladesh, Bhutan, Thailand	Leaf	Ethanol extract	Treatment of cough, headaches, rheumatism, cold, dermatitis, sexual disorder and fever.	Anti nociceptive, antioxidant, anti-inflammatory, anti-parasitic, anti transcription	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 13.97 ± 4.62%	NP	Quercetin-3-O-β-D-glucopyranoside, chrysin-7-O-β-D-glucopyraniside, koaburanin and pinocembrin-7-O-β-D-glucopyranoside	(Aye et al., 2019; Temkitthawon et al., 2011)
38	*Bauhinia acuminata* L.	Caesalpiniaceae	Dwarf white bauhinia, white orchid-tree and snowy orchid-tree	Philippines, Malaysia, Indonesia	Leaf	Ethanol extract	Treatment of sexual dysfunction, dysentery, diarrhea, haemorrhoids,	Antioxidant, hypolipidemic, immunomodulatory, anti- inflammatory, antimicrobial,	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard.	NP	5-hydroxyflavone, 3,5,7,3′,4′-pentahydroxyflavone, 3,5,7,2′,4′-pentahydroxyflavone, 5,7,3′,4′-tetrahydroxyflavone-3-O-rhamnoside	(Sinou et al., 2009; Temkitthawon et al., 2011)

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Sl. No.	Plant name	Family	Common name	Geographical location	Part used	Type of extract or fraction	Traditional use	Pharmacological properties	Experimental method	Active chemical constituent (s)	Other identified phytochemicals	References
							piles and edema. Also used as laxative, anthelmintic, astringent, antileprotic, antigoitrogenic, antitumor agent and as an antidote for snake poisoning	insecticidal, antibacterial, antidiabetic, antiulcer, hepatoprotective, anti-arthritic, antimutagenic, cytotoxic, trypsin inhibitor, anti-goitrogenic	Percentage PDE5 inhibitory effect = 36.94 ± 4.23%			
39	*Bauhinia glauca* (Wall. ex Benth.) Benth.	Caesalpiniaceae	Glaucous climbing bauhinia	India, China, South east Asia	Leaf	Ethanol extract	Used as aphrodisiac, and as a remedy for skin diseases, worms, tumors, diabetes, biliousness, common cold, bladder stone, leprosy and asthma	Antibacterial, antifungal, anti anxiety, anti depressant, antidiabetic, antimicrobial, anti-inflammatory, antioxidant, wound healing effect	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 23.89 ± 3.06%	NP	Lupeol, kamepferol, 3, 5,7-dehydroxy- and 5,7-dimethoxy-flavanone-4-O-α-L-rhamnopyranosyl-β-D-glucopyranosides, quercetin, apigenin	(Sinou et al., 2009; Temkitthawon et al., 2011)
40	*Bauhinia winitii* Craib	Fabaceae	Orchid tree, Thai Bauhinia	Thailand	Leaf	Ethanol extract	Astringent	NP	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 45.92 ± 4.36%	NP	NP	(Sinou et al., 2009; Temkitthawon et al., 2011)
41	*Butea monosperma* (Lam.) Taub.	Fabaceae	Flame tree	India, South Asian peninsula	Leaf	Ethanol extract	Astringent, aphrodisiac, tonic, for treatment of antidote, filariasis, night blindness, dyspepsia, sore throat, diuresis, remedy against intestinal worms, bleeding piles, urinary stones, eye diseases, diarrhea, ulcer, leucorrhoea	Anti-filarial, antidiabetic, anti-inflammatory, antioxidant, anthelmintic, anti-diarrhoeal, anticonvulsant, wound healing activity, hepatoprotective, antimicrobial, estrogenic, postcoital anti-contraceptive, anti-stress activity	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 41.48 ± 0.64%	NP	Butein, isobutrin, coreopsin, sulphurein, isocoreopsin, monospermoside, chalcones, isomonospermoside, linoleic, palmitic and lignoceric acid	(More et al., 2018; Temkitthawon et al., 2011)
42	*Caesalpinia coriaria* (Jacq.) Willd.	Caesalpiniaceae	Cascalote, American Sumac	Caribbean, Northern South America and South East Asia	Leaf	Ethanol extract	Used in bleeding piles, freckles, in treatment of acute colic pain and diabetes	Anti-inflammatory, analgesic, hemostatic, antidiarrheal, hypercholesterolemic, antiarthritic, antiacne, hepatoprotective, anticancer, anthelmintic and antimicrobial.	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 47.50 ± 4.67%	NP	Methyl gallate, and gallic acid	(Mohana and Raveesha, 2006; Temkitthawon et al., 2011)
43	*Cassia fistula* L.	Caesalpinaceae	Golden shower, Purging cassia, Indian laburnum	Native to Indian subcontinent and adjacent to	Leaf	Ethanol extract	Aphrodisiac, antipyretic, analgesic, laxative. Useful for	Antidiabetic, hypolipidaemic, hepatoprotective, antioxidant,	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil	NP	Fistulic acid, rhein, rheinglucoside, galactomannan, sennosides A and B, phlobaphenes, emodin,	(Siddiqua et al., 2018; Temkitthawon et al., 2011)

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Sl. No.	Plant name	Family	Common name	Geographical location	Part used	Type of extract or fraction	Traditional use	Pharmacological properties	Experimental method	Active chemical constituent (s)	Other identified phytochemicals	References
				nearby regions of Southeast Asia			treatment of diabetes, hematemesis, leucoderma, pruritis, intestinal disorder, burns, cancer, constipation and convulsions	antipyretic, anti inflammatory, antitussive, antileishmanial, CNS activity, antimicrobial, antitumor, larvicidal, ovicidal, antiparacitic, anti-itching, anti ulcer, wound healing activity,	standard. Percentage PDE5 inhibitory effect = 10.60 ± 0.25%		chrysophanic acid, fistuacacidin, barbaloin, lupeol, β-sitosterol, and hexacosanol	
45	*Delonix regia* (Bojer ex Hook.) Raf.	Fabaceae	Royal Poinciana or Flamboyant	Taiwan, India, Vietnam, Malaysia, and the central region of South America	Leaf	Ethanol extract	Antiperiodic, aphrodisiac, febrifuge, antirheumatic, spasmogenic, cathartic, emetic, used for treatment of anemia, fever, bronchitis, pneumonia and rheumatic joints pain	Insecticidal, antifertility, wound healing, antifeedant, anthelmintic, anti-inflammatory, antiulcer, antifungal, and cytotoxic activities and also inhibits the malaria parasite in humans.	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 31.03 ± 10.19%	NP	Anthocyanins, cyanidine 3-O-glucoside, cyanidine 3-O-rutinoside, kaempferol, quercetin trihexoside, quercetin 3-*O*-robinobioside	(Modi et al., 2016; Temkitthawon et al., 2011)
46	*Leucaena leucocephala* (Lam.) de Wit	Fabaceae	White lead tree, White popinac, Jumbay, Wild tamarind	Southern Mexico and Northern Central America, parts of south east Asia	Leaf	Ethanol extract	Treat internal pain, used as contraceptive, depilatory, diabetes treatment, hypolipidaemic	Anthelmintic, antibacterial, anti-proliferative, antidiabetic, antimicrobial, diuretic, anti-inflammatory, antioxidant, antihistaminic, nematicide, pesticide, antiandrogenic, hypocholesterolemic and hepatoprotective	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 29.82 ± 8.64%	NP	Ficaprenol-11, squalene, lupeol, *trans*- and *cis*- coumaric acids, pheophytin-a	(Deivasigamani, 2018; Temkitthawon et al., 2011)
47	*Pithecellobium dulce* (Roxb.) Benth.	Leguminosae	Manilla tamarind, Madras thorn, Sweet tamarind	Caribbean, Florida, Guam, India, Bangladesh, Sri Lanka, Pakistan, Thailand and the Philippines	Leaf	Ethanol extract	Treatment of intestinal disorders, ear and tooth ache, indigestion, ulcers, dermatitis, eye inflammation. Also used as emollient, astringent and spermicidal.	Antidiabetic, anti inflammatory, anti oxidant, anti tubercular, CNS Depressant, anti microbial, anti fungal, analgesic, larvicidal, anthelmintic, anti bacterial, anti diarrhoeal, hypolipidaemic	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 30.25 ± 0.84%	NP	Quercetin, Kaempferol, Cyclitol, Dulcitol, Afezilin, Octacosanol, α-spinasterol, kaempferol-3-O-rhamnoside	(Manna et al., 2011; Temkitthawon et al., 2011)
48	*Samanea saman* (Jacq.) Merr.	Fabaceae	Rain tree	Mexico, Peru, Brazil, Southeast Asia and Pacific Islands	Leaf	Ethanol extract	Traditional remedy for cold, diabetes, diarrhea, headache, sore throat, intestinal ailments and stomach ache. Used as laxative and sedative	Antioxidant, anti microbial, antidiabetic, anti-inflammatory, antiulcer, antianxiety, insecticidal, cytotoxic, hepatoprotective	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 47.59 ± 6.59%	NP	Pithecolobine- I, II, catechin, epicachin, cyanidin, anthocyanin, monoglycones, malidin and delphinidin	(Temkitthawon et al., 2011; Vinodhini and Devi Rajeswari, 2018)

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Sl. No.	Plant name	Family	Common name	Geographical location	Part used	Type of extract or fraction	Traditional use	Pharmacological properties	Experimental method	Active chemical constituent (s)	Other identified phytochemicals	References
49	*Saraca thaipingensis* Cantley ex Prain	Fabaceae	Yellow Ashoka, Yellow Saraca	South east Asia	Leaf	Ethanol extract	Anti-cough and expectorant	Antimicrobial, antioxidant, cytotoxic	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 21.53 ± 2.63%	NP	Stigmasterol and other terpenoids	(Prachayasittikul et al., 2012; Temkitthawon et al., 2011)
50	*Senna alata* (L.) Roxb.	Fabaceae	Candle bush	Ghana, Brazil, Australia, Egypt, India, Somalia, Sri Lanka	Leaf	Ethanol extract	Treatment of wound, burns, respiratory tract infection, diarrhea, constipation, haemorrhoids, syphilis, diabetes	Antibacterial, abortifacient, hepato-renal protective, anti allergic, antilipogenic, antidiabetic, anti fungal, antigonadotropic, antiprogestronic, anti inflammatory, anticancer, antiviral, immunomodulatory, antiplasmodial	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 19.78 ± 5.29%	NP	Kaempferol, luteolin, aloe emodin, limonene, quercetin, anthrol, tocopherol, naringenin, methaqualone, astragalin, cinnamic acid	(Oladeji et al., 2020; Temkitthawon et al., 2011)
51	*Senna siamea* (Lam.) Irwin & Barneby	Fabaceae	Siamese cassia, kassod tree, cassod tree and cassia tree	South and South east Asia	Leaf	Ethanol extract	Used to treat malaria, liver disorders, urogenital disorders, herpes, rhinitis, and scabies. Also used as laxative, purgative.	Anti inflammatory, analgesic, anti malarial, antidiabetic, antilipemic, anti oxidant, anti tumor, antihypertensive, anxiolytic, antidepressant, sedative, antifungal	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 19.94 ± 5.18%	NP	Barakol, cassiarin A, cassiarin B, Anhydrobarakol, Chrobisiamone A, Cassiamin A, cassiamin B, Chrysophanol	(Mohammed et al., 2013; Temkitthawon et al., 2011)
52	*Senna surattensis* (Burm.f.) Irwin & Barneby	Fabaceae	Glaucos cassia, Glossy shower	India, China, Thailand, Indonesia, several parts of South east Asia	Leaf	Ethanol extract	Remedy for gonorrhea, jaundice and blennorrhoea	Anti diabetic, antioxidant, antimicrobial, antihyoerlipidaemic and hepatoproective	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. IC_{50} value of 12.00 ± 3.68 μg/mL	NP	Chrysophanol, physcion, kaempferide, and quercetin	(Temkitthawon et al., 2011; Thilagam et al., 2018)
53	*Sesbania grandiflora* (L.) Desv.	Fabaceae	Vegetable hummingbird	India, Malaysia, Indonesia, Myanmar and the Philippines	Leaf	Ethanol extract	Aperient, aphrodisiac, diuretic, emetic, emmenagogue, febrifuge, laxative, and tonic. Also used for treatment of bruises, catarrh, dysentery, fevers, headaches, smallpox and sore throat	Anticancer, hepatoprotective, antioxidant, cardioprotective, antiurolithiatic, wound healing, antiulcer, antibacterial, anthelmintic, hypolipidaemic, immunomodulatory, anti-tubercular, antiarthritic, analgesic, CNS depressant.	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil standard. Percentage PDE5 inhibitory effect = 32.97 ± 5.39%	NP	Sesbagrandiflorain A and B, grandifloral, kaempferol, leucocyanidin, cyanidin, kaempferol-3-rutinoside	(Noviany et al., 2018; Temkitthawon et al., 2011)
54	*Tamarindus indica* L.	Fabaceae	Tamarind	Africa and southern Asia	Leaf	Ethanol extract	Cures chronic or acute constipation, liver and gall bladder ailments,	Analgesic, anthelmintic, antiasthmatic, antiatherosclerotic,	*In vitro;* using PDE5 isolated from mouse lung tissue and sildenafil	NP	2-hydroxy-3', 4'-dihydroxyacetophenone (TAO), methy l-3, 4-dihydroxybenzoate (TA1), 3, 4-	(Ahmad et al., 2018; Temkitthawon et al., 2011)

