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REVIEW ARTICLE

Phytochemical Phosphodiesterase Inhibitors: A Comprehensive Review of Molecular Mechanisms and Therapeutic Potential

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Conflict of Interest
All the authors have no conflict of interest.

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ABSTRACT

Phosphodiesterase (PDEs), a superfamily of enzymes, catalyze the hydrolysis of guanosine 3',5'-cyclic monophosphate (cGMP) that is a cyclic nucleotide, adenosine 3',5'-cyclic monophosphate (cAMP) thereby playing a critical role in the precise intracellular signaling cascades regulation and consequently, cellular function. The identification of 11 distinct PDE isoenzyme families, each exhibiting unique substrate specificities, tissue distributions, and regulatory mechanisms, has significantly advanced our understanding of their physiological and pathophysiological roles at the cellular and molecular levels. This increased knowledge has facilitated the way for the emergence of highly selective PDE isoenzyme inhibitors, offering promising therapeutic avenues for a wide range of diseases. PDE inhibitors include many pharmacological agents and they are widely used due to their many pharmacological effects like pleiotropic, vasodilator, cardio tonic, smooth muscle relaxant, antidepressant, anti-inflammatory, antithrombotic and cognitive-enhancing properties. On clinical side, PDE inhibitors have validated efficacy to manage various conditions , including erectile dysfunction, chronic obstructive pulmonary disease (COPD), and pulmonary arterial hypertension and Alzheimer's disease. Most importantly, with the advancements of indications, states that vast variety of pharmacologically active phytochemicals derived from various plants produce PDE inhibitory activity. All these pharmacologically active phytochemicals belong to the classes of alkaloids, glycosides, phenols and flavonoids which signify a rich reservoir of potential therapeutic agents. This review provides a comprehensive summary of documented phytochemicals which are involved in inhibitory activity of PDE and their diverse roles in the management of specific diseases, emphasizing that various phytochemicals are potential source of PDE inhibition.

Keywords: Phosphodiesterase inhibitors, Phytochemicals, Cyclic nucleotides, Vasodilator, Diseases

1. INTRODUCTION

The normal functioning of intracellular signaling pathways play an important role in various physiological processes and to maintain cellular homeostasis A number of research have identified the importance of cyclic nucleotide phosphodiesterase (PDEs) enzymes. PDEs belong to complex superfamily which include 11 distinct families (PDE1-PDE11) identified in mammals, play a pivotal role in controlling the intracellular production of the second messengers, cyclic guanine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP). PDEs undergo the hydrolysis of these cyclic nucleotides and they control the signaling interval and magnitude of cGMP and cAMP, hence regulating a wide array of cellular functions(1).

In human physiology, the importance of PDEs is shown by the fact that if they don't function properly (dysregulation), leads to various pathological conditions. The decrease in the amount and activity

of cAMP and cGMP, results in the pathogenesis of diseases like erectile dysfunction, asthma, diabetes, and Alzheimer's disease, indicating the therapeutic potential of PDE activity modulation(2).

Some isoforms of PDE are particular for either cGMP or cAMP . While other enzymes such as PDE11, have the ability to undergo degradation of both cAMP and cGMP, but PDE4, which selectively degrades cAMP and PDE5, which specifically targets cGMP(3).

PDE is a superfamily which has complex organizational structure, each family is composed of multiple subtypes and isoforms. For e.g., PDE1 has 3 subtypes PDE1A, PDE1B, and PDE1C, which is further divided into various isoforms. PDE2 enzymes are expressed in various tissues e.g. the brain, platelets, heart, endothelial cells, adrenal medulla and macrophages, have been involved in regulating many diverse intracellular processes, including aldosterone secretion from the adrenal gland(4,5).

In immune and inflammatory cells, PDE4 enzymes are more likely to express, making them potential therapeutic targets for inflammatory disorders. In preclinical studies and model systems, specific PDE4 inhibitors have exhibited potent anti-inflammatory actions, suggesting that we can use those phytochemicals which carry PDE4 inhibitory activity, for the treatment of psoriasis(6) which is a chronic obstructive pulmonary disease.

A crucial mechanism of penile erection in primates, including humans, the L-arginine-nitric oxide-guanylyl cyclase-cGMP pathway is mediated by PDE5, which is mostly found in the visceral smooth muscle, corpus cavernosum,vascular and platelets. NO is released directly into the penis by nerves and endothelial cells in response to sexual stimulation. NO enters smooth muscle cells' cytoplasm and attaches itself to guanylyl cyclase. When NO interacts with guanylyl cyclase, the enzyme undergoes a conformational change that catalyzes the conversion of guanosine 5′-triphosphate into 3′-5′–cyclic guanosine monophosphate.

