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Specifying Human Platelet cAMP and cGMP Phosphodiesterase Inhibitory Activity of the Plants Used in Traditional Iranian Medicine for the Purpose of Erectile Dysfunction

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Abstract: In the present study, cAMP and cGMP phosphodiesterase inhibitory (PDEI) activities of the ethanolic extracts of nineteen plants of Traditional Iranian Medicine (TIM) with aphrodisiac effects were investigated. The plants were extracted in a similar way and then three concentrations (0. 1, 1, 5 mg mL^{-1}) from each were tested for PDEI activity against control and sildenafil. Among plants tested, 8 including *Allium cepa*, *Trigonella foenum-graecum*, *Brassica rapa*, *Alpinia officinarum*, *Tribulus terrestris*, *Urtica pilulifera*, *Linum usitatissimum* and *Zingiber zerumbet* exhibited a significant dose-dependent cAMP-PDEI activity and 6 including *A. cepa*, *A. officinarum*, *T. terrestris*, *L. usitatissimum*, *Withania somnifera* and *Z. zerumbet* gave a remarkable dose-dependent cGMP-PDEI effects in comparison to control. Among tested herbs, *Zingiber officinalis* and *Peganum harmala* at dose of 5 mg mL^{-1} demonstrated better cGMP-PDEI in comparison to sildenafil. The results of this study give idea for discovery of safe and better drugs in management of erectile dysfunction.

Key words: Phosphodiesterase inhibitor, sildenafil, traditional Iranian medicine, cAMP, cGMP

INTRODUCTION

Phosphodiesterases (PDEs) are a class of enzymes that exist in nearly all tissues regulating the second messengers cAMP and cGMP involving in many diverse physiological functions. PDE inhibitors (PDEIs) are used for management of clinical disorders such as dementia, depression, cardiovascular diseases, diabetes, chronic obstructive pulmonary diseases, colitis, toxicities, pulmonary hypertension and Erectile Dysfunction (ED) (Abdollahi *et al*., 2003a, b, c; Jeon *et al*., 2005; Khoshakhlagh *et al*., 2007; Milani *et al*., 2005). Inhibitors of PDE type 5 (PDE5I) i.e., sildenafil, vardenafil and tadalafil are now used in treatment of ED but have some common side effects like headache, flushing and blurred vision. As reviewed by Rahimi *et al*. (2010), there are many single and combination herbal formulas in Traditional Iranian Medicine (TIM) for ED that needs experimental and clinical testing. The aim of the present study was to evaluate PDEI activity of the medicinal plants claimed to be beneficial for ED in TIM.

MATERIALS AND METHODS

Materials: Different parts of nineteen plants that were selected on the basis of TIM data were prepared from the clinic of Traditional Medicine, Tehran University of Medical Science (TUMS), Tehran, Iran, in May 2010. Voucher specimens have been deposited in the Central Herbarium of Medicinal Plants (ACECR, Karaj, Iran). All chemicals or reagents needed in this study were purchased from Sigma-Aldrich Company (Germany) unless otherwise stated.

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Extraction method: Dried and semi powdered plants (20 g) were extracted using ethanol 80% (3×60 mL) at room temperature for a week. After removal of the solvent in the vacuum at 30°C, the residues were used for further analysis.

Assay of platelet cAMP and cGMP PDEI activity: The human platelets as a rich source of PDE enzymes were purchased from Tehran blood transfusion organization and stored at 25°C in a shaker during the process of experiment. An aqueous stock solution of 40 mM NaCl, 0.1 mM $MnCl_2$, 125 μM phenol red were prepared and the pH of this solution adjusted at 8.0. The assay mixture (200 μL) for control contained 53 μL of stock solution and 49 μL of platelets. Then cAMP and cGMP (1. 9 mM) were added separately to the wells. The method is based on the absorbance level of the incorporating phenol red with titratable proton liberated from hydrolysis of cyclic nucleotide to corresponding 5'-phosphate ester by PDE (Frielle *et al*., 1979). The 49 μL of plant extract that was dissolved in dimethyl sulfoxide (DMSO) 10% was added to 53 μL of stock solution and 49 μL of platelets and incubated for 20 min at 25°C. 49 μL of cAMP and cGMP (1. 9 mM) were separately added to the wells and then after 5 min the absorbance of the test samples were read at 560 nm using a fluorescence microplate ELISA reader. The extracts with various concentrations ranging from 0.1 to 5 mg mL^{-1} were tested. Each experiment was carried out in duplicate wells and the absorbance was read triplicate. Sildenafil was used as the standard solution and blank was 53 μL of stock solution and 49 μL of platelets with DMSO 10%. Three concentrations (0.1, 1, 5 mg mL^{-1}) of the extracts and sildenafil (40, 2, 20 μM) were tested.