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Sl. No.	Plant name	Family	Common name	Geographical location	Part used	Type of extract or fraction	Traditional use	Pharmacological properties	Experimental method	Active chemical constituent (s)	Other identified phytochemicals	References
							bilious vomiting, alcohol intoxications, fever, pharyngitis, stomatitis, sexual dysfunction, haemorrhoids and diabetes	antidiabetic, anti-emetic, anti-inflammatory, antimicrobial, antinociceptive, antioxidant, antiulcer, fungicidal, hepatoprotective, hypolipidemic and immunomodulatory	standard. Percentage PDE5 inhibitory effect = 55.79 ± 2.68%		dihydroxyphenylacetate (TA2) and (−)-epicatechin, hordenine and proanthocyanidin, tartaric acid, malic acid, citric acid and lactic acid, orientin, isoorientin	
55	*Maclura pomifera* (Raf.) Schneid.	Moraceae	Osage orange, horse apple, mock orange or hedge apple	Native to southern Oklahoma, northern Texas and throughout the United States	Leaves and bark	Ethyl acetate and chloroform extracts	Used for the treatment of sore eyes, tooth pain, uterine haemorrhage, cancer treatment	Antibacterial, antifungal, antiviral, cytotoxic, antitumor, estrogenic and antimalarial, antimicrobial activities	*In silico*, in comparison to Icarisid II	Scandenone, Pomiferin, Osajin, Auriculasin	Iso-osajin, iso-pomiferin	(Ribaudo et al., 2017; Saloua et al., 2009)
56	*Campsiandra angustifolia* Spruce ex Benth.	Fabaceae	Huacapurana	South America	Tree bark	Methanol: Water (50:50)	Aphrodisiac, treatment of malarial fever, arthritis, rheumatism, wounds, remedy for diarrhea; as a tonic, to clean sores and in ulcers.	Anti-inflammatory, anticancer	*In vitro*, 89.37 ± 0.65% inhibition of PDE5 at 200 μg/mL and 81.32 ± 2.23% at 100 μg/mL with respect to standard sildenafil	NP	Caffeoylquinic acid, proanthocyanidins, gallotannins, hydroxygenistein, wogonin	Schmeda-Hirschmann et al. (2019)
57	*Swartzia polyphylla* DC.	Leguminosae	Cumaseba	South America - Brazil, Peru, Colombia, Venezuela, the Guyanas	Tree bark	Methanol: Water (50:50)	Aphrodisiac, postpartum tonic, for female disorders, yeast infections, colds, flu, rheumatism, malaria, bone fracture treatment	Antifungal, antimicrobial, antiseptic, antitubercular	*In vitro*, 21.03 ± 1.90% inhibition of PDE5 at 200 μg/mL and 13.82 ± 1.98% at 100 μg/mL with respect to standard sildenafil	NP	Biochanin A, dalbergioidin, dihydrocajanin, dihydrolicoisoflavone, dihydrobiochanin A, ferreirin, ferreirinol, formononetin, naringenin, and T-cadinol	(Rojas et al., 2006; Schmeda-Hirschmann et al., 2019)
58	*Tynanthus panurensis* (Bureae ex Baill.) Sandwith	Bignoniaceae	Clavo Huasca	Tropical South America and Amazon rainforest	Tree bark	Methanol: Water (50:50)	Aphrodisiac, used for treating arthritis, rheumatism, inflammation and digestive problems.	Anti inflammatory, antioxidant.	*In vitro*, 28.10 ± 3.82% inhibition of PDE5 at 200 μg/mL and 22.96 ± 1.99% at 100 μg/mL with respect to standard sildenafil	NP	Tinantina, verbascoside, isoverbascoside, and leucosceptoside, katchimoside	(Cansian et al., 2015; Morales et al., 2011; Schmeda-Hirschmann et al., 2019)
59	*Matricaria recutita* L.	Asteraceae	German chamomile, Roman chamomile, English chamomile, Camomilla, and Flos Chamomile	South and south west of Iran	Entire dried and sifted flowers	Infusion	Wound healing property, used in aromatherapy, calming agent, aids in sleep.	Anti-allergic antispasmodic, antibacterial activities, anti-inflammatory, immunomodulatory activity, arcaricadal property, antihyperglycemic, anticancer, antipruritic effect	*In vitro*, IC_{50} for dried flowers are 17.9 and 27.2 μg/mL, whereas sifted flowers showed IC_{50} value of 20.5–40.5 μg/mL by using sildenafil as reference compound	Apigenin-7-O-glucoside (IC_{50} = 10.2 ± 1.7 μM), luteolin-7-O-glucoside (IC_{50} = 14.9 ± 2.6 μM), hyperoside (IC_{50} = 11.8 ± 0.9 μM), patuletin-7-O-	Chamazulene, 1,8-cineole, β-pinene, α-pinene, α-bisabolol, terpinen-4-ol, guargazulene	(Maschi et al., 2008; Vikas Gupta1 et al., 2010)

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										glucoside (IC_{50} = 14.9 ± 0.4 μM), apigenin (IC_{50} = 4.1 ± 0.9 μM), luteolin[a] (IC_{50} = 1.3 ± 0.1 μM)		
60	*Prismatomeris memecyloides* Craib	Rubiaceae	Congselen	Cambodia and Vietnam	Roots	Methanol	Erectile dysfunction	PDE5 inhibition	*In silico* investigation of seven isolated compounds in comparison to sildenafil	Damna canthal, lucidin-ω-methyl ether, 3-methy lalizarin and rubiadin-3-methyl ether, 1-O-methy lrubiadin 3-O-primeveroside	Asperulosidic acid and aitchisonide A	(Khanh et al., 2018; Son, 2017)
61	*Leonurus artemisia* (Lour.) S.Y.Hu	Lamiaceae	True Chinese Motherwort, Lion's Tail and Lion's Ear	Native to Asia, including Korea and Japan, and China to Cambodia	Leaves	Methanol	Regulating menstrual disturbance, dysmenorrhea, menorrhea, blood stasis, and postpartum haemorrhage, as well as activating blood circulation, diuretics, and dispelling edema.	Vasorelaxant effect, coagulant, cytotoxic, angiogenic, antibacterial, antiplatelet aggregative activity, uterotonic, hypotensive, antipyretic, anti-inflammatory, diuretic, anthelmintic.	*In silico* investigation using Leonurine and its 13 derivatives to predict the inhibitory effect on PDE5 enzyme.	Leonurine	Leonurinine, Preleoheterin, Leopersin G, Sibiricinone A-E, Leosibrinone A and B, Quercetin, Hyperoside, Leonurusoide A-E, Lavandulifolioside	(Miao et al., 2019; Ruslin et al., 2014)
62	*Serenoa repens* (W.Bartram) Small	Arecaceae	Saw palmetto	Subtropical Southeastern United States, south Atlantic and Gulf Coastalplains	Berry	Saw Palmetto Extract capsules	Treating stomach ache, relieve mucous membrane irritations and diarrhea and used as diuretic, sexual tonic, increases testicular function, and breast size.	Treatment of Benign prostatic hyperplasia/ lower urinary tract symptoms, antiestrogenic,	*In vitro,* using phosphorus colorimetric quantitative assay kit purchased from GENMED Scientifics Inc.	NP	β-sitosterol, stigmasterol, cycloartenol, lupeol, lupenon and methylcloartenol	(Van Coppenolle et al., 2000; Yang et al., 2013)
63	*Swietenia macrophylla* King	Meliaceae	Big Leaf mahogany or Honduras mahogany	Central America and tropical South America	Bark	Aqueous	Improves blood circulation, skin condition, hypertension, diabetes, relieves pain, for treating leishmaniasis and as an abortion medicine	Antiviral, anti-inflammatory, anti-infective, anticancer, antitumor, antimutagenic, antidiabetic, antinociceptive, hypolipidemic, antioxidant, antimicrobial, anti-diarrhoeal, antimalarial,	*In vitro* evaluation using penile tissue homogenate and sildenafil citrate as standard. IC_{50} = 470.66 ± 1.99 μg/mL.	Gallic acid, catechin, ellagic acid, quercetin are present in the active extract	Swietemacrophyllanin, epicatechin	(Moghadamtousi et al., 2013; Oboh et al., 2017a)

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								antifeedant and acaricidal.				
64	*Moringa oleifera* Lam.	Moringaceae	Drumstick tree, horseradish tree, benzolive tree	India, Phillippines, Indonesia, Central America, Caribbean, South America, Arica, Southeast Asia.	Leaves	Water: Ethanol (50:50)	Treating various ailments including constipation, headache, fever, and diabetes, hiccough (emetic in high doses); cooked leaves are given in influenza and catarrhal affections.	Antimicrobial, anti-inflammatory, antioxidant, anticancer, antifertility, hepatoprotective, cardioprotective, anti-ulcer, analgesic, antipyretic, wound healing, antidiabetic, diuretic, anti-urolithiatic, antiallergic and anthelmintic	*In vitro*, PDE-Glo™ Phosphodiesterase Assay Kit (Promega Corp., Thailand) was used for the assay.	NP	Quercetin, isoquercetin, kaemfericitin, isothiocyanates, niazirin, niazirinin, niaziminin, quercetin glucosides, rutin, kaempferol glycosides and chlorogenic acid, gallic acid	(Morvin Yabesh et al., 2014; Prabsattroo et al., 2015)
65	*Musa sapientum* L.	Musaceae	Southwestern Pacific, India, West Coast of Africa	French plantain banana	Mature unriped and riped fruits	Aqueous	Aphrodisiac, hypotensive, antidiabetic, and used as a remedy for diarrhea, dysentery, intestinal lesions in ulcerative colitis, uremia, nephritis, gout, eczema, cholera, otalgia, haemoptysis, as a cool dressings for blister and burns	Antidiarrhoeal, antiulcerative, antimicrobial, hypoglycemic, antihypertensive, cardioprotective, hypocholesterolaemic, antioxidant, diuretic, wound healing effect, anti-allergic, antimalarial.	*In vitro*, unripped extract were found to be more active (IC_{50} = 3.10 μg/mL) as compared to that with that of riped fruits with IC_{50} = 4.33 μg/mL.	Gallic and caffeic acids, rutin, quercitrin and quercetin were found abundant in unripped extracts, while catechin, kaempferol, chlorogenic and ellagic acids were the dominant in riped extracts	Norepinephrine, serotonin, dopamine, leucocyanidin, quercetin, cyclomusalenol, cyclomusalenone, 24-methylene-cycloartanol, stigmast-7-methylenecycloartanol, stigmast -7-en-3-ol, lanosterol, 7, 8-dihy-droxy-3-methylisochroman-4-one and β-amyrin	(Abe and Ohtani, 2013; Oboh et al., 2017c)
66	*Ferula hermonis* Boiss.	Apiaceae	Lebanese viagra	Syria, Israel, Lebanon	Root	Methanol	Aphrodisiac, enhance sexual behavior, improves sexual weakness, infertility, asthma and sexual potency.	Anti-infertility, osteoprotective, antidiabetic, antimicrobial, cytotoxic, anti-inflammatory and insecticidal activity.	*In vitro* evaluation using PDE5A1 enzyme and sildenafil stanadard	NP	Ferutinin, Feruhermonin B, lancerdiol p-hydroxybenzoate, lancerdiol vanillate, lancerotriol benzoate, jaeschkeanin, vaginatin, teferidin, teferin	(Dell'Agli et al., 2008; Hadidi et al., 2003)
67	*Tribulus terrestris* L.	Zygophyllaceae	Caltrop, small caltrops, cat's-head, devil's eyelashes, devil's-thorn, devil's-weed, puncture vine, and tackweed	India, China, southern USA, Mexico, Spain, and Bulgaria	NP	Purchased extract	Tonic, aphrodisiac, palliative, astringent, stomachic, antihypertensive, diuretic, lithotriptic, urinary disinfectant, treatment for impotence, venereal diseases, sexual debility, eye trouble, edema, abdominal distension and leukorrhea	Diuretic, anti urolithic, aphrodisiac, immunomodulatory, antidiabetic, absorption enhancer, hypolipidemic, hepatoprotective, anti-inflammatory, analgesic, antispasmodic, anticancer, antibacterial, anthelmintic, larvicidal	*In vitro* evaluation using PDE5A1 enzyme and Sildenafil stanadard	44% furostanolic saponins and perlolyrine	Protodioscin, protogracillin, kaempferol, kaempferol-3-glucoside, kaempferol-3-rutinoside, tribuloside, rutin, terrestribisamide, 25*R*-spirost-4-en-3, 12-dione, tribulusterine	(Dell'Agli et al., 2008; Drewes et al., 2003; Mutheeswaran et al., 2011; Zheng et al., 2018)

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Sl. No.	Plant name	Family	Common name	Geographical location	Part used	Type of extract or fraction	Traditional use	Pharmacological properties	Experimental method	Active chemical constituent (s)	Other identified phytochemicals	References
68	*Cinnamomum cassia* (L.) J. Presl	Lauraceae	Chinese cassia or Chinese cinnamon	China, India, Vietnam, Indonesia and parts of Southeast Asia	NP	Purchased oil extract	Treating dysuria, abdominal pain, diarrhea, vomiting, cold, gastritis, dyspepsia, edema, cardiopalmus, insomnia, hyperplasia, dizziness, palpitation, heat stroke, hernia, algomenorrhea.	Anti tumor, anti-inflammatory, analgesic, antidiabetic, anti obesity, antibacterial, antiviral, cardioprotective, cytoprotective, neuroprotective	*In vitro* evaluation using PDE5A1 enzyme and Sildenafil stanadard	NP	Cinnamaldehyde, cinncassiol A-G, cinnacasol, perseanol, cinnamoid A-E, coniferaldehyde, eugenol, cinnamic acid, cinnacasolide A-F, cinnacassoside A-C, evofolin B	(Bansode, 2012; Dell'Agli et al., 2008)
69	*Glycyrrhiza glabra* L.	Fabaceae	Liquorice	Mediterranean and certain areas of Asia	Roots	Ethyl acetate extract	Promotes lactation, treating anaemia, hematemesis, haemorrhage, wounds, bruises, burns, used on erysipelas, acute and chronic conjuctivitis.	Immunomodulatory, antitussive, anti-inflammatory, chronic fatigue, antinociceptive, antiulcer, hepatoprotective, memory enhancing, anticonvulsant, cytotoxic, antimalarial, antiviral, anticancer, estrogenic, antimycobacterial, antidyslipidaemic, antimicrobial, antiulcer, antimycobacterial, analgesi, uterine relaxant, antioxidant, antiallergic.	*In vitro* evaluation using PDE5A1 enzyme and Sildenafil stanadard	Isoliqu iritigenin	Glycyrrhizin, glycyrrhizic acid, licopyranocoumarin, licoarylcoumarin, glisoflavone, semilicoisoflavone B, 1-methoxy-ficifolinol, isoangustone A, licoriphenone, glucoliquiritin apioside, prenyllicoflavone A, shinflavanone, shinpterocarpin, 1-methoxyphaseolin	(Kaur et al., 2013; Liu et al., 2008)
70	*Melicope confusa* (Merr.) Liu	Rutaceae	Pau, Silang kampong	Northern and southern areas of Taiwan, Borneo, the Philippines, and part of Indonesia	Leaves	Ethanol extract	Used for treating spleen enlargement, as a decoction to cure hives.	Antimicrobial, antioxidant, cytotoxic, antiplatelet aggregation activity	*In vitro*, the percentage inhibition of hPDE5A isoenzyme was measured	Kokusaginine ($17.1 \pm 0.7\%$), skimmianine ($17.1 \pm 0.7\%$), evolitrine ($52.7 \pm 0.6\%$), and confu sameline[a] ($14.6 \pm 0.3\%$) were found to inhibit the PDE5A isoenzyme at 0.1 mM concentration	Confu sameline, skimmianine, kokusaginine, O-methylconfusameline	(Eliaser et al., 2018; Nam et al., 2005)
71	*Dictamnus albus* L.	Rutaceae	South and central Europe	Burning Bush, Gasplant, White Dittany	Root bark	Ethanol extract	Lowers fever, bacterial, fungal infections, induce menstruation, abortion,	Anticancer, anti-inflammatory, antimicrobial, anti-HIV, antiplatelet, insecticidal,	*In vitro*, the percentage inhibition of hPDE5A isoenzyme was measured	Haplopine[a] ($14.7 \pm 0.6\%$), robustine ($17.1 \pm 07\%$), dictamine	Evolitrin, kokusaginin, maculosidin, isodictamnine, dictamnoside K, luteolin 3′-methyl ether, isorhamnetin, isoquercetin, rutin, cnidioside A,	(Lv et al., 2015; Nam et al., 2005)