. Cyclic GMP is the intracellular trigger for penile erection. cGMP-dependent protein kinase (PKG),is activated by cyclic GMP which undergoes phosphorylation of multiple proteins. When these protein kinase interact results will be the reduced levels of intracellular calcium and consequently, relaxation of arterial and trabecular smooth muscle takes place, leading to arterial dilatation , rigidity of penile erection and venous constriction. Since cGMP plays a major role in this process, potential interventions for inadequate smooth muscle relaxation include increasing the level of intracellular cGMP. PDE5 is abundant in the corpus cavernosum penile smooth muscles.By hydrolyzing cGMP, PDE5 typically prevents penile erection. PDE5 inhibitors, by competing with cGMP for binding to PDE5, elevate cGMP levels, thereby smooth muscular relaxation is facilitated and erectile functioning gets enhanced. Importantly, NO pathway stimulation is required for the PDE5 inhibitor efficacy, which limits the side effects of this inhibitors to tissues outside of the penis(7).

PDE6, restricted to the pineal gland and retinal photoreceptor cells, mediates the visual response to light. PDE7, localized to the Golgi apparatus, interacts with AKAP proteins.PDE8 controls cAMP signaling and is expressed in airway smooth muscles. PDE9A specifically hydrolyzes cGMP with high affinity. PDE10, predominantly found in the brain and testes, exhibits high expression levels in the basal ganglia(8,9).

The wide distribution in tissues, specificities and functional roles of PDE isoforms highlights their importance in health and management of diseases. This review will surely explain the potential of some phytochemicals that regulate the activity of PDE, focusing on howthey might be used therapeutically for the treatment of various diseases.

This review presents a thorough explanation of phytochemicals that have been shown to regulate phosphodiesterase (PDE) activity.

2. PHENOLIC COMPOUNDS

Phenolic compounds are complex class of phytochemicals, have established significant potential as phosphodiesterase (PDE) enzymes inhibitors, providing therapeutic implications for various diseases. This portion provides a systematic review of those phenolic compounds which exhibit activity of PDE inhibition, aiming on their resources, mechanisms of action, and potential clinical applications.

2.1 Caffeic Acid

The stem bark of Cylicodiscus gabunensis (CG) and the seeds of Hunteria umbellata (HU) both contain

phenolic compounds such as caffeine that inhibits PDE5 and arginase enzymes. This inhibition causes increased levels cGMP, promoting cavernously smooth muscle relaxation, which results in the treatment of erectile dysfunction. Moreover, caffeic acid also inhibit type 2 linked diabetes enzymes such as α-glucosidase and α-amylase. Bark extract of Cylicodiscus gabunensis and Hunteria umbellata also exhibit antioxidant properties, demonstrating radical scavenging (DPPH and OH) and metal chelating (Fe2+) abilities(10).

2.2 Chicoric Acid

Chicoric acid is a phenolic compound, extracted from the plant Solenostemon monostachyus which inhibits PDE5, resulting in smooth muscle relaxation of cavernosum and increased cGMP levels, indicating its efficacy in erectile dysfunction treatment. In albino rats oral administration of chicoric acid (100, 200, 400 mg/kg) for seven days did not show toxicity (11).

2.3 Ethyl Acetate and Butanol Extracts (Phoenix dactylifera)

Phenolic extracts (ethyl acetate and butanol) from Phoenix dactylifera (Pd) inhibit PDE5. Aqueous fractions of Pd exhibit the highest PDE5 and angiotensin-converting enzyme (ACE) inhibition, indicating potential antihypertensive properties(12).

2.4 Kaempferol Derivatives

Kaempferol derivatives, such as 3-O-beta-neohesperidoside-7-O-[2-O-(trans-p-coumaroyl)]-beta-D-glucopyranoside, kaempferol 3-O-beta-neohesperidoside-7-O-[2-O-(trans-p-coumaroyl)-3-O-beta-D-glucopyranosyl]-beta-D-glucopyranoside, kaempferol 3-O-beta-neohesperidoside-7-O-[2-O-(trans-feruloyl)]-beta-D-glucopyranoside, and kaempferol 3-O-beta-neohesperidoside-7-O-[2-O-(trans-p-coumaroyl)-3-O-beta-D-glucopyranosyl]-beta-D-glucopyranoside are derived from Allium ursinum.

compounds contribute to blood pressure reduction through PDE5A inhibition in pulmonary hypertension in rats(13).