Statistical analysis: Mean and standard error values were determined for all the parameters and the results were expressed as Mean±SEM. All data were analyzed using analysis of variance ANOVA followed by Newman Keuls. Differences between groups was considered significant when p = 0. 05.

RESULTS AND DISCUSSION

Nineteen plants of TIM with aphrodisiac effects were selected and extracted with ethanol. The extraction ratio for each plant was shown in Table 1. As shown in Fig. 1, significant dose-dependent cAMP-PDEI activity were observed from eight plants including *Allium cepa*, *Trigonella foenum-graecum*, *Brassica rapa*, *Alpinia officinarum*, *Tribulus terrestris*, *Urtica pilulifera, Linum usitatissimum* and *Zingiber zerumbet*. They showed the most cAMP-PDEI activity at 0.1 mg mL^{-1}, whereas the extracts of *Zingiber officinalis* and *Peganum harmala* demonstrated the most cAMP-PDEI effect at 5 mg mL^{-1}. The rest of the extracts showed similar cAMP-PDEI effect in three tested concentrations in comparison to sildenafil. As shown in Fig. 2, six plants including *Allium cepa*, *Alpinia officinarum*, *Tribulus terrestris*, *Linum usitatissimum*, *Withania somnifera* and *Zingiber zerumbet* showed significant dose-dependent cGMP-PDEI activity. The most cGMP PDEI effect was seen with 0.1 mg mL^{-1} of these plants, while *Zingiber officinalis* and *Peganum harmala* had the most effect at 5 mg mL^{-1}. The rest of the extracts showed the same cGMP-PDEI effect in the three concentrations used in comparison to sildenafil. In this study, a total of 19 plants were screened for assaying inhibitory potential on platelets cAMP and cGMP PDEs. In comparison to sildenafil, 10 plants showed better cAMP-PDEI effect and 8 plants exhibited better cGMP-PDEI effect. These extracts showed the most PDEI activity at 0.1 mg mL^{-1}, whereas *Z. officinalis* and *P. harmala* showed a different pattern with the most PDEI effect at 5 mg mL^{-1} that might be related to antiplatelet activity of both plants (Guh *et al*., 1995; Im *et al*., 2009; Thomson *et al*., 2002). *A. cepa* and *P. harmala* have been previously shown for antiasthmatic effect (Duke, 2002; Wagner *et al*., 1990). *A. cepa, B. rapa*, *L. usitatissimum, T. foenum-graecum*, *U. pilulifera*, *W. somnifera*, *Z. officinalis* and *Z. zerumbet* have already shown antioxidant activity (Hu *et al*., 2007; Singh *et al*., 2009; Kim *et al*., 2006). *A. cepa, A. officinarum*, *P. harmala*, *T. foenum-graecum*, *W. somnifera*, *Z. officinalis* and *Z. zerumbet* have already shown anticancer or antitumor effects (Brown *et al*., 2009; Huang *et al*., 2005; Kaileh *et al*., 2007; Lamchouri *et al*., 1999; Singh *et al*., 2009; Sur *et al*., 2001; Yasukawa *et al*., 2008). *A. cepa* and *Z. officinalis* are currently used as cardiotonic and cardiovascular (Shoji *et al*., 1982; Park *et al*., 2009). *A. officinarum* and *P. harmala* are found as antispasm (Duke, 2002; Gruenwald *et al*., 2007). *A. officinarum*, *T. foenum-graecum*, *W. somnifera*, *U. pilulifera, Z. officinalis* and *Z. zerumbet* are used as anti-inflammatory agents (Aimbire *et al*., 2007; Kavalali and Tuncel, 1997; Lee *et al*., 2009; Vyas *et al*., 2008; Zakaria *et al*., 2010a). *P. harmala* and *T. terrestris* have shown vasodilator property (Berrougui *et al*., 2006; Phillips *et al*., 2006). *W. somnifera* and *Z. zerumbet* exhibited immunomodulatory action (Rasool and Varalakshmi, 2006; Yob *et al*., 2011). *P. harmala* and *Z. zerumbet* were identified as analgesic (Farouk *et al*., 2008; Zakaria *et al*., 2010b). *P. harmala, Z. officinalis* and