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Sl. No.	Plant name	Family	Common name	Geographical location	Part used	Type of extract or fraction	Traditional use	Pharmacological properties	Experimental method	Active chemical constituent (s)	Other identified phytochemicals	References
							antispasmodic, mild tonic, diuretic, expectorant, febrifuge, galactagogue, stimulant, tonic.	antidepressant, neuroprotective, antimutagenic, anti-fertility and antioxidant		(21.6 ± 0.6%), and γ-fagarine (67.0 ± 0.9%) were found to inhibit the PDE5A isoenzyme at 0.1 mM concentration	methylcnidioside A- B, cnidioside B	
72	*Eulophia macrobulbon* (E. C. Parish & Rchb. f.) Hook. f.	Orchidaceae	Corduroy orchid	Eastern Himalayas, Northern Myanamar, Thailand, Laos, Cambodia and Vietnam	Tuber	95% Ethanol extract	Relieve pain, fatigue, used as aphrodisiac, antiseptic, and antimicrobial.	Erectile dysfunction, anti oxidant, anticarcerogenic, anti-inflammatory.	*In vitro* evaluation by using rat lung tissue.	IC_{50} value of 9,10-dihydro-4-(4′-hydroxy benzyl)-2,5-dimethoxy phenanthrene-1,7-diol, 1-(4′-hydroxy benzyl)-4,8-dimethoxy phenanthrene-2,7-diol[a], 1,5,7-trimethoxyphenanthrene-2,6-diol are 62.3 ± 3.3 μM, 1.7 ± 0.5 μM, 98.1 ± 13.3 μM.	4-Methoxy-9,10-dihydro-2,7-phenanthrenediol, 4-Methoxy-2,7-phenanthrenediol, 1,5-Dimethoxy-2,7-phenanthrenediol, 1,5,7-Trimethoxy-2,6-phenanthrenediol, 1-(4-Hydroxybenzyl)-4,8-dimethoxy-2,7-phenanthrenediol	(Preedapirom et al., 2018; Temkitthawon et al., 2017)
73	*Decussocarpus rospigliosii* (Pilg.) De Laub.	Podocarpaceae	Pino hayuelo, pino laso, pino de montana, pino romeron and romerillo macho	Venezuela, Colombia, Peru, Ecuador and Bolivia in South America.	Leaves	Ethyl acetate extract	NP	Phosphodiesterase inhibitor	*In vitro,* evaluation of the isolated biflavones against PDE5 isolated from bovine aortic myocytes with respect to other flavones and Zaprinast as standard	The IC_{50} values of isolated compounds: amento flavone[a], podocar pusflavone, sequioia flavone, podocarpus flavone B, 7,7″-di-O-methylamento flavone, heveaflavone are 1.13 ± 0.04 μM, 1.1 ± 0.1 μM, 2.7 ± 0.1 μM, 9.2 ± 0.9 μM, >100 and > 100 μM	Nagilactone E-G, β-sitosterol, and β-sitosterol 3-0-β-D-glucopyranoside	Chaabi et al. (2007)
74	*Eurycoma longifolia* Jack	Simaroubaceae	Tongkat ali	Indonesia, Malaysia, Vietnam and also Cambodia,	Root barks	Aqueous	Aphrodisiac, treatment of intermittent fever (malaria),	Cytotoxic and antiproliferative, antimicrobial, aphrodisiac, anti-	*In vitro* evaluation using rat penile tissue homogenate.	Ellagic acid, Rutin, Quercetin	Eurycomanone (pasakbumin-A, B), eurycomanols, hydroxyklaineanones, eurycomalactones,	(Mohamed et al., 2015; Oboh et al., 2018a)

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				Myanmar, Laos and Thailand			lumbago, indigestion, dysentery, high blood pressure, diarrhea, leukemia, osteoporosis, anxiety, constipation used as vermifuge, appetite stimulant and health supplement.	inflammatory, antitussive, antidiabetic, anti osteoporotic and erectogenic	$IC_{50} = 251.8 \pm 5.26$ μg/mL		eurycomadilactones, eurylactones, laurycolactones, longilactones, and hydroxyglaucarubol, 5,9-dimethoxycanthin-6-one; 9,10-dimethoxycanthin-6-one, 11-hydroxy-10-methoxycanthin-6-one; 10-hydroxy-9-methoxycanthin-6-one; and 9-methoxy-3-methylcanthin-5,6-dione	
75	*Spondias mombim* L.	Anacardiaceae	Yellow mombin or hog plum	South America, Africa, India	Leaves	Ethyl acetate fraction	Treatment of various nervous disorders, used as antitumoral, antidepressive, and anxiolytic agent	Cytotoxic, antioxidant, anti ulcer, hepatoprotective, anti-inflammatory, photoprotective antiarthritic, analgesic, antipyretic, thrombolytic, antifertitlity, antihypertensive, antimicrobial, hypoglycemic, anthelmintic, diuretic	*In vitro* evaluation using rat penile tissue homogenate and using sildenafil as standard. $IC_{50} = 84.27 \pm 0.02$ μg/mL	NP	Geraniin, galloyl geraniin, stigmasta-9-en-3,6,7-triol, 3-Hydroxy-22-epoxystigmastane, lupeol, cadinene	(dos Santos Sampaio et al., 2018; Ojo et al., 2019a)
76	*Ocimum gratissimum* Linn	Lamiaceae	Clove basil, African basil, wild basil	Africa, Madagascar southern Asia, Mexico, Panama, West Indies, Brazil, and Bolivia	Leaves	Aqueous extract	Treatment of epilepsy, high fever, diarrhea, mental illness, fungal infections, cold, catarrh, sedative, abdominal pains, sore eyes, ear infections, coughs, barrenness.	Antimicrobial, antifungal, ovicidal, leishmanicidal, anti-diarrhoeal, anti-inflammatory, analgesic, antimutagenic, wound healing, cytotoxic, antihypertensive, immunostimulatory, antidiabetic, hepatoprotective, anti oxidant, anticonvulsant, nematicidal.	*In vitro*, the extract inhibits PDE5 enzyme present in penile tissue with IC_{50} value of 43.19 μg/mL and 44.67 μg/mL in testicular tissue.	NP	Eugenol, (Z)-α-Bisabolene, Thymol, γ-Terpinene, β-Caryophyllene, *p*-Cymene, germacrene D, (E)-β-Ocimene, α-Selinena, (E)-β- Farnesene	(Ojo et al., 2019b; Prabhu et al., 2009)
77	*Mallotus philippensis* Muell. Arg.	Euphorbiaceae	Kamala tree, red kamala or kumkum tree	South Asia, Southeast Asia, and Australia	Fruit	NP	Used as bitter, cooling, appetizer, purgative, anthelmintic, detergent, carminative, treatment of bronchitis, abdominal diseases, spleen enlargement, expelling tape worms.	Antifilarial, antifertility, antibacterial, anti-inflammatory, immunoregulatory, antioxidant, anticestodal, anthelmintic, antitubercular, hepatoprotective, cytotoxic, anti-HIV, antiallergic, wound healing.	*In silico* and *in vitro* evaluation using PDE5 assay kit (BPS Biosciences, USA)	Rottlerin, $IC_{50} = 17.33$ μM	Coroglaucigenin, Corotoxigenin, Lupeol, Friedelin, Bergenin, Kamalachalcone A, Kamalachalcone B, Mallotophilippen B, Mallotophilippen C, Isorottlerin	(Dar et al., 2019; Gangwar et al., 2016)

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78	*Allium cepa* L.	Liliaceae	Iran, western Indian subcontinent and Central Asia	Onion	FRS 1000 a beverage containing flavonoids	Onion peel	Used as aphrodisiac. Improves ocular ailments, aids in sleep, oral sores, toothaches, lumbago and dysentery.	Antiplatelet, antidiabetic, anticancer, antimicrobial, antioxidant, hepatoprotective, anti-inflammatory	*In vitro* evaluation using Zaprinast standard	Quercetin[a] and kaempferol showed PDE5 inhibition with IC_{50} value of 1.9 and 2.5 μM.	Quercetin 3,4′-diglucoside, myricetin, isorhamnetin, peonidin 3′-glucoside, malvidin 3′-glucoside, delphinidin 3′-glucoside, petunidin 3′-glucoside acetate	(Lines and Ono, 2006; Marrelli et al., 2019)
79	*Piptadenia stipulacea* (Benth.) Ducke	Fabaceae	Several parts of South America	Jurema Branca	Aerial parts	96% Ethanol exract	Used to treat wounds, as healing agent	Antiviral, antinociceptive, anti-inflammatory, vasorelaxant, spasmolytic.	*In vivo,* Galetin 3, 6-Dimethyl ether potentiated the relaxant effect of aminophylline and sildenafil, suggesting PDE5 inhibition.	Galetin 3,6-dimethyl ether	Santin, demethoxycentaureidin	(de Queiroz et al., 2010; Macêdo et al., 2014)
80	*Vitis vinifera* L.	Vitaceae	Common grape vine	Native to the Mediterranean region, Central Europe, and southwestern Asia	Grape skin	Selective extraction with wine like solution	Treatment of skin diseases, diarrhea, throat infections, condylomata, uterine tumors, and tonsils. Also used as aphrodisiac, astringent, demulcent	Antioxidant, cardioprotective, hepatoprotective, antimicrobial, antiviral, anticarcinogenic, antidiabetic.	*In vitro* evaluation using sildenafil and zaprinast as standard	Anthocyanins mixture[a], IC_{50} = 11.6 μM, malvidin-3-O-β-glucoside (IC_{50} = 35.4 μM) and malvidin (IC_{50} = 24.9 μM)	Kaempferol-3-O-glucosides, quercetin, myricetin, (+)-catechins, (−)-epicatechin, (−)-epicatechin-3-O-gallate, procyanidins dimers, procyanidins	(Dell'Agli et al., 2005; Valli Kanagarla et al., 2013)
81	*Sophora flavescens* Aiton	Fabaceae	Shrubby sophora	Asia, Oceania, and the Pacific Islands	Roots	Methanol extract and Ethyl acetate fraction	Treatment of fevers, dysentery, jaundice, vaginal itching, abscesses, carbuncles, enteritis, leukorrhea, scabies, swelling, and pain. diuretic, stomachic, antipyretic, and anthelmintic	Antibacterial, estrogenic, antitumor, antiandrogenic, antidiabetic, antifungal, antiviral, anti-inflammatory, insecticidal, hepatoprotective, anti-angiogenetic	*In vitro,* IC_{50} value for Methanol extract is 4.77 μg/mL and that of Ethyl acetate fraction is 1.54 μg/mL	Kushenol H (IC_{50} = 4.75 μM), kushenol K (IC_{50} = 10.6 μM), kurarinol (IC_{50} = 6.1 μM), sopho flavescenol[a] (IC_{50} = 0.013 μM), and kuraridine (IC_{50} = 0.64 μM), isolated from Ethyl acetate fraction.	Kushenol G, citrusinol, rutin, Isokurarinone, leachianone, kosamol A, formononetin, kuradin, maackiain, flavascensine, lupeol, citrusin A and B	(He et al., 2015; Shin et al., 2002)
82	*Baccharis trimera* (Less.) De Candolle	Asteraceae	Carqueja	South America	Whole plant	Dichloromethane and Methanol extract	Digestive, tonic, febrifuge, antidiarrheal, hepatoprotective, contraceptive, against woman sterility and as aphrodisiac	Antioxidant, anti-inflammatory, gastroprotective, hepatoprotective, anthelmintic, prypanocidal, antifungal, antibacterial, antiviral, antiproliferative, insecticidal, anti-	*In vitro*, 70% relaxation of smooth muscle of the corpus cavernosum of Guinea pig at 10 mg/ml of extract in comparison to Sildenafil.	NP	Quercetin, luteolin, rutin, quercetin 3-0-α-L-rhamnosyl-(1 → 6) -β-D-glucoside, Coumaroylquinic acid; 5-O-feruloylquinc acid; 3-O-Isoferuloylquinc acid	(Hnatyszyn et al., 2003; Silveira Rabelo and Caldeira Costa, 2018)