2.5 1-(4-hydroxy benzyl)-4,8-dimethoxyphenanthrene-2,7-diol (HDP)

HDP which is present in the ethanolic extract of E. macrobulbon, inhibits PDE5. This inhibition leads to pulmonary vasodilation via increased cGMP concentrations in rats(14).

2.6 Gallic Acid, p-hydroxybenzoic Acid, and Ethyl Gallate

These compounds contribute to increased cGMP levels and enhanced nitric oxide (NO) bioavailability by inhibiting PDE5. This mechanism facilitates relaxation of penile tissue, addressing erectile dysfunction (15).

2.7 α-Tocopherol

α-Tocopherol, obtained from Scandix pecten-veneris L., inhibits PDE1. This inhibition increases cGMP concentrations, potentially helps to treat pulmonary arterial hypertension and benign prostatic hyperplasia (BPH) (16).

2.8 n-Butanol Extracts and Ethyl Acetate (Syzygium cumini)

Methanolic extracts (n-butanol and ethyl acetate) from Syzygium cumini L. (Jamun) inhibit PDE, α-glucosidase, and urease. PDE1 inhibition leads to diuresis. PDE1 hydrolyzes both cAMP and cGMP, increasing their concentrations(17).

2.9 Chromones and Pyrones

Chromones and pyrones, phenolic substances from Aloe barbadensis, inhibit PDE4. The PDE4 inhibition, which reduces cAMP hydrolysis in immune and inflammatory cells, is relevant for chronic obstructive pulmonary disease (COPD) and asthma management(18).

2.10 Methyl 1,2-dihydroxy-2-(3-methylbut-2-enyl)-3-oxo-2,3-dihydro-1H-indene-1-carboxylate, 2-hydroxy-3-(3-methylbut-2-enyl) naphthalene-1,4-dione, and 2,2-dimethyl-3,4-dihydro-2H-benzo[g]chromene-5,10-dione

These compounds inhibit PDE1 isoforms (PDE1A, PDE1B, and PDE1C). PDE1 isoforms are mostly located in the cardiovascular systems and central nervous system (CNS)(13).

2.11 Chlorogenic Acid

Tetracarpidium conophorum seeds contain chlorogenic acid, which interacts with acetylcholinesterase (AChE), PDE5, arginase, and ACE. These enzymes are linked to the generation of malondialdehyde (MDA) in penile tissue by Fe2+ and erectile dysfunction (ED). One important factor contributing to ED is elevated PDE5 activity in penile tissue(19).

3. ALKALOIDS AS PHOSPHODIESTERASE INHIBITORS

3.1 Caffeine

A purine alkaloid called caffeine (1,3,7-trimethylxanthine) inhibits phosphodiesterase, specifically the enzyme that hydrolyzes cyclic adenosine monophosphate (cAMP) to AMP. The cAMP signaling cascade, activated by β-adrenergic stimulation, mediates various adrenergic effects, including appetite suppression, increased energy expenditure, and lipolysis. Furthermore, caffeine enhances the expression of uncoupling proteins, thereby promoting thermogenesis through the combined mechanisms of phosphodiesterase inhibition and cAMP-mediated activation of protein kinase A. These pharmacological properties suggest that caffeine may hold therapeutic potential in the management of obesity(20).

3.2 Galantamine

Galantamine, an alkaloid derived from plants of the Galanthus genus, exhibits inhibitory activity against phosphodiesterase1 (PDE1) and acetylcholinesterase. This dual inhibitory action underlies its clinical utility in the management of Alzheimer's disease. PDE isoforms are expressed within the brain, where they regulate the concentrations of cAMP or cGMP which are the intracellular second messengers.By inhibiting PDE1, galantamine increases cGMP concentrations, thereby influencing neuronal plasticity and potentially enhancing cognitive function, particularly memory (21).

3.3 Oxirane, Carbohydrazide, Neophytadiene, and Squalene

Alkaloid extracts derived from Vernonia amygdalina (bitter leaf) and Solanum nigrum (black nightshade) contain compounds including oxirane, carbohydrazide, neophytadiene, and squalene, which demonstrate inhibitory activity against phosphodiesterase-5 (PDE5) and arginase. PDE5 inhibition by these alkaloidal extracts results in an increased concentration of cGMP, a key second messenger that mediates penile erection, thereby promoting relaxation of cavernosal smooth muscle. Moreover, In rat penile tissues, these alkaloids produce Fe2+-induced lipid peroxidation inhibition. Herbal extracts made from these plants are traditionally used for the treatment of numerous medical disorders, like diabetes, cancer and hypertension. There are many effects, like analgesic, purgative, antispasmodic, antimicrobial, antinarcotic, diuretic, emollient and antineoplastic, due to which these plants have been traditionally used. Some of their extracts have also been used in the management of neurological disorders. Vernonia amygdalina has been researched to contribute to the regulation of cholesterol levels, if it is consumed on regular basis. Moreover, in traditional herbal extracts, these plants are employed for the treatment of fever, joint pain, febrile conditions, GIT related problems and parasitic infections like malaria(22).