Table 1: The plants used in TIM for erection dysfunction

Scientific name	Voucher number	Family name	Part used	Extraction ratio (%)	Persian name	Chemical constituents	Pharmacological effect
Allium cepa L.	1322	Liliaceae	Seed	10	Piaz	Alliins, fructosans, saccharose, othersugars, steroidesaponin, flavonoids (Gruenwald *et al.* (2007), essential oil (DerMarderosian, 2008)	Antiasthmatic and antiallergic Wagner *et al.* (1990), antioxidant, anticancer Singh *et al.* (2009), cardiovascular support Park *et al.* (2009)
Alpinia officinarum Hance	1323	Zingiberaceae	Rhizome	15.2	Khulenjan	Volatile oil, diarylheptatonoid, gingerole, starch, tanin, flavonoids Gruenwald *et al.* (2007), sesquiterpens (DerMarderosian, 2008)	Antispasmodic Gruenwald *et al.* (2007), enhancer of sperm count and motility DerMarderosian (2008), anti-inflammatory Lee *et al.* (2009), antitumor Yasukawa *et al.* (2008)
Alyssum homolocarpum Boiss	1324	Cruciferae	Seed	7.25	Ghodumeh	Mucilage Koocheki *et al.* (2010)	-
Armeniaca vulgaris Lam	1325	Rosaceae	Kernel	Bitter: 14.1, Sweet: 6.9	Zardalou	Mono- and polysaccharides, polyphenols, fatty acids and sterol derivatives, carotenoids, cyanogenicglucosides, volatile components Erdogan-orhan and Kartal (2011)	Antioxidant Yurt and Celik (2011.) antimicrobial, antimutagenic, inhibitory activity against several enzymes, cardioprotective, anti-inflammatory, antinociceptive (Erdogan-orhan and Kartal (2011)
Brassica rapa L.	1326	Cruciferae	Seed	12.7	Shalgham	Fatty oil, sterols Gruenwald *et al.* (2007)	Attenuation of oxidative stress Kim *et al.* (2006), aphrodisiac Qureshi *et al.* (1989)
Daucus carota L.	1327	Umbelliferae	Fruit	12.2	Gazar	Carotenoids, volatileoil, polyenes, mono and oligosaccharides Gruenwald *et al.* (2007), flavonoids (DerMarderosian, 2008), coumarin Gilani *et al.* (2000)	Relaxant, vasodilator, aphrodisiac DerMarderosian (2008), antinociceptive, anti-inflammatory Vasudevan *et al.* (2006), antispasmodic Gambhir *et al.* (1979), hypotensive Gilani *et al.* (2000)
Descurainia sophia L.	1328	Cruciferae	Seed	6.5	Khakshi	Essential oils (ß-ocimene, menthol, neoisomenthyl acetate) Li *et al.* (2010), sulfur glycosides Sun *et al.* (2005)	Cardiotonic Fu-hua (1987), antitussive, diuretic, expectorant Mei-fang *et al.* (2008)
Gundelia tournefortii L.	1329	Compositae	Seed	4.2	Kangar	Caffeic acid derivatives, phenolic content Haghi *et al.* (2011)	Antioxidant Coruh *et al.* (2007)
Lepidium sativum L.	1330	Cruciferae	Seed	15.15	Shahi	Glucosinolates, cucurbitacins, cardiac steroids Gruenwald *et al.* (2007)	Antiasthmatic Gruenwald *et al.* (2007), anti-inflammatory, antipyretic, analgesic Al-yahya *et al.* (1994)
Linum usitatissimum L.	1331	Linaceae	Seed	10	Katan	Lignan Waldschläger *et al.* (2005), essential fatty acids (omega3) Kuhn and Winston (2000), sterole, triterpene, cyanogenic glycosides Blumenthal *et al.* (2000)	Antioxidant Hu *et al.* (2007), phytoestrogenic activity Waldschlager *et al.* (2005)