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								alzheimer, anti-hemorrhagic				
83	*Haplopappus rigidus* Phil.	Astereaceae	Bailabuena	South America	Whole plant	Dichloromethane extract	Treatment of grip, pneumonia, cold, urinary deseases and as aphrodisiac	Anti oxidant, Cytotoxic, hypolipidaemic	*In vitro*, 87% relaxation of smooth muscle of the corpus cavernosum of Guinea pig at 10 mg/ml of extract in comparison to Sildenafil.	NP	Feruloylquinic acid, Caffeoylquinic acid, Kaempferol 3-*O*-hexoside pentoside, Quercetin methyl ether pentoside hexoside, Kaempferol-3-*O*-hexoside, Kaempferol	(Hnatyszyn et al., 2003; Schmeda-Hirschmann et al., 2015)
84	*Huperzia saururus* (Lam.) Trevis	Lycopodiaceae	Cola de quirquincho	South America	Whole plant	Methanol extract	Purgative, emmenagogue, abortifacient, stimulant and aphrodisiac; treatment of impotence in old men	Anticholinesterase inhibition and used in Alzheimer's disease	*In vitro*, 88% relaxation of smooth muscle of the corpus cavernosum of Guinea pig at 10 mg/ml of extract in comparison to Sildenafil.	NP	6-hydroxylycopodine, lycopodine, lycodine and clavolonine, N-methyllycodine, N-acetyllycodine, sauroine and sauroxine	(Hnatyszyn et al., 2003; Ortega et al., 2006)
85	*Maytenus ilicifolia* Mart. ex Reisseck	Celasteraceae	Cangorosa	South America	Whole plant	Both Methanol and Dichloromethane extracts	Sialagogue, emmenagogue, abortifacient, contraceptive, antispasmodic, digestive and aphrodisiac; treatment of whooping cough, asthma and menstrual pains	Antinociceptive, anti-inflammatory and antihypertensive	*In vitro*, 70% relaxation of smooth muscle of the corpus cavernosum of Guinea pig at 10 mg/ml of extract in comparison to Sildenafil.	NP	6-oxotingenol, pristimerin, 6-Oxopristimerol, 3-Methyl-6-oxotingenoI, Tingenone	(Hnatyszyn et al., 2003; Tabach et al., 2017)
86	*Satureja parvifolia* (Phil.) Epling	Lamiaceae	Oreganillo	South America	Whole plant	Dichloro methane extract	Digestive, laxative, purgative, emmenagogue, stimulant, against women sterility and aphrodisiac	Antimicrobial, antioxidant, cytotoxic, acetylcholinesterase inhibitory effect, insecticidal, butyrylcholinesterase inhibition, antispasmodial, typanosidal, antiprotosoal,	*In vitro*, 95% relaxation of smooth muscle of the corpus cavernosum of Guinea pig at 2.5 mg/ml of extract in comparison to sildenafil.	NP	cis-piperitenone epoxide, piperitenone, piperitenone oxide, pulegone	(Hnatyszyn et al., 2003; van Baren et al., 2006)
87	*Senecio eriophyton* J. Remy	Asteraceae	Chachacoma	South America	Whole plant	Dichloromethane extract	Digestive, emmenagogue, stimulant and aphrodisiac	Smooth muscle relaxant	*In vitro*, 94% relaxation of smooth muscle of the corpus cavernosum of Guinea pig at 5 mg/ml of extract in comparison to Sildenafil. (Hnatyszyn et al., 2003)	NP	NP	Hnatyszyn et al. (2003)

(*continued on next page*)

Table 3 (*continued*)

Sl. No.	Plant name	Family	Common name	Geographical location	Part used	Type of extract or fraction	Traditional use	Pharmacological properties	Experimental method	Active chemical constituent (s)	Other identified phytochemicals	References
88	*Epimidium brevicornum* Maxim	Berberidaceae	Barrenwort, bishop's hat, fairy wings, horny goat weed, or yin yang huo	Endemic to China, parts of Asia and in the Mediterraniand	Aerial parts	Ethanol	Improve sexual performance, sexual desire, used to treat weak back, knees, joint pain, arthritis, fatigue, memory loss.	Treat coronary artery disease, erectile dysfunction, Alzheimer's disease, antiosteoporetic and antihypertensive	Extract containing 20.9% Icariin showed 80% inhibition against human recombinant PDE5A1 enzyme at 50 μg/mL	Icariin[a] (IC_{50} = 5.9 μM), Icariside II	3′-Hydroxyl epimedoside A, Neo-sagittasine A, Dihydrofuran-baohuoside I, epimedin A-C, diphylloside C, diphylloside B, icariside I, luteolin	(Dell'Agli et al., 2008; Li et al., 2017)
89	*Ammi visnaga* (L.) Lam.	Apiaceae	Tooth pick plant, toothpickweed	Europe, Asia, North Africa	Fruit	Purchased Visnagin	Treatment of angina symptoms, respiratory tract infections, asthma, urinary calculi, gastrointestinal cramps, emmenagogue, diuretic	Antimicrobial, antioxidant, treatment of vitiligo, cardiovascular effects	*In vitro* evaluation using PDE5 isoform isolated from the media layer of bovine aorta	Visnagin, khellin	Khellinol, amminol, linalool, bornyl acetate, thymol, khellol, khellinin	(Duarte et al., 1999; Esmail, 2013)
90	Citrus fruits	Rutaceae		South East Asia	Fruit	Purchased (±)-Naringenin	Appetizer, cardio-stimulant, and antiemetic, antidiarrheal, improves digestion	Anti-inflammatory, antioxidant, antiallergic, hepatoprotective, antiviral, antithrombotic, anticarcinogenic	*In vitro* evaluation by using PDE5 enzyme isolated by anion exchange chromatography from a bovine aortic smooth muscle cytosol fraction.	(±)-Naringenin, IC_{50} = 68 μM	Flavones, flavanones, flavanols, anthocyanidins, chalcones	(Chaudhari et al., 2016; Orallo et al., 2005)
91	*Pistacia lentiscus* L.	Anacardiaceae	Mastic	Greece, Mediterranian area	Leaves	Aqueous, 30% ethanol and 70% ethanol	Treatment of gastrointestinal disorders	Antioxidant, antimicrobial, antifungal, anti-inflammatory, chemopreventive, cardioprotective, wound healing,	*In vitro* evaluation using Zaprinast standard	NP	α-pinene, β-pinene, β-myrcene, verbenene, α-ylangene, α-copeane, β-bourbonene,	(Badreddine and Jean-Marc, 2008; Pachi et al., 2020)
92	*Anaxagorea luzonensis* A. Gray	Annonaceae	Bobonoyang, Cha Wua Talông	Thailand	Heartwood	Methanol	Blood tonic, stomachic, antipyretic, treatment of muscular pain	Phosphodiesterase inhibitor, antioxidant	*In vitro,* IC_{50} = 3.0 μM	The IC_{50} values of the isolated compounds: 6-deoxyisojacar-eubin; 1,3,5,6-tetrahydro xyxanthone; 1,3,5-trihy-droxy-4-pre-nylxanthone; 1,3,5-trihydroxy-4-(3-hydroxym ethylbutyl) xanthone[a]; 1,3,6-trihy-droxy-5-methoxyxan-thone are 42.7, 26.1, 3.0, 35.0 μM	6-deoxyisojacareubin, 1,3,5,6-tet-rahydroxyxanthone, quercetin, taxifolin, aromadendrin	(Gonda et al., 2000; Sabphon et al., 2015)

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Table 3 (*continued*)

Sl. No.	Plant name	Family	Common name	Geographical location	Part used	Type of extract or fraction	Traditional use	Pharmacological properties	Experimental method	Active chemical constituent (s)	Other identified phytochemicals	References
93	*Phyllanthus amarus* Schum. and Thonn.	Euphorbiaceae	Black catnip, Carry me seed	Tropical and subtropical countries	Whole plant	96% Ethanol extract	Astringent, stomachic, diuretic, aphrodisiac, febrifuge, antiseptic, antispasmodic, antidyspnoic	Antiamnesic, antibacterial, anticancer, antidiarrhoeal, antifungal, analgesic, antiplasmodial, aphrodisiac, antidiabetic, immunomodulatory	*In vivo*, with respect to Sildenafil as control	NP	Phyllanthin, niranthin, lintetralin, geraniin, amariin, fursin, hinokinin	(Bankole et al., 2011; Patel et al., 2011)
94	*Terminalia catappa* L.	Combretaceae	Almond	Asia, Africa, Australia	Leaf and stem bark	Aqueous	Antihypertensive, leprosy, scabies, stomachic, headache	Antioxidant, antimicrobial, anti-inflammatory, analgesic, wound healing, antidiabetic, hepatoprotective, anticancer, antiaging	*In vitro*, IC_{50} = 238.44 ± 3.57 μg/mL and 273.43 ± 4.03 μg/mL using Sildenafil citrate as positive control	NP	Catechin, protocatechuic acid, prenylated benzoic acid, 2-prenylated benzoic acid	(Anand et al., 2015; Oyeleye et al., 2018)
95	*Cnidium monnieri* (L.) Cusson ex Juss.	Apiaceae	Shechuangzi	India, China, Korea, Laos, Mongolia, Vietnam, Russia, Europe	Fruit	Ethanol	Treatment for female genitals, male impotence, frigidit, skin diseases	Antipruritic, anti-allergic, antidermatophytic, antibacterial, antifungal, antiosteoporotic	*In vitro*, (PDE-Glo Phosphodiesterase assay kit, Promega, USA) IC_{50} = 33.7 μg/mL	NP	Osthole, imperatorin, bergapten, isopimpinellin, xanthotoxol, xanthotoxin, cnidimonal, cnidimarin	(Lee et al., 2012; Sun et al., 2020)
96	*Cuscuta chinensis* Lam.	Convolvulaceae	Chinese Dodder	Eastern Asia, Russia	Seed	Ethanol	Tonic, aphrodisiac, lambago, treatment of cold, improve eye sight, soreslower abdominal and back pain	Hepatoprotective, anti-osteoporotic, immunomodulatory, antioxidant, anti-aging, antidiabetic, anti-depressant, renoprotective, anti-inflammatory	*In vitro*, (PDE-Glo Phosphodiesterase assay kit, Promega, USA) IC_{50} = 65.7 μg/mL	NP	Quercetin, astragalin, hyperoside, rutin, calycopteretin, apigenin, chlorogenic acid, caffeic acid, arbutin,	(Donnapee et al., 2014; Lee et al., 2012)
97	*Morinda officinalis* How.	Rubiaceae	Indian mulberry	South East Asia, Northeastern Australia, Caribbean	Root	Ethanol	Treatment of kidney problems, impotence, weak tendons and bones, diabetes, hypertension	Anti-depressant, antiosteoporotic, anti-inflammatory, anti-aging, antioxidant, immunomodulation, cardioprotective	*In vitro*, (PDE-Glo Phosphodiesterase assay kit, Promega, USA) IC_{50} = 48.7 μg/mL	NP	Monotropein, asperuloside, physcion, rubiadin, morindolide	(Lee et al., 2012; Zhang et al., 2018)

NP represents no presented information.

[a] represents the most active constituent exhibiting PDE5 inhibition.

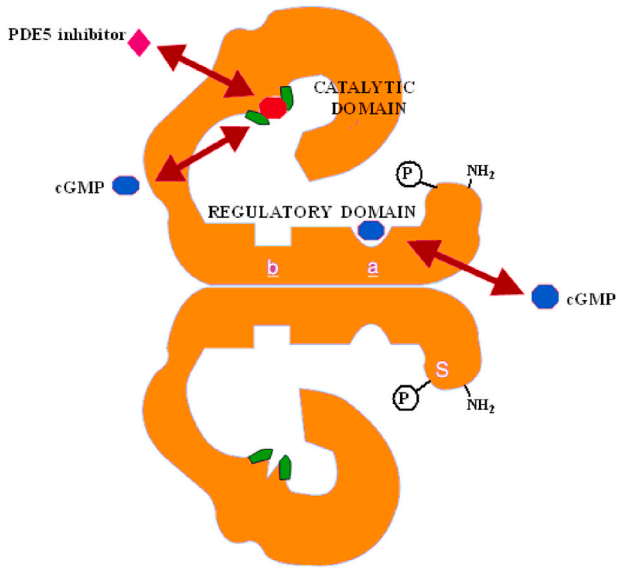


Fig. 1. Structure of PDE5 enzyme.

The mechanism of PDE5 inhibition on different body ailments, share a similar pathway for cGMP signaling through the activation of cGMP-dependant protein kinase or Protein Kinase G (PKG) (Corbin et al., 2000; Francis and Corbin, 2003; Moreira et al., 2000).

PDE5 is a cGMP selective homodimeric enzyme, containing a catalytic and a regulatory domain, where the catalytic domain accommodates a C-terminal of each monomer with two binding sites for Zinc and a cGMP binding allosteric site. The regulatory N-terminal contains two non-catalytic GAF domains (GAFa and GAFb) responsible for the allosteric binding of cGMP; which upon binding will cause the phosphorylation at Ser-92 by PKG. This process takes part in activating the enzyme and at the catalytic site of C-terminal, thereby increasing the binding affinity for cGMP. Hence, this binding of cGMP to both the catalytic and regulatory domains create a negative feedback loop (Corbin et al., 2000; H. Wang et al., 2006). This synergistic interaction between cGMP and the catalytic site improves the binding of cGMP to the allosteric site which increases the phosphorylation of the enzyme responsible for further degradation of cGMP, ultimately leading to the relaxation of smooth muscle. The structure of PDE5 enzyme is shown in Fig. 1. There are three PDE5 isoforms, PDE5A1, PDE5A2 and PDE5A3 which are generated from one gene; PDE5A on chromosome 4q26. These isoforms vary in their N-terminal sequence but possess similar functional and biochemical properties (Card et al., 2004; Rybalkin et al., 2003).

The entire process is initiated by the release of NO from both the noradrenergic and non-cholinergic nerve terminals, as well as from the blood vessel walls lined by the endothelial cells. NO and heme moiety forms a high-affinity complex in the cytosolic guanyl cyclase (GC) as it gets diffused into the vascular smooth muscle cells (Fiscus, 2002). The GC is activated as the NO gets bound to heme and forms a complex; concomitantly Guanosine triphosphate (GTP) gets converted to cGMP and its production is increased. The cGMP that is produced will bind and activate PKG which further phosphorylates numerous cellular proteins. During this process, the intracellular Ca^{2+} gets reduced due to an increase in extrusion and sequestration of Ca^{2+} ions in the intracellular structures and thus having decreased sensitivity towards target proteins. This entire process results in the relaxation of smooth muscles and consequently, the vasomotor tone in the smooth muscle cells gets reduced (Fig. 2). The allosteric binding sites for cGMP in PDE5 enzyme are biochemically and evolutionarily distinct from the catalytic site. Also, the cyclic phosphate bonds of cGMP and cAMP will not be hydrolyzed by other cellular PDEs as the PDE5 inhibitors have structures similar to that of cGMP and can occupy the catalytic site causing blockage of access to cGMP (Fig. 3). The synthetic PDE5 inhibitors such as sildenafil, tadalafil and vardenafil have approximately 1000–5000 times greater affinities for PDE5 catalytic site than cGMP due to their additional molecular contacts with the catalytic site (Corbin and Francis, 1999; Rotella, 2002). Therefore, the competitive occupation by the inhibitor to the catalytic site prevents cGMP breakdown as the access to catalytic machinery is occupied. So in this ongoing process of cGMP synthesis, the specific PDE5 inhibitors create an accumulation of cGMP in the corpora cavernosa, thereby contributing to improved erectile function.