3.4 Piperine, Senkirkine, and Angustifoline

Alkaloids like piperine, lupanine, senkirkine, undulatine, myristicin, poweline, safrole, angustifoline, and indicate-N-oxide are found in seeds of the Aframomum melegueta also called alligator pepper and Aframomum danielli also called bastard melegueta, hence improving sexual function in folkloric medicine. These seeds contain alkaloids which inhibit or decrease the activity of arginase, phosphodiesterase-5 (PDE5), acetylcholinesterase (AChE), and angiotensin-1-converting enzyme (ACE) which are involved in erectile dysfunction. These alkaloids inhibit PDE5 enzyme, which increase the concentration of cGMP a key second messenger mediating penile erection leading to relaxation of cavernosum smooth muscles. Seeds extracts of these plant inhibit ED-related enzymes in a concentration-dependent manner. (19).

3.5 Hydrangine/Umbelliferone

Hydrangine also called umbelliferone which is an alkaloid extracted from the roots of Zomisa absinthifolia, a plant which shows property of

potentiating sildenafil which is the effects of PDE5 inhibitors, thus restoring penile erection. This alkaloid is used to treat erectile dysfunction which is linked to diabetes mellitus. In vivo studies on diabetic rats, intra cavernously administration of umbelliferone have established the beneficial effects in erectile dysfunction by producing relaxation of corpus cavernosum smooth muscles, through the nitric oxide (NO)/cGMP pathway. In diabetes-induced erectile dysfunction, the combination of umbelliferone with other PDE5 inhibitors may be used as a therapeutic alternative(23).

3.6 Berberine

Berberine is an alkaloid, obtained from plants of the Berberis and Coptis chinensis genera. This alkaloid has an ability to inhibit monoamine oxidase in the brain and mainly phosphodiesterase 5 (PDE5) in cavernosum smooth muscles. PDEs in penile smooth muscle belong to a class of enzymes that selectively hydrolyze cAMP and/or cGMP, resulting in smooth muscle contraction. Berberine, inhibits enzyme PDE5 located in the corpus cavernosum, increases in cGMP levels, resulting in relaxation penile smooth muscles and penile erection. This alkaloid is also employed in the management of Parkinson's disease and chronic obstructive pulmonary disease (COPD). Therapeutic dose of berberine (200 mg/kg/day) and normal saline administration for 4 weeks to streptozotocin-induced diabetic male rats resulted in the restoration of erectile function(24).

3.7 Bufotenine, N, N-Dimethyltryptamine, and Methyl mescaline

Legume seeds contain alkaloids such as bufotenine, N, N-dimethyltryptamine, and methylmescaline. In penile tissue homogenates, PDE5 activity is inhibited by fermented legume extracts. PDE5 is an essential enzyme in the NO/cGMP signaling system, which stops NO-induced cGMP-mediated vasorelaxation, reestablishing penile flaccidity and basal smooth muscle tone. Seed extracts also inhibit AChE activity and arginase in rat penile tissues. These extracts may also promote adenosine-mediated vasorelaxation by stimulating adenosine synthesis.

4. FLAVONOID PHOSPHODIESTERASE INHIBITORS

4.1 Curcumin and Epigallocatechin-3-gallate (EGCG)

Curcumin and Epigallocatechin-3-gallate (EGCG) flavonoids extracted from *Ginkgo biloba* L., demonstrate inhibitory activity against phosphodiesterase 5 (PDE5). This inhibition causes increased concentrations of cAMP and cGMP within tissues, subsequently stimulating cyclic nucleotide-regulated protein kinases. These flavonoids have been found to produce antitumor activity through the regulation of signal transduction pathways and are considered for the management of erectile dysfunction(16).

4.2 Amentoflavone

Ginkgo biloba dimeric flavonoids, including amentoflavone, inhibit PDE5 and promote vasorelaxation. Amentoflavone induces endothelium-dependent relaxation of rat aorta rings via enhanced nitric oxide production, leading to concentration-dependent elevations in cGMP levels. This mechanism contributes to the relaxation of penile cavernosum smooth muscle, suggesting therapeutic potential for erectile dysfunction. The inhibitory potency of *Ginkgo biloba* flavonoids on PDE5 follows the order: ginkgetin > bilobetin > sciadopitysin > amentoflavone > sequoiaflavone(16).

4.3 FRS 1000

By inhibiting PDE5, the beverage FRS 1000, which contains flavonoids derived from onion peel, shows an unexpected improvement in male sexual function. *In vitro* enzyme assays confirm that FRS 1000 exhibits strong PDE5 inhibitory activity, considered crucial for erectile dysfunction treatment. Quercetin, an antioxidant flavonoid from orange peel, is identified as a significant contributor to the inhibitory activity of PDE5. The ability of the onion peel flavonoids for elimination of free radicals is not directly connected with the inhibition of PDE5 by FRS 1000(25).

4.4 Dimethoxyflavone

The 7-methoxyflavone components of Kaempferia parviflora rhizome extract have a moderately inhibiting effect on PDE5. This inhibition increases cGMP concentrations in penile smooth muscle,

resulting in vasodilation and increased blood flow to penile tissue in erectile dysfunction.7-methoxyflavone and *Kaempferia parviflora* rhizome extract causes PDE5 inhibition, is demonstrated in mice with contracted cavernosum smooth muscle(26).

4.5 Xanthomicrol, Cirsimaritin, Vicenin-2, Luteolin 5-O-glucoside, Luteolin 7-, and Quercetin

Ocimum gratissimum L., this plant is used in various medicinal systems to increase erectile function, contains flavonoids including xanthomicrol, cirsimaritin, vicenin-2, luteolin 5-O-glucoside, luteolin 7-, and quercetin. These flavonoids inhibit PDE5, arginase, angiotensin I-converting enzyme (ACE), and acetylcholinesterase (AChE) in penile and testicular tissues of rats with erectile dysfunction. Male albino mice were given doses of flavonoids ranges 100, 250, and 500 mg/kg body weight for 7 days and it turned out that these flavonoids inhibit enzymes involved in erectile dysfunction by increasing cGMP concentrations and decreasing nitric oxide levels, resulting in the treatment of erectile dysfunction(27).

4.6 Osajin and Pomiferin

Maclura pomifera, a plant from which Osajin and pomiferin, natural isoflavone derivatives are obtained, belong to a novel class of PDE5 inhibitors. These compounds promote a relaxant effect on rat cavernosum smooth muscle pretreated with sodium nitroprusside, enhancing cGMP levels and improving erectile dysfunction. These PDE5 inhibitors may also contribute to the management of other health conditions, including chronic obstructive pulmonary disease ,hypertension, cancer and diabetes mellitus,They may also contain anti-inflammatory, antimicrobial and antibacterial properties, and are considered beneficial for skin diseases(28).

4.7 Saw Palmetto Extract

The active components of saw palmetto extract, which is made from Serenoa repens berries, include fatty acids, plant sterols, and flavonoids (isoflavones, including genistein). High molecular weight polysaccharides found in the berries may also improve immune function or lessen inflammation. Saw palmetto extract enhances erectile responses by inhibiting PDE5 in corpus cavernosum of rat and rabbit, producing vasodilation. Saw palmetto extract is used to treat Benign prostate hyperplasia (BPH) and is linked with decreased Urinary tract symptoms, such as urgency, frequency, nocturia, incomplete emptying, weak stream.(29).

5. PYRAZOLOPYRIMIDINONE-BASED PDE5 INHIBITORS

Pyrazolopyrimidinone-based potent PDE5 inhibitors are utilized in erectile dysfunction treatment. These compounds exhibit higher *in vitro* selectivity for PDE5 compared to sildenafil, although their precise mechanism of action remains to be fully elucidated(30).

6. TERPENOIDS AS PHOSPHODIESTERASE INHIBITORS

6.1 β-Caryophyllene (BCP)

A natural sesquiterpene lactone compound found in β-Caryophyllene (BCP) is abundant with the essential oil of *Cannabis sativa* leaves, exhibits inhibitory activity against phosphodiesterase 5 (PDE5), acetylcholinesterase, and arginase, enzymes implicated in erectile dysfunction. Effective treatment of erectile dysfunction may involve multiple mechanisms, including the elevation of cyclic guanosine monophosphate (cGMP) levels in cavernous tissues, endothelial dysfunction repair, improved antioxidant status and increased nitric oxide (NO) generation. Studies have demonstrated that BCP possesses antioxidant, antimicrobial, anticancer, anti-arthritic, cardioprotective, anticholinesterase and anti-inflammatory effects in both *in vivo* and *in vitro* models(31).