The blood is carried by the penile artery to the sinusoidal spaces of the corpus cavernosum and corpus spongiosum and exits towards the post cavernous venules. These arteries and sinusoids contain a layer of smooth muscle cells along their walls, and the relaxation or dilation of these cells allows more blood to flow into the penis, and thereby increases the blood flow to the sinusoids as well as the volume within these compartments, thus causing a state of penile tumescence. Hence, the corpora cavernosa expands and press against the inflexible tunica albuginea and reduces the outflow of venous blood (Corbin, 2004; Francis et al., 2008). This causes the pressure inside the corpora cavernosa to increase and approach the systolic blood pressure and finally resulting in penile erection. An outline of penile blood flow and erection is shown in Fig. 4.

1.3. *Current status of PDE5 inhibitors for the treatment of ED*

Pfizer laboratories, in 1989 synthesized a compound UK-92,480 (Sildenafil citrate), suggesting its effectiveness for decreasing vascular resistance and reducing platelet aggregation. So in 1991, clinical trials were conducted on the drug as an anti-anginal agent, but the results were found to be less significant with moderate vasodilatory effect (Jiann, 2016). Further studies also supported the use of UK-92,480 for its vasodilatory and antihypertensive effects. However, multiple studies on healthy volunteers to investigate the pharmacokinetics, pharmacodynamics, and tolerance of UK-92,480 indicated reports of headaches, flushing, indigestion and muscle aches along with penile erections after a mere several days of administration. This side effect of penile erection led to undertake sildenafil for treating ED which led to the identification of sildenafil as a potential selective PDE5 inhibitor. But in 1990, the Ignarro group reported that in rabbits, the mediation of penile erection occurs in corpus cavernosum smooth muscles through the elevation of NO-induced cGMP (Fiscus, 2002). With the supporting reports, the first clinical study of sildenafil for treating ED was started as a two-phase crossover study and was found to improve penile erection upon sexual stimulation in patients, leading to phase III clinical study in 1998, which was supported and validated by a 15- item self-reported questionnaire by the IIEF (Halcox et al., 2002; Yafi et al., 2018). Thus, sildenafil became the first PDE5 inhibitor approved for treating ED in 1998 and was marketed under the brand name of Viagra® for treating ED and was also used for treating pulmonary arterial hypertension under the brand name Revatio®. The approval of sildenafil led to sales exceeding US$ 1 billion and subsequently, Vardenafil (Levitra®) and Tadalafil (Cialis®) were also approved in 2003.

With the success of first-generation PDE5 inhibitors, new molecules had been developed such as Udenafil (Zydena®), which were fast-acting and had a long duration of action. But Udenafil is only approved in South Korea and has been approved for distribution in Russia and the Philippines (Kouvelas et al., 2009). Avanafil was approved by the United States FDA in 2012 and by the European Medicines Agency in 2013 and was marketed under the brand name of Stendra or Spedra, having a short half-life and a rapid onset of action in comparison with other PDE5 inhibitors (Bourin, 2018). Mirodenafil was found to be highly selective of PDE5 isoenzyme but had low inhibitory effects when compared to that of Sildenafil in the preclinical studies but was approved in Korea in 2007 (Kim et al., 2011).

Currently, PDE5 inhibitors are the second-line treatment for erectile

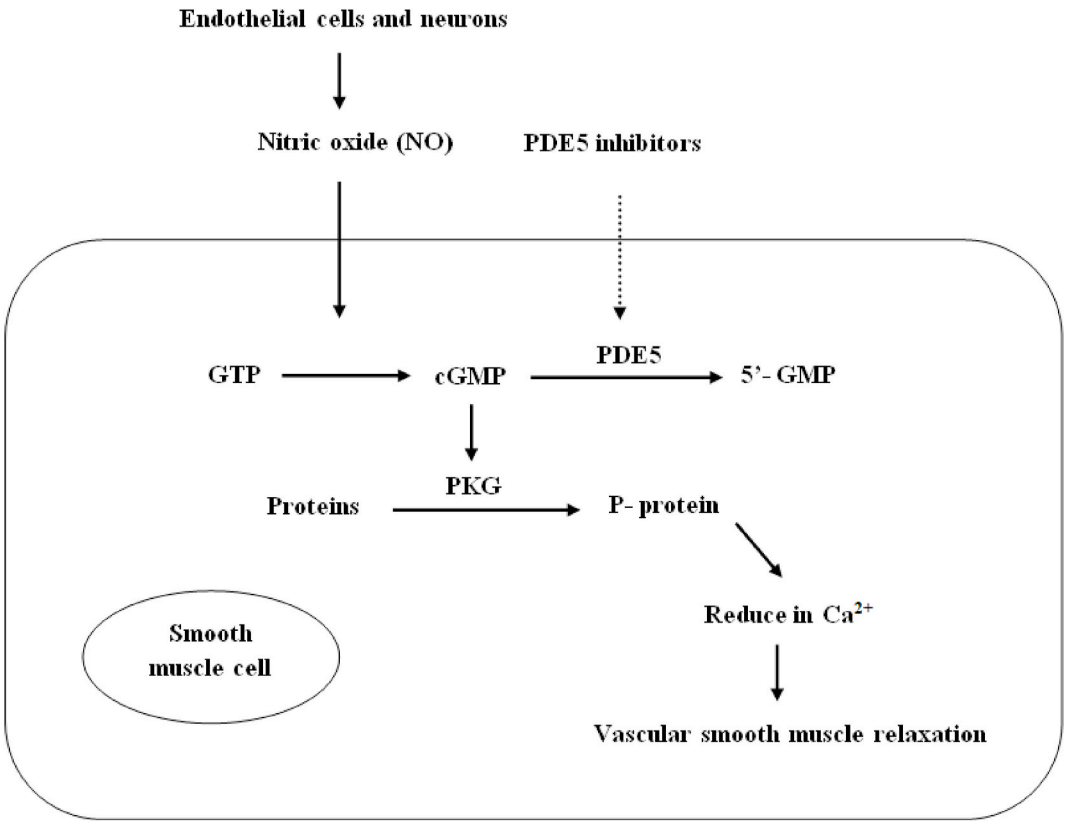


Fig. 2. Mechanism of smooth muscle relaxation through PDE5 inhibition, where GTP = Guanosine triphosphate, cGMP = cyclic Guanosine monophosphate, 5′GMP = Guanosine-5′-monophosphate, PKG = Protein kinase G.

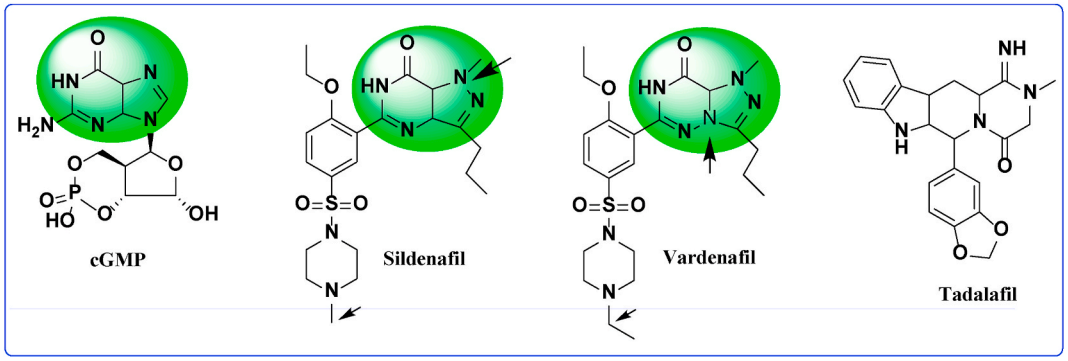


Fig. 3. Comparison of the molecular structures of cyclic guanosine monophosphate (cGMP), sildenafil, vardenafil, and tadalafil. *Circled areas* indicate the ring structures in sildenafil and vardenafil that resemble the purine moiety in cGMP. The *arrows* denote differences between structures of sildenafil and vardenafil.

dysfunction after behavioral modifications as these drugs only help in improving the erectile quality for men by enhancing blood flow in the corpora cavernosa. But the efficacy of PDE5 inhibitors is reported to be about 70% and is significantly lower in harder-to-treat subpopulations (Park et al., 2013). Also, the treatment failures might be due to the severe performance anxiety, unrealistic patient expectations, underlying pathophysiology, improper use of medication, difficult patient relationship dynamics, and psychological problems. Some of the reasons for initial non-response to PDE5 inhibitors are because of comorbidies such as cardiovascular disease (CVD), endothelial dysfunction and metabolic syndrome; inappropriate use of prescription by patients, misdiagnosis, psychological and partner issues. Also, decreased efficacy in PDE5 inhibitor usage is now more common in populations containing diabetes and pelvic surgeries (Lau et al., 2006; Palmer et al., 2007). The percentage of more than 8000 patients on sildenafil and 1500 patients on both vardenafil and tadalafil, non-responsive to one PDE5 inhibitor but responsive to another is only reported to be 5%. Some reports suggest that the patients treated with sildenafil are becoming resistant with time and several reports indicate that some patients initially responded well with sildenafil but became less responsive within 1 or 2 years, this eventually led the patients to seek for higher doses or discontinuation of treatment (Park et al., 2013; Yafi et al., 2018) due to tachyphylaxis, which can only be treated with other alternative therapy to PDE5 inhibitors.

But nowadays PDE5 inhibitors are the major targets for drug discovery as NO/cGMP pathway is involved in many physiological functions such as the urogenital, respiratory, and gastrointestinal system, heart, platelets, immunity, central nervous system, vision, and in the pathophysiology of a wide range of diseases. Presently, the use of sildenafil is the best effective oral therapy for treating erectile dysfunction

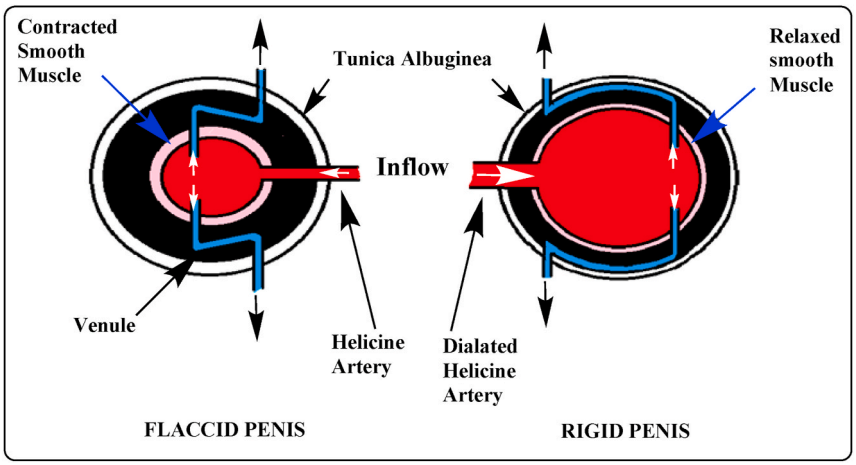


Fig. 4. Modified schematic representation of hemodynamic events associated with penile erection.

despite its common adverse effects such as headache, flushing and gastrointestinal upset which are related to the distribution of PDE enzyme (Jiann, 2016). However, severe toxicities have also been reported such as nonarteritic anterior ischemic optic neuropathy (NAION), hearing loss, nasopharyngitis and priapism (Yafi et al., 2018). A list of the marketed PDE5 inhibitors, their applications and the adverse effects are given in Table 2. Therefore, to eliminate or minimize these adverse effects of synthetic PDE5 inhibitors, the search for alternative sources for PDE5 inhibitors has become a new trend. The use of medicinal or traditional herbs are considered the best alternative sources for the establishment of new active pharmacophores as they are capable of displaying bioactivities with potential utility for the improvement of health (Dell'Agli et al., 2008; Rahimi et al., 2010). For example, YingYangHuo, commonly known as horny goat weed has been used in combinations with other herbs in Traditional Chinese Medicine (TCM) as a remedy for skeletal diseases, hay fever, atherosclerosis, hypertension, nerve pain, fatigue and erectile dysfunction. However, icariin isolated from the herb was found to be an excellent PDE5 inhibitor concerning Sildenafil. Further structural modifications were made on Icariin to enhance the PDE5 inhibitory effect, and Icaritin was obtained which had IC_{50} values very near to that of Sildenafil (Dell'Agli et al., 2008). In addition, gingketin from *Gingko biloba;* kokusaginine, skimmianine, evolitrine, confusameline, pomiferin from *Maclura pomifera;* haplopine, robustine, fagarine from *Dictamnus albus;* rottlerin from *Mallotus philippensis* and several flavonoids from *Eulophia macrobulbon, Decussocarpus rospigliosii* etc. are used as traditional remedies for erectile dysfunction according to the ethnobotanical survey from China, South east Asia, South America and Africa (Dell'Agli et al., 2006; Ribaudo et al., 2017).

Despite the abundance in traditional herbs and remedies used for treating ED and as aphrodisiacs, many scientific studies report only the extract level identification of PDE5 inhibition and have not identified the bioactive constituent(s) responsible for the action. This review aims to provide an overview of the ethnobotanical aspects of the traditionally used aphrodisiacs which are proven to be PDE5 inhibitors.

2. Materials and methods

An extensive literature search was made for procuring information about medicinal plants and herbs as PDE5 inhibitors without any time limit. The search was conducted on available online scientific databases where the primary search terms such as-medicinal plants, natural products, herbs, and PDE5 inhibitors; and plant name-accepted or synonyms, traditional uses, phytochemical constituents, pharmacological effects, and/or ethnobotany for the secondary searches were used. A total of 4127 scientific articles were screened (for e.g. Google scholar = 3880, ScienceDirect = 143, Scifinder = 66, Pubmed = 24 and Mendeley = 14), where screened and included if found relevant to the present review. Studies that focused on the management of ED, through medicinal plants or herbs that are aphrodisiacs or sexual stimulants without any significant PDE5 inhibition were excluded. The research papers that are included were also subjected to the guidelines proposed by (Mullane et al., 2015) to ensure the credibility, relevance, and sustainability of the research process in the biomedical field. The synonym, botanical names, family, distribution and biodiversity of different plants were confirmed using various online databases, such as http://www.worldagroforestry.org/, https://www.gbif.org/, www.theplantlist.org.

3. Results

3.1. Search results

From the above search, a total of 97 medicinal plants were identified to inhibit the PDE5 enzyme, where 76 plants are having ethnobotanical significance as aphrodisiacs or sexual stimulants and the remaining 21 are selected according to their effect against predisposing factors for ED.

3.2. Ethnobotany

The variety of medicinal plants cited for PDE5 inhibition effect have been used as aphrodisiacs, sexual performance enhancers or sex stimulants in traditional systems of medicine in various countries. These traditional remedies work either by stimulating or increasing the quantity of semen, as testosterone enhancers, ejaculatory performance and functions or promoting arousing of sexual desire in the patient, as circulatory stimulants. However, the plants mentioned in Table 3 are from different locations and have different traditional uses (Arya et al., 2018; Shin et al., 2015; Wang et al., 2018).

In the continent of Africa, medicinal plants have always been a dependable source of remedy for several acute and chronic diseases. The various tribes, communities and societies of the continent have their own traditional remedies for diseases such as diabetes, arthritis, hypertension, and also for erectile dysfunction. The majority of the African countries have many locally made, plant-derived sexual stimulants under various trade names, namely Tigerpower™, SuperLove™, Burantashi™, etc. Several medicinal herbs belonging to various genera and families with diverse chemical constituents are reported to possess aphrodisiac properties from regions of South Africa, Uganda, Nigeria, Kenya, Tanzania and Zimbabwe (Ajao et al., 2019). For example, the roots of *Ericosema* species are used as a remedy for ED and impotence in South Africa for centuries. Infusions made up of hot milk and Ericosema roots are administered in small doses during morning and night as a

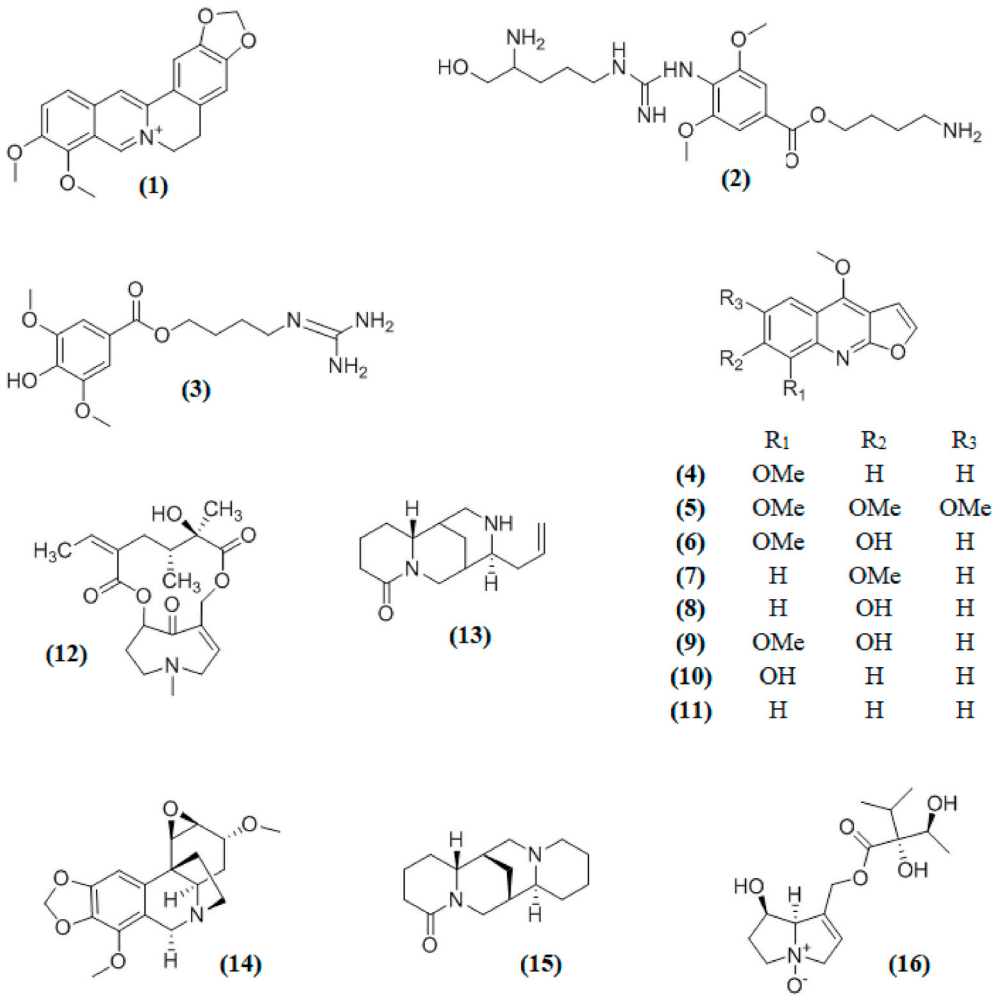
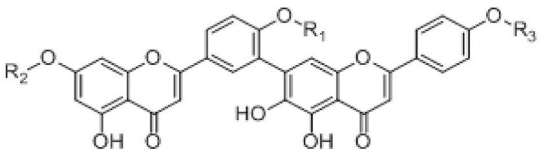


Fig. 5. Alkaloids or nitrogen containing compounds identified from the active plant fraction or extract as PDE5 inhibitors.

treatment of impotence. Medicinal plants belonging to families such as Fabaceae, Rubiaceae, Euphorbiaceae, Apocynaceae, Asteraceae, and Rutaceae were found abundant to have aphrodisiac properties. Plant parts such as roots, leaves, stem bark, stem, fruit and whole plants are used in different traditional formulations used as aphrodisiacs. But roots are the most preferred part for herbal preparations for sexual dysfunction as it is the most metabolite abundant plant part. However, the parts used for the traditional preparations may differ in terms of plant families, where the bulb is the preferred part of Hyacinthaceae, roots from Polygonaceae and stem bark from the Melianthaceae family. Despite the plant parts used, decoctions are the preferred preparation method followed by infusions, chewing and pounding (Ajao et al., 2019; Ojewole, 2007). Out of the 209 plant species reported to be aphrodisiacs from the Sub-Saharan region of Africa, only a handful of these medicinal herbs have been studied for their mechanistic activity as aphrodisiacs such as *Aframomum melegueta* (K. Schum), *Aframomum danielli* (Hook.f.) K. Schum, Anogeissus leiocarpus (DC.) Guill. & Perr., *Clerodendron capitatum* (Willd), *Hunteria umbellata* (K. Schum) Hallier, *Cylicodiscus gabunensis* Harms, *Drosera burmannii* Vahl, *Elephantopus scaber* L., *Tinospora crispa (L.)* Miers ex Hook. f. & Thomson, *Senna alata* (L.) Roxb., *Tamarindus indica* L., *Musa sapientum* L., *Spondias mombim* L., *Ocimum gratissimum* Linn, *Mallotus philippensis* Muell. Arg, *Vitis vinifera* L., *Sophora flavescens* Aiton, *Ammi visnaga* (L.) Lam., *Phyllanthus amarus* Schum. and Thonn., *Terminalia catappa* L. which are proven for their PDE5 inhibitory effect for treating ED. Among the various genera used as aphrodisiacs; *Cassia*, *Bersama*, *Elephantorrhiza*, *Hypoxis*, *Piper* and *Vachellia* are the most prominently used by the local communities.

Asian countries such as India, China, Indonesia, Thailand and Indonesia exhibit a plethora of medicinal herbs that are extensively used as natural aphrodisiacs. Traditional Chinese Medicine and Ayurvedic system of Indian medicine include a wide number of medicinal herbs that are found across different Asian countries as a remedy for sexual dysfunction. Some of the commonly used traditional preparations include the use of black gram, *Mucuna pruriens* (L.) DC., *Asparagus racemosus* Willd., *Madhuca indica* J.F.Gmel. and *Withania somnifera* (L.) Dunal; which are boiled in water and administered as a decoction (Dalal et al., 2013). Ayurvedic preparations such as *Bala* consisting of *Sida cordifolia* L., *Phaseolus trilobus* Ait., *Teramnus labialis* Spreng, *Leptadenia reticulata* (Retz.) Wight & Arn., *Withania somnifera* (L.) Dunal, *Pueraria tuberosa* (Willd.) DC., *Vitis vinifera* L. are cooked together and are administered along with black gram and sugar as a remedy for sexual dysfunction. The herbal products that are available in the market as sexual stimulants are VigRX Oil™, Maxoderm™, Virility Pills, VP-RX®, ExtenZe®, ProEnhance™ and Virility Patch RX™ (Kotta et al., 2013). However, some of the most commonly known natural aphrodisiacs which are still being used in Asia are Chinese yam, which is used as a tonic for reproductive system; Ginseng for its adaptogenic properties; *Eucommia ulmoides* Oliv., for its potent ability to treat impotency; *Ginkgo biloba* L. for its ability to improve sexual energy according to Chinese material medica; *Tribulus terrestris* L. as it has been long used in Eastern Europe and Bulgaria for sexual deficiency; *Eurycoma longifolia* Jack, found throughout South East Asia is a natural aphrodisiac; *Ptychopetalum olacoides* Benth., which is extensively used as folk medicine by Amazonian people to improve libido and penile hardness; *Pausinystalia*



	R_1	R_2	R_3
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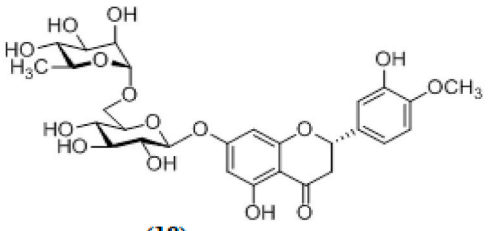
(36)	H	Me	Me
(37)	Me	Me	Me
(39)	Me	Me	H
(40)	Me	H	H



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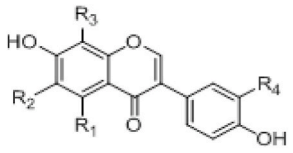
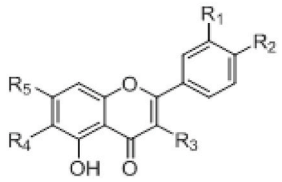
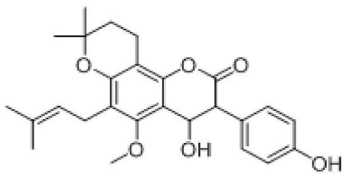


	R_1	R_2	R_3	R_4
(23)	OH	Prenyl	Prenyl	H
(24)	OMe	Prenyl	Prenyl	H
(25)	OH	H	H	H
(26)	OH	Prenyl	H	Prenyl



	R_1	R_2	R_3	R_4	R_5
(19)	H	OH	OH	H	OH
(20)	OH	OH	OH	H	OH
(21)	OH	OH	Rutinose	H	OH
(48)	H	OH	H	H	O-glucose
(49)	OH	OH	H	H	O-glucose
(51)	OH	OH	OH	OMe	O-glucose
(52)	H	OH	H	H	OH
(53)	OH	OH	H	H	OH



(27)

	R_1	R_2	R_3
(22)	OH	Prenyl	H
(28)	OMe	Prenyl	H
(29)	OH	H	Prenyl

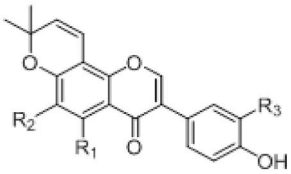


Fig. 6. Phenolic compounds identified from the active plant fraction or extract as PDE5 inhibitors (contd.).

yohimba Pierre ex Beille, which produces the first plant derived drug for treating impotency approved by the US FDA, *Epimedium* extracts commonly called 'yin yang huo' in Chinese which have shown exceptional PDE5 inhibition; *Lepidium meyenii* Walp. similar to ginseng for its adaptogenic and sexual function improving properties; *Erythroxylum catuaba* A.J.Silva used in several traditional preparations as a remedy for sexual weakness and low libido; *Smilax officinalis* Kunth called as 'khao yen' in Chinese for its ability to act as an aphrodisiac and sexual stimulant (Lim, 2017; Sheng-Ji, 2001); *Cassia auriculata* L., used for restoring sexual vitality, increase sperm count and to counteract ejaculatory disorders which is scientifically supported as a sexual stimulating agent by *in vivo* studies (Haripriya et al., 2019).