7. GLYCOSIDES AS PHOSPHODIESTERASE INHIBITORS

7.1 1-Methylalizarin

1-Methylalizarin, an anthraquinone glycoside obtained from *Prismatomeris memecyloides*, functions as a PDE5 inhibitor. This inhibition causes an increase in the amount of the second messenger cGMP, resulting in the relaxation of cavernosal smooth muscle and suggesting therapeutic potential for erectile dysfunction(23). A description of the

plants, their chief constituents acting as PDEI, and their mechanism of action as presented in table 1.

Table 1. Summary of all active phytochemicals inhibiting phosphodiesterase enzyme activity and clinical implications of these active constituents.

Plant	Component used	Mechanism of action
Hunteria umbellata	Caffeic acid	↓PDE5 ↓arginase ↑cGMP Cavernosum smooth muscle relaxation.
Solenostemon monostachyus	Chicoric acid	↓PDE5 ↓arginase ↑cGMP Cavernosum smooth muscle relaxation.
Phoenix dactylifera	Butanol, ethyl acetate	↓PDE5 ↓ACE ↑cGMP Cavernosum smooth muscle relaxation, Treat hypertension.
Alliom ursinun	Kaempferol	↓PDE5 Treat pulmonary hypertension.
E. macrobulbon	HDP	↓PDE5 Treat pulmonary hypertension.
Physalis angulata	Gallic acid, ethyl gallate	↓PDE5 ↑NOS ↑cGMP Cavernosum smooth muscle relaxation
Scandix pecten	Alpha tocopherol	↓PDE1 ↑cGMP Treat pulmonary hypertension, BPH.
Aloe barbadensis	Chromones, pyrones	↓PDE4 ↓cGMP Treats asthma and COPD
Ilex paraguariensis	Caffeine	↓PDE4, ↓PDE10 ↑cGMP ↑lipolysis Treats obesity
Galantus genus	Galantamine	↓PDE4, ↓PDE6 ↑cGMP Treats Alzheimer
Vernononia amygdalina, Solanum nigrum	Oxirane, carbohydrazide, neophytadiene, squalene	↓PDE5, ↑cGMP Smooth muscles relaxation of penile tissues
Framomum melegueta	2 piperine, senkirkine,	↓PDE5,

	angustifoline,	↑cGMP ↓arginase ↓AChE Smooth muscles relaxation of penile tissues
Zomisa absinthifolia	Hydrangea	↑cGMP ↓PDE5, Smooth muscles relaxation of penile tissues of diabetic rats
Coptis chinensis	Berberine	↑cGMP ↓PDE5, Smooth muscles relaxation of penile tissues of rats
Legume plants	Bufotenine, methyl mescaline N, N-dimethyl tryptamine,	↓PDE5, ↑cGMP ↓arginase ↓AChE Smooth muscles relaxation of penile tissues
Stephania tetrandra	Tetrandrine	↑cGMP ↓PDE5, Smooth muscles relaxation of penile tissues of rats
Ginko biloba	EGCG, curcumin	↑cGMP ↓PDE5, Smooth muscles relaxation of penile tissues of rats, Alos has anti- tumor activity
Ginkgo biloba	Amentoflavone	↑cGMP ↓PDE5, Smooth muscles relaxation of penile tissues of rats,
Allium cepa	FRS1000, quercetin	↑cGMP ↓PDE5, Smooth muscles relaxation of penile tissues of rats
Kaempferia parviflora	7-methoxyflavone	↑cGMP ↓PDE5, Smooth muscles relaxation of penile tissues of rats
Ocimum gratissimum	cirsimaritin, luteolin 5-*O*-glucoside, luteolin 7-quercetin, 4-xanthomicrol, vicenin-2,	↑cGMP ↓PDE5, Smooth muscles relaxation of penile tissues of rats
Maclura pomifera	Pomiferin , osajin	↑cGMP ↓PDE5, Smooth muscles relaxation of penile tissues of rats
Serenoa repens	Genistein	↑cGMP

		↓PDE5, Smooth muscles relaxation of penile tissues of rats
Cannabis sativa	Beta Caryophyllene	↑cGMP ↓PDE5, Smooth muscles relaxation of penile tissues of rats
Prismaomeris memecyloides	Methylalizarin	↑cGMP ↓PDE5, Smooth muscles relaxation of penile tissues of rats
Syzygium cumini	Methanolic extracts	↓PDE1

8. CONCLUSION

The exploration of phytochemicals as natural phosphodiesterase (PDE) inhibitors represents a promising frontier in the development of novel therapeutics targeting a range of pathophysiological conditions. While several phytochemicals exhibit efficacy comparable to synthetic PDE inhibitors in preclinical studies, their favorable safety profiles and multitarget potential further accentuate their clinical relevance. However, translating these findings into clinical practice requires more extensive pharmacokinetic profiling, standardized extraction methods, and robust clinical trials. Future research focusing on structure–activity relationships and molecular docking approaches may accelerate the rational design of phytochemical-based PDE inhibitors with improved efficacy and selectivity. In summary, phytochemicals offer a valuable reservoir of bioactive molecules with PDE inhibitory potential, paving the way for innovative, nature-inspired interventions in modern pharmacotherapy.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not Applicable.

CONSENT FOR PUBLICATION

All authors agreed to publish the manuscript.

AVAILABILITY OF DATA AND MATERIAL

Data and material are available upon request.

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REFERENCES

1. Roks AJM. Phosphodiesterase-1 in the cardiovascular system. Cell Signal. 2022;92:110251.
2. Fu Q, Wang Y, Yan C, Xiang YK. Phosphodiesterase in heart and vessels-From Physiology to Diseases. Physiol Rev. 2024;104(2):765–834.
3. Dunkerly-Eyring B, Kass DA. Myocardial Phosphodiesterases and Their Role in cGMP Regulation. J Cardiovasc Pharmacol. 2020;75(6):483–93.
4. Zhang C, Yu Y, Ruan L, Wang C, Pan J, Klabnik J, et al. The Roles of Phosphodiesterase 2 in the Central Nervous and Peripheral Systems. Curr Pharm Des. 2014;21(3):274–90.
5. Das UN. Arachidonic Acid as Mechanotransducer of Renin Cell Baroreceptor. Nutrients. 2022;14(4):749.
6. Crocetti L, Floresta G, Cilibrizzi A, Giovannoni MP. An Overview of PDE4 Inhibitors in Clinical Trials: 2010 to Early 2022. Molecules. 2022;27(15):4964.
7. Simsek A, Tugcu V, Erturkuner P, Alkan F, Ozbek E, Tasci AI. Effects of the recreational use of PDE5 inhibitors on the corpus cavernosum of young, healthy rats. Int Urol Nephrol. 2014;46(10):1889–93.
8. Ahmad F, Murata T, Shimizu K, Degerman E, Maurice D, Manganiello V. Cyclic nucleotide phosphodiesterases: Important signaling modulators and therapeutic targets. Oral Dis.