The medicinal plants such as *Anemopaegma arvense* (Vell.) Stellfeld & J.F.Souza, where the commercially available formulations are used for its aphrodisiac property in Brazil (Manabe et al., 1992). *Heteropterys aphrodisiaca* Machado known for its stimulant and aphrodisiac property in central Brazil was also proven to be effective through *in vivo* evaluation on adult Wister rats against Cyclosporine A induced testicular toxicity, which leads to male infertility (Monteiro et al., 2008). *Pfaffia glomerata* (Spreng.) Pedersen is commonly known as Brazilian ginseng distributed all over South America whose roots are known for its aphrodisiac and stimulant property. Further studies on the plant also suggest the *P. glomerata* hydroalcoholic root extracts increase testicular nitric oxide levels in adult male mice, showing effectiveness as a natural aphrodisiac (Dias et al., 2018) while another recent study also suggests that *P. glomerata* hydroalcoholic root extracts stimulate penile tissue in adult Swiss mice further supporting the traditional use (Dias et al., 2020). In addition, *Cyprus rotundus* L., *Jacaranda semiserrata* Cham., *Herreria salsaparilha* Mart. and *Macrosiphonia velame* (A. St.-Hil.) Mull. Arg., are also among some of the commonly used natural aphrodisiacs among central South America and Brazil (Rieder, 2010). *Citrullus lanatus* (Thunb.) Matsum. & Nakai, found in Brazil, commonly called as red watermelon, was also proven to improve sexual behavior through *in vivo* investigation in male rats (Munglue et al., 2014). However, the roots are

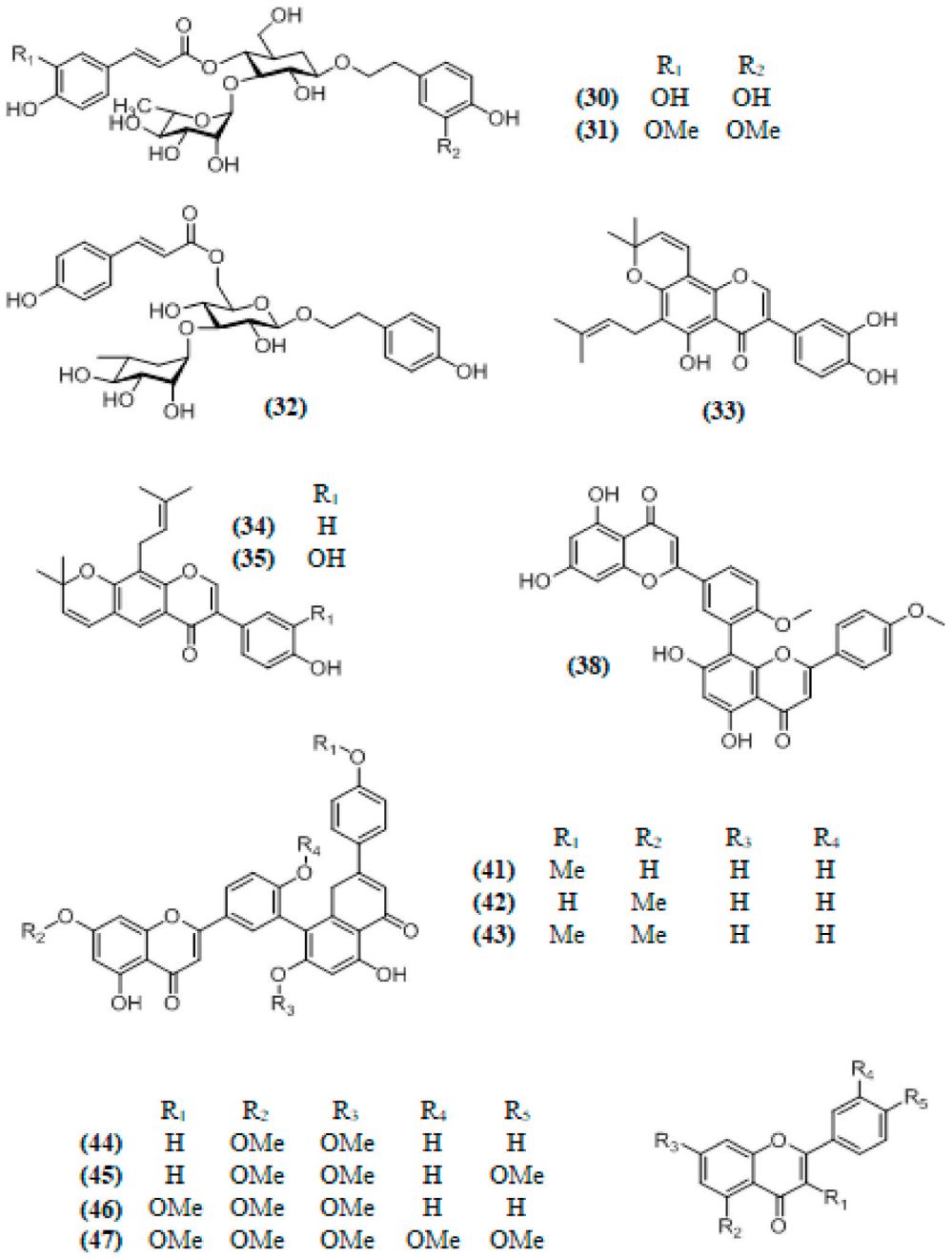


Fig. 6. (*continued*).

used for many of the traditional preparations which are extracted in wine or rum (Kotta et al., 2013; Srinivas et al., 2018). Some of the herbs such as *Pithecellobium dulce* (Roxb.) Benth. *Samanea saman* (Jacq.) Merr., *Senna alata* (L.) Roxb., *Campsiandra angustifolia* Spruce ex Benth., *Swartzia polyphylla* DC., *Tynanthus panurensis* (Bureae ex Baill.) Sandwith, *Serenoa repens* (W.Bartram) Small, *Swietenia macrophylla* King are also proven for their PDE5 inhibition effect (Agbabiaka et al., 2009; Oboh et al., 2017a). However, abundant medicinal plants having sexual stimulating effects have been screened for their PDE5 inhibitory effect, yet a large number of unexplored herbs are remaining which are yet to be identified and studied for their traditional properties.

3.3. Phytochemical constituents

Among the reviewed ninety-seven medicinal plants, a total of 85 compounds were identified, either through bioactivity guided fractionation or *in silico* studies as the bioactive constituents responsible for PDE5 inhibition. Some of the phytoconstituents are species or plant-specific such as the polyphenols rottlerin and icariin from *Mallotus philippensis* Muell. Arg and *Epimiedium genus* (Dar et al., 2019; Dell'Agli et al., 2008), while others are known to be present in many plants like the flavonoids quercetin, rutin and kaempferol, which were found responsible for PDE5 inhibition of FRS 1000 (red onion peel extract), *Eurycoma longifolia* Jack and *Swietenia macrophylla* King (Lines and Ono, 2006; Oboh et al., 2018a, 2017a), plants which are extensively used as aphrodisiacs across Eastern Asia, Central and South America. We hereby classify these phytochemical compounds according to their chemical features as follows: alkaloids or nitrogen-containing compounds (16) (Fig. 5), phenolic compounds (61) (Fig. 6) and compounds derived from polycyclic aromatic hydrocarbons (8) (Fig. 7).

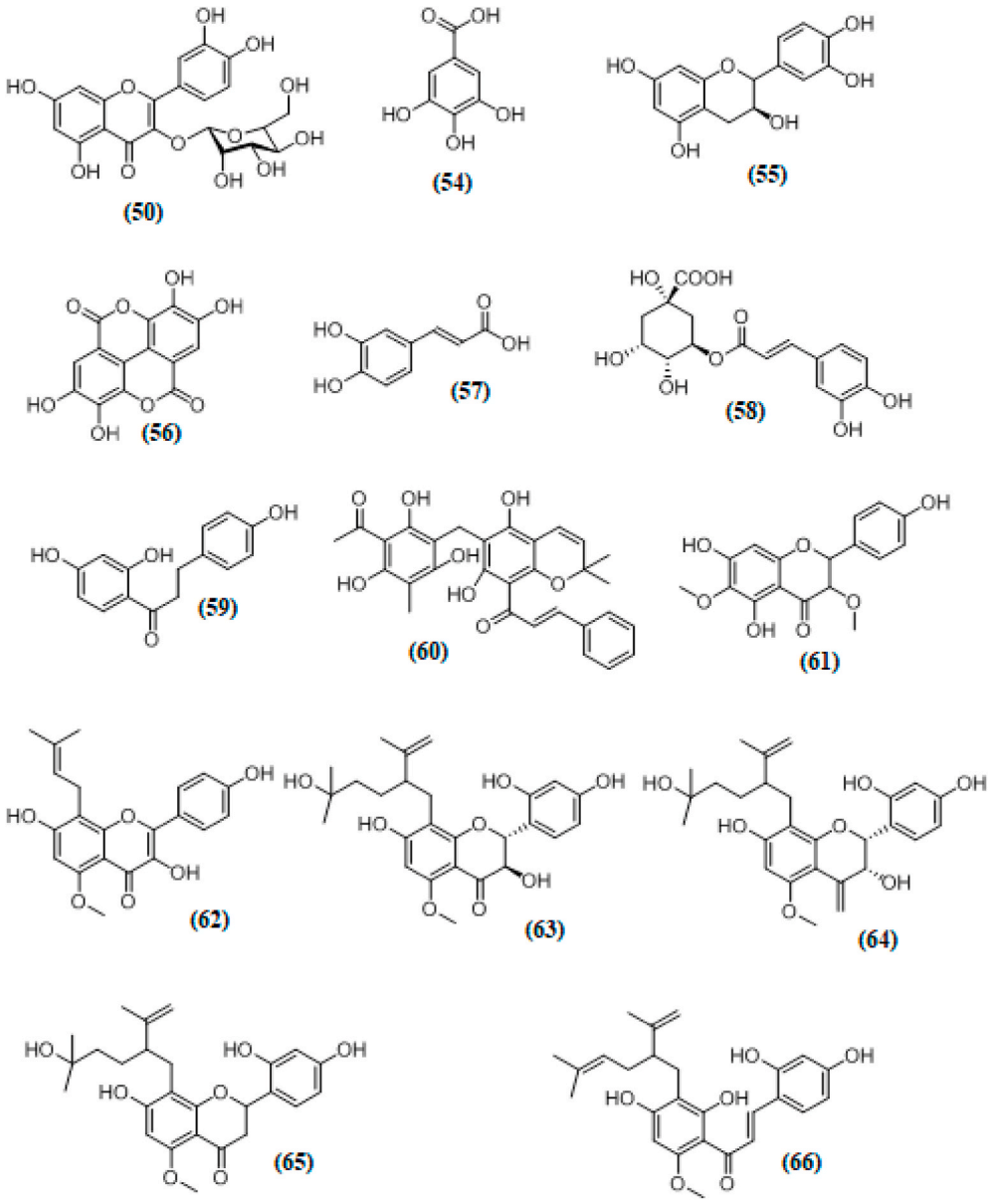


Fig. 6. (*continued*).

3.3.1. Alkaloids or nitrogen-containing compounds

A number of alkaloidal and non-alkaloidal phytochemicals have been reported to be PDE5 inhibitors. Theophylline and caffeine are the first non-selective PDE5 inhibitors isolated from tea leaf, leading to the discovery of selective PDE5 inhibition. *Berberis othrobotrys* Bien ex Aitch. (Berberidaceae) is an indigenous shrub of Pakistan which is used by the local people of Gilgit region for treatment of hypertension. The major compound berberine (1) is an isoquinoline alkaloid present in several *Berberis* and *Mahonia* species which has uses described in both Ayurvedic and Chinese medicines for its antibacterial, hyperglycemic and anti-inflammatory activities. However, studies have identified berberine along with other isoquinoline alkaloids in the butanol fraction of the roots, which was found to inhibit the calmodulin-activated PDE1 and PDE5 enzymes through the vascular reactivity studies on pig hearts (Alamgeer et al., 2016).

An *in silico* pharmacokinetic and docking study conducted by (Ruslin et al., 2014) reported a pseudoalkaloid, Leonurine (2) present in *Leonuris artemisia* L. used for its aphrodisiac, antihypertensive and diuretic properties along with several of its derivatives concluded that 4-amino-butyl 4-(3-(4-amino-5-hydroxypentyl)guanidino)-3,5-dimethoxybenzo ate (3) has the potential to be further developed as a PDE5 inhibitor. In addition, out of the eight furoquinoline alkaloids isolated from *Melicope confusa* and *Dictamnus albus* (Rutaceae), γ-fagarine (4) was the most active PDE5 inhibitor *in vitro* indicating that a single methoxy group at C-8 position is crucial for PDE5 inhibition (Nam et al., 2005). The other phytochemicals are-kokusaginine (5), skimmianine (6), evolitrine (7), confusameline (8), haplopine (9), robustine (10) and dictamine (11). The ethnomedicinal spices *Aframomum melegueta* and *Aframomum danielli* (Zingeberaceae) are locally prepared as soup meals by the Nigerian community for their penile rigidity improvement properties. Therefore, a study conducted on their seeds for PDE5 inhibitory effect revealed the presence of senkirkine (12), angustifoline (13), undulatine (14), lupanine (15), and indicine-N-oxide (16) through Gas Chromatography analysis of their alkaloid extracts (Adefegha et al., 2017).

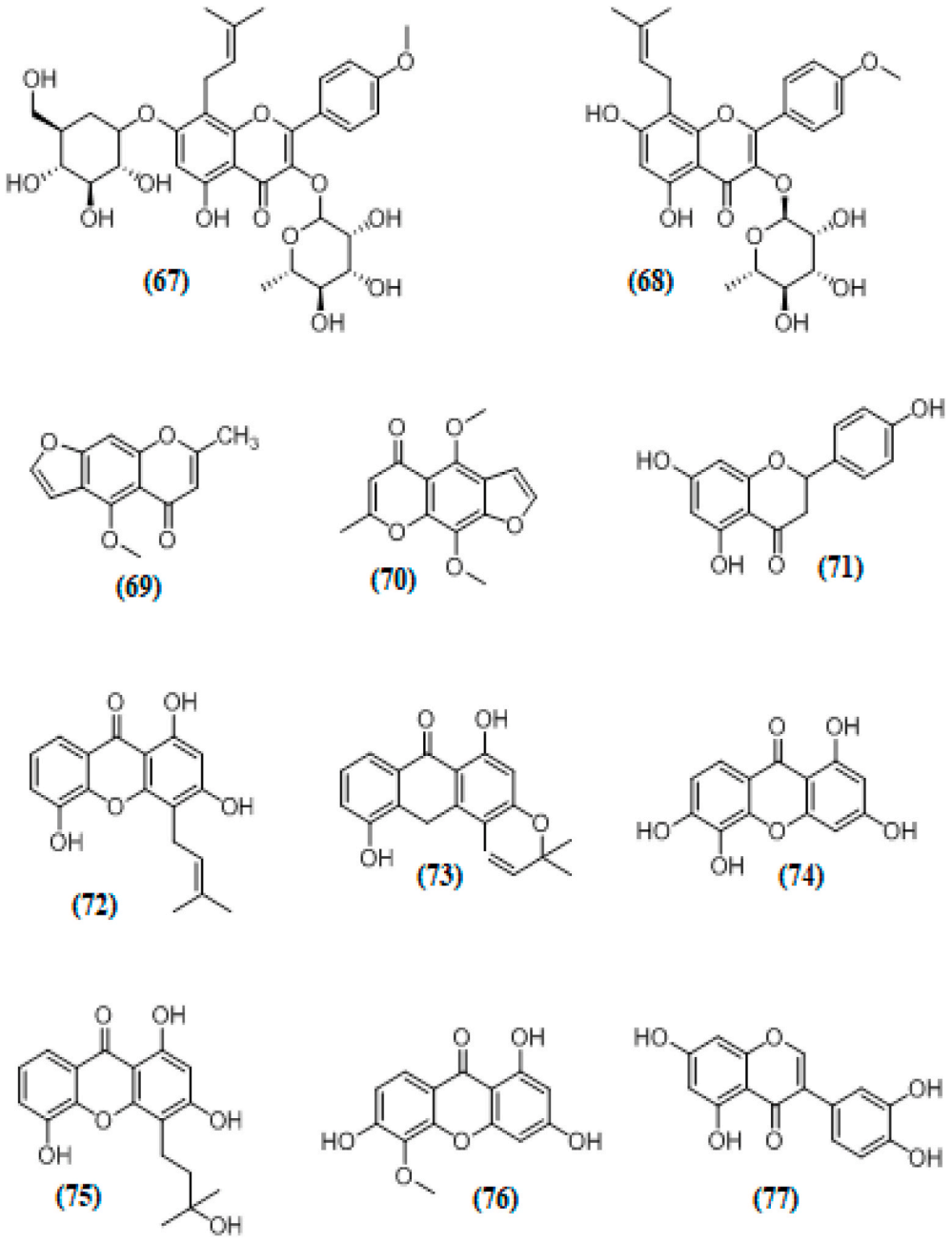


Fig. 6. (*continued*).

3.3.2. Phenolic compounds

A wide range of phenolic compounds has been identified as putative principles in the medicinal plants that have been reviewed. Many flavones, isoflavones, biflavones, flavonols, flavonoid glycosides, phenylethanoid glycosides, phenolic acids, prenylated flavonols and xanthones have been identified as potential PDE5 inhibitors from herbal sources.

The PDE5 inhibition efficacy of *Cnidoscolus aconitifolius* (Mill.) I. M. Johnst. (Euphorbiaceae) was evaluated by (Ajiboye et al., 2018) revealing the presence of chemical compounds such as amentoflavone (17), hesperidin (18), kaempferol (19), quercetin (20), rutin (21) from the active ethyl acetate fraction of the leaves, accounting for its aphrodisiac properties. *Derris scandens* (Roxb.) Benth (Fabaceae) has been widely used in Thai traditional medicine for its rejuvenating properties and was evaluated for PDE5 inhibitory activity. However, out of the eight isolated compounds belonging to groups of isoflavone analogues, cyclized isoflavone analogues, and cyclized coumarin structures from the ethanol extract of stem, only osajin (22), 4′,5,7-trihydroxybiprenylisoflavone (23) and derrisisoflavone A (24) were found to inhibit the PDE5 enzyme. The other identified phytochemicals from the active extract are genistein (25), lupalbigenin (26), scandenin (27), scandinone (28) and scanderone (29). Among the isoflavones the importance of prenyl substitution was found important for achieving effective PDE5 inhibition (Chaichamnong et al., 2018). In addition, the antihypertensive herb, *Clerodendrum colebrookianum* Walp., used in folk medicine in India, China, Korea and Japan was evaluated for its PDE5 potential through *in silico* computational studies by (Arya et al., 2018) led to the identification of acteoside (30), martinoside (31), and osmanthuside B6 (32) as potential PDE5 drug targets. The *in silico* investigation of isoflavones from *Maclura pomifera* (Raf.) Schneid also revealed osajin, pomiferin (33), scandenone (34), and auriculasin (35) as potential PDE5 inhibitors.

Traditionally, *Ginkgo biloba* L. (Ginkgoaceae) is believed to enhance

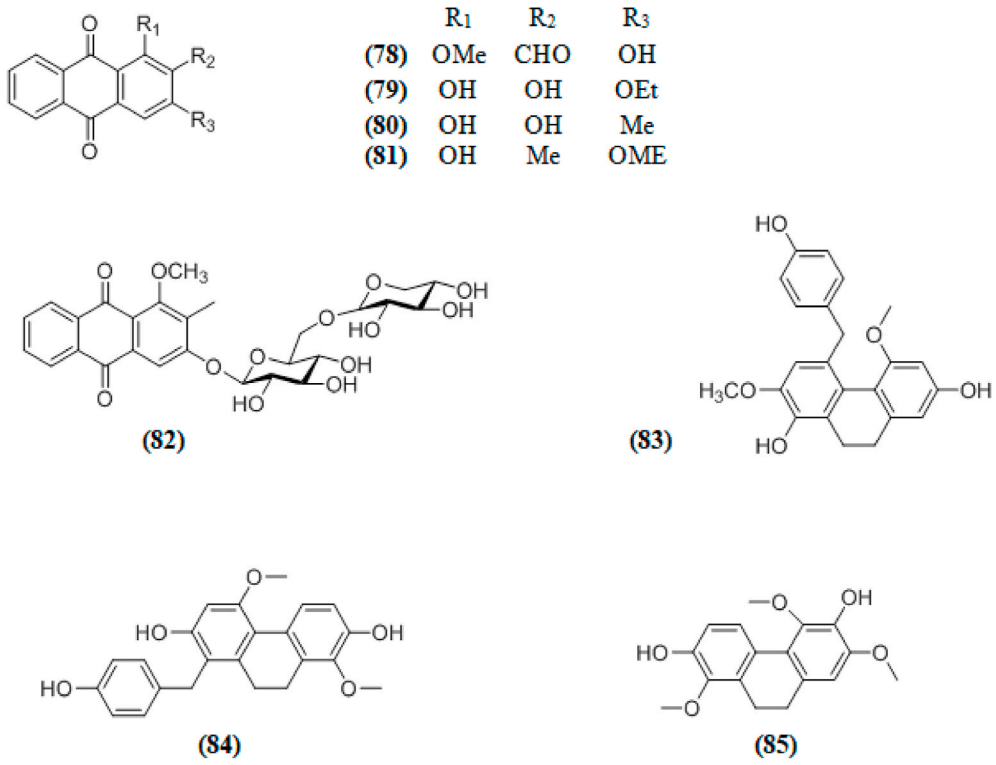


Fig. 7. Compounds derived from polycyclic aromatic hydrocarbons from the active plant fraction or extract as PDE5 inhibitors.

the male sexual function by penile erection in Korea and is used as herbal medicine for the treatment of circulation disorders, peripheral vascular diseases, and cerebrovascular insufficiency diseases. Despite the various traditional uses, a study conducted by (Dell'Agli et al., 2006) led to the identification of five biflavones namely, amentoflavone, sequoaflavone (36), sciadopitysin (37), isogingketin (38), gingketin (39), bilobetin (40), as potential PDE5 inhibitors. In addition, four biflavones (amentoflavone, podocarpusflavone A (41), sesquoiaflavone (42) and podocarpusflavone B (43)) isolated from *Decussocarpus rospigliosii* (Pilg.) De Laub (Podocarpaceae) from the forests of Andes was also reported to be effective PDE5 inhibitors. *Kaempferia parviflora* Wall. Ex. Baker (Zingeberaceae) commonly called Thai Gingseng is used extensively in Thai traditional medicines for its sexual enhancing properties, health promotion, diuretic and antidysentric properties. In an attempt to identify potential PDE5 inhibitors for the treatment of ED from Thai medicinal plants by (Temkitthawon et al., 2011), identified four flavone compounds responsible for PDE5 inhibition from *K. parviflora* Wall. Ex. Baker. 5,7-dimethoxyflavone (44); 5,7,4′-trimethoxyflavone (45); 3,5,7-trimethoxyflavone (46); 3,5,7,3′,4′-pentamethoxyflavone (47) are found as PDE5 inhibitors such that the methoxyl group at C-5 position of 7-methoxyflavones are needed for PDE5 inhibition.

Matricaria reticutita L. (Asteraceae), commonly called as chamomile is used extensively in Europe, Australia and the United States as herbal tea for its carminative, antispasmodic, anti-inflammatory and antiseptic properties. Therefore, a study was conducted to investigate whether the spasmolytic effect of chamomile could be ascribed to PDE inhibition by Maschi et al. (2008). The results indicated the presence of flavonoids and flavonoid glycosides (Apigenin-7-O-glucoside (48), luteolin-7-O-glucoside (49), hyperoside (50), patuletin-7-O-glucoside (51), apigenin (52) and luteolin (53)) as cGMP-PDE5 inhibitors. As diabetes is also responsible for causing ED, *Swietenia macrophylla* King (Meliaceae) an antidiabetic plant used in India was investigated for the possible mechanistic study for managing ED through PDE5 inhibition. The results indicated that the phenolic constituents gallic acid (54), catechin (55), ellagic acid (56), and quercetin may act as a source for both erectogenic and anti-diabetic agents (Oboh et al., 2017a). The use of plantains or bananas for treating ED is long used as a traditional medicine in various cultures. However, the plantain peels were not investigated for ED management. Hence, a study conducted by (Oboh et al., 2017c) identified unripe plantain peels had higher PDE5 inhibition than riped ones. In addition, the HPLC-DAD analysis revealed the presence of gallic acid and caffeic acid (57), rutin, quercetin, catechin, kaempferol, chlorogenic acid (58) and ellagic acid. Similarly, the PDE5 evaluation of the roots from *Eurycoma longifolia* Jack and *Allium cepa* L. (FRS 1000) also led to the identification of similar flavonols (Lines and Ono, 2006; Oboh et al., 2018a).

The PDE5 inhibitory effect of roots from *Glycyrrhiza glabra* L. on the guinea-pig airway smooth muscles were evaluated due to the isoliquiritigenin-induced vasorelaxant effect and it was observed that isoliquiritigenin (59) significantly increased intracellular cGMP levels and inhibited the PDE5 enzyme in human platelets (Liu et al., 2008). Also, Rottlerin (60) was identified as a PDE5 inhibitor from *Mallotus philippensis* (Lam.) Muell Arg. (Euphorbiaceae) in an *in silico* investigational study (Dar et al., 2019). Galentin 3,6-dimethyl ether (61), a flavonoid isolated from the plant *Piptadenia stipulacea* (Benth.) Ducke (Fabaceae) was found to inhibit the PDE5 isoenzyme as the compound had shown maximum relaxant potency in rat aorta (Macêdo et al., 2014). The flavonoids from the well known Chinese traditional medicine *Sophora flavescens* Aiton when investigated for their cGMP specific PDE5 inhibitory effect, sophoflavescenol (62), a C-8 prenylated flavonol, along with kushenol H (63), kushenol K (64), kurarinol (65) and kuraridine (66) were identified (Shin et al., 2002).

Icariin (67) and icarisde II (68) are the most effective natural PDE5 inhibitors that are isolated from *Epimidium brevicornum* Maxim (Horny goat weed), a well known Traditional Chinese Medicine for treating impotence and erectile dysfunction (Dell'Agli et al., 2008; Gao et al., 2018). Similarly, Visnagin (69) and Khellin (70) isolated from *Ammi visnaga* (L.) Lam were found to inhibit the vascular smooth muscle through inhibition of PDE5 (Duarte et al., 1999). The citrus fruits, which are abundant sources of naringenin (71), are also proven to be PDE5 inhibitors through its vasoactive effects (Orallo et al., 2005). Phytochemicals from *Anaxagorea luzonensis* A. Gray (Annonaceae) used in

Thai medicine are the first reports showing natural xanthones as PDE5 inhibitors. 1,3,5-trihydroxy-4-prenylxanthone (72) was the most potent inhibitor, along with ten other phytochemicals isolated from the heartwood (Sabphon et al., 2015). The other identified compounds are as follows, 6-deoxyisojacareubin (73), 1,3,5,6-tetrahydroxyxanthone (74), 1,3,5-trihydroxy-4-(3-hydroxymethylbutyl)xanthone (75), 1,3,6-trihydroxy-5-methoxyxanthone (76), quercetin, naringenin, aromandrin, taxifolin, kaempferol, orobol (77).

3.3.3. Compounds derived from polycyclic aromatic hydrocarbons

The Vietnamese plant, *Prismatomeris memecycloides* Craib (Rutaceae) is traditionally used as a remedy for ED, and the *in silico* investigation of the phytochemicals identified four anthraquinones and one anthraquinone glycoside: damnacanthal (78), lucidin-ω-methyl ether (79), 3-methylalizarin (80) and rubiadin-3-methyl ether (81) and 1-O-methylrubiadin 3-O-primeveroside (82), were isolated PDE5 inhibitors from the methanol extract of roots (Khanh et al., 2018). In addition, the PDE5 inhibitory effect of *Eulophia macrobulbon* (E.C. Parish & Rchb. f.) Hook. F (Orchidaceae) led to the isolation of three phenantheres 9,10-dihydro-4-(4′-hydroxybenzyl)-2,5 dimethoxyphenanthrene-1,7-diol (83), 1-(4′-hydroxybenzyl)-4,8- dimethoxyphenanthrene-2,7-diol (84) and 1,5,7-trimethoxyphenanthrene-2,6-diol (85) as potential PDE5 inhibitors (Temkitthawon et al., 2017).

4. Conclusion

Despite major scientific advancements, the PDE5 inhibitors in the market such as Viagra® (sildenafil) and Cialis® (tadalafil), there exist severe adverse effects in the usage of these pleasure-inducing love drugs. The major side effects are priapism (painful erections lasting for more than 6 h), non-arteritic anterior ischemic optic neuropathy (NAION), headache and dyspepsia. Therefore, the need for alternative treatment methods or medications with fewer side effects is essential for effective management of ED as PDE5 inhibition works through the negative feedback mechanism of cGMP which directly regulates the smooth muscles of the penis. The use of natural aphrodisiacs or sexual stimulants may prove effective in the current scenario as a majority of herbal ingredients are used for centuries before the discovery of modern medicine. Therefore, the utilization of herbal source for the identification and discovery of effective PDE5 inhibitors may prove useful with far lower side effects than conventional drugs.

The screening and selection of medicinal herbs for PDE5 inhibition can occur through different methods such as (1) use of valued ethnobotanical herbs or ingredients that are effective as aphrodisiacs (2) selection of medicinal plants that are effective against the predisposing factors for ED (3) screening of medicinal plants containing phytochemicals similar to that of the identified PDE5 inhibitors. The screening through these methods has identified effective PDE5 inhibitors such as icariin from *Epimedium brevicornum* Maxim (horny goat weed), biflavones from *Ginkgo biloba* L., flavones from *Kaempferia parviflora* Wall. ex Baker, phenyl propanoids from *Clerodendrum colebrookianum* Walp., flavonols from *Eurycoma longifolia* Jack and *Vitis vinifera* L. are also found to be inhibitors of PDE5 enzyme. In addition, several studies have also identified the major substituent groups that are necessary for their inhibitory action.

Although a handful of medicinal herbs have been used as aphrodisiacs or sex stimulants among various communities for managing infertility and ED, only a few among them are screened for the identification of effective PDE5 inhibitors. Therefore, proper and effective screening methods involving sufficient information regarding the mechanism of action, side effects and toxicity studies through quality research are in need for the identification of promising drug candidates with PDE5 inhibitory activity.

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