2015;21(1):e25–50.
9. Azevedo MF, Faucz FR, Bimpaki E, Horvath A, Levy I, De Alexandre RB, et al. Clinical and molecular genetics of the phosphodiesterases (pdes). Endocr Rev. 2014;35(2):195–233.
10. Oboh G, Adebayo AA, Ademosun AO. Erection-stimulating, anti-diabetic and antioxidant properties of Hunteria umbellata and Cylicodiscus gabunensis water extractable phytochemicals. J Complement Integr Med. 2018;15(1).
11. Ehigiator BE, Adesida AS, Omotuyi IO. Chicoric Acid, a Phytochemical Compound of Solenostemon Monostachyus: Possible Drug Candidate for the Relief of Erectile Dysfunction. Int J Eng Appl Sci Technol. 2020;04(11):509–18.
12. Obode OC, Adebayo AH, Li C. Gas chromatography-mass spectrometry analysis and in vitro inhibitory effects of Phoenix dactylifera L. On key enzymes implicated in hypertension. J Pharm Pharmacogn Res. 2020;8(5):475–90.
13. Jasemi SV, Khazaei H, Aneva IY, Farzaei MH, Echeverría J. Medicinal Plants and Phytochemicals for the Treatment of Pulmonary Hypertension. Front Pharmacol. 2020;11:145.
14. Saikia Q, Hazarika A, Mishra R. A Review on the Pharmacological Importance of PDE5 and Its Inhibition to Manage Biomedical Conditions. J Pharmacol Pharmacother. 2022;13(3):246–57.
15. ElHady AK, El-Gamil DS, Abdel-Halim M, Abadi AH. Advancements in phosphodiesterase 5 inhibitors: unveiling present and future perspectives. Pharmaceuticals. 2023;16(9):1266.
16. Rauf A, Khan IA, Muhammad N, Al-Awthan YS, Bahattab O, Israr M, et al. Phytochemical composition, in vitro urease, α-glucosidase and phosphodiesterase inhibatroy potency of Syzygium cumini (Jamun) fruits. South African J Bot. 2021;143:418–21.
17. Shah ZA, Abu-Izneid T, Rauf A, Rashid U, Nizam M, Muhammad N, et al. Phosphodiesterase 1 inhibition and molecular docking study of phytochemicals isolated from stem heartwood of Heterophragma adenophyllum Seem. South African J Bot. 2020;135:274–9.
18. Zapata FJ, Rebollo-Hernanz M, Novakofski JE, Nakamura MT, Gonzalez de Mejia E. Caffeine, but not other phytochemicals, in mate tea (Ilex paraguariensis St. Hilaire) attenuates high-fat-high-sucrose-diet-driven lipogenesis and body fat accumulation. J Funct Foods. 2020;64:103646.
19. Oboh G, Adebayo AA, Ademosun AO. HPLC phenolic fingerprinting, antioxidant and anti-phosphodiesterase-5 properties of Rauwolfia vomitoria extract. J Basic Clin Physiol Pharmacol. 2019;30(5):20190059.
20. Wang JH, Luan F, He XD, Wang Y, Li MX. Traditional uses and pharmacological properties of Clerodendrum phytochemicals. J Tradit Complement Med. 2018;8(1):24–38.
21. Wahab A, Jan SA, Rauf A, Rehman Z ur, Khan Z, Ahmed A, et al. Phytochemical composition, biological potential and enzyme inhibition activity of Scandix pecten-veneris L. J Zhejiang Univ Sci B. 2018;19(2):120–9.
22. Khanh PN, Huong TT, Spiga O, Trezza A, Son NT, Cuong TD, et al. In silico screening of anthraquinones from Prismatomeris memecyloides as novel phosphodiesterase type-5 inhibitors (PDE-5Is). Rev Int Androl. 2018;16(4):147–58.
23. Lentini A, Tabolacci C, Provenzano B, Rossi S, Beninati S. Phytochemicals and protein-polyamine conjugates by transglutaminase as chemopreventive and chemotherapeutic tools in cancer. Plant Physiol Biochem. 2010;48(7):627–33.
24. Adefegha SA, Oboh G, Olopade EO. B-Caryophyllene Improves Sexual Performance Via Modulation of Crucial Enzymes Relevant To Erectile Dysfunction in Rats. Toxicol Res. 2021;37(2):249–60.
25. Zhong J, Huang Y, Ding W, Wu X, Wan J, Luo H. Chemical constituents of Aloe barbadensis Miller and their inhibitory effects on phosphodiesterase-4D. Fitoterapia. 2013;91:159–65.
26. Akomolafe SA, Oyeleye SI, Olasehinde TA, Oboh G. Phenolic characterization, antioxidant activities, and inhibitory effects of physalis angulata and newbouldia laevis on enzymes linked to erectile dysfunction. Int J Food Prop. 2018;21(1):645–54.
27. García-Osta A, Cuadrado-Tejedor M, García-Barroso C, Oyarzábal J, Franco R. Phosphodiesterases as therapeutic targets for Alzheimer's disease. ACS Chem Neurosci. 2012;3(11):832–44.
28. Lines TC, Ono M. FRS 1000, an extract of red onion peel, strongly inhibits phosphodiesterase 5A (PDE 5A). Phytomedicine. 2006;13(4):236–9.
29. Park HJ, Won JEJ, Sorsaburu S, Rivera PD, Lee SW. Urinary Tract Symptoms (LUTS) Secondary to Benign Prostatic Hyperplasia (BPH) and LUTS/BPH with Erectile Dysfunction in Asian Men: A Systematic Review Focusing on Tadalafil. World J Mens

Health. 2013;31(3):193.
30. Ismail EA, El-Sakka AI. An overview of conventional and investigational phosphodiesterase 5 inhibitors for treating erectile dysfunction and other conditions. Expert Opin Investig Drugs. 2024;33(9):925–38.
31. Krishnamoorthi R, Ganapathy A A, Hari Priya VM, Kumaran A. Future aspects of plant derived bioactive metabolites as therapeutics to combat benign prostatic hyperplasia. J Ethnopharmacol. 2024;330:118207.
32. Ataei Ataabadi E, Golshiri K, Jüttner A, Krenning G, Danser AHJ, Roks AJM. Nitric Oxide-cGMP Signaling in Hypertension: Current and Future Options for Pharmacotherapy. Hypertension. 2020;76(4):1055–68.