Table 1: Continued

Scientific name	Voucher number	Family name	Part used	Extraction ratio (%)	Persian name	Chemical constituents	Pharmacological effect
Peganum harmala L.	1332	Zygophylaceae	Seed	6.63	Esfand	Harmin, harmalin, harmane, harmalol Hemmateenejad *et al.* (2006), vasicine, vasicinon Pulpati *et al.* (2008)	Analgesic Farouk *et al.* (2008), vasorelaxant Berrougui *et al.* (2006) antispasmodic, aphrodiasiac, antiasmathic Duke (2002), anticancer Lamchouri *et al.* (1999), antiplatelet activity Im *et al.* (2009)
Pinusgeradiana Wall ex D. Don	1333	Pinaceae	Seed	12.55	Chalghouzeh	-	-
Tribulus terrestris L.	1334	Zygophyllaceae	Fruit	13. 25%	Kharkhasak	Steroidal saponin Bedir *et al.* (2002), phenolic compound Ivanova *et al.* (2009), flavonoids Bhutani *et al.* (1969)	Diuretic DerMarderosian (2008), aphrodisiac Malviya *et al.* (2011), management of ED, Gauthaman and Ganesan (2008) vasodilator Phillips *et al.* (2006)
Trigonella foenum-graecum L.	1335	Papilionaceae	Seed	13.8	Shanbalile	Mucilages, protein, steroidal saponins, sterols, flavonoids, trigonellin, volatile oil Gruenwald *et al.* (2007)	Anti-inflammatory Vyas *et al.* (2008), antitumor Sur *et al.* (2001), antioxidant Genet *et al.* (2002)
Urtica pilulifera L.	1336	Urticaceae	Seed	7.80	Anjoreh	-	Increasing sperm count and motility Irshaid and Mansi (2009) antioxidant Ozen *et al.* (2010), hypoglycemic activity Kavalali *et al.* (2003), anti-inflammatory Kavalali and Tuncel (1997)
Withania somnifera (L.) Dunal	1337	Solanaceae	Root	8.85	Bouzidan	Highly oxygenated steroid, alkaloids, flavonolglycosides, phenolic acid DerMarderosian (2008)	Immunomudolatory Rasool and Varalakshm (2006), antioxidative Misra *et al.* (2009), aphrodisiac Malviya *et al.* (2011), anti-inflammatory, anticancer Kaileh *et al.* (2007)
Zingiber officinalis Roscoe	1338	Zingiberaceae	Rhizome	16.1	Zanjebil	Volatile oil, arylalkanes, gingerols, shogaols, gingerdiols, diarylheptanoids, starch Gruenwald *et al.* (2007), sesqiterpens DerMarderosian (2008), alkaloide Syamkumar *et al.* (2003)	enhancer of testosterone production DerMarderosian (2008), aphrodisiac Qureshi *et al.* (1989), anti-inflammatory Aimbire *et al.* (2007), antioxidant Stoilova *et al.* (2007), antitumor Brown *et al.* (2009), cardiotonic Shoji *et al.* (1982), antithrombotic Thomson *et al.* (2002), antiplatelet activity Guh *et al.* (1995)
Zingiber zerumbet (L.) Sm.	1339	Zingiberaceae	Rhizome	9.05	Zorombad	Zerumbone Huang *et al.* (2005), essential oil Zakaria *et al.* (2010a), humulene, monoterpenes, sesquiterpenoids, flavonoids, aromatic compounds Yob *et al.* (2011)	Antitumor Huang *et al.* (2005), anti-inflammatory Zakaria *et al.* (2010a), antinociceptive Zakaria *et al.* (2010b),antipyretic,hepatoprotective,immunomodulatory, antiplatelet aggregation, antioxidant Yob *et al.* (2011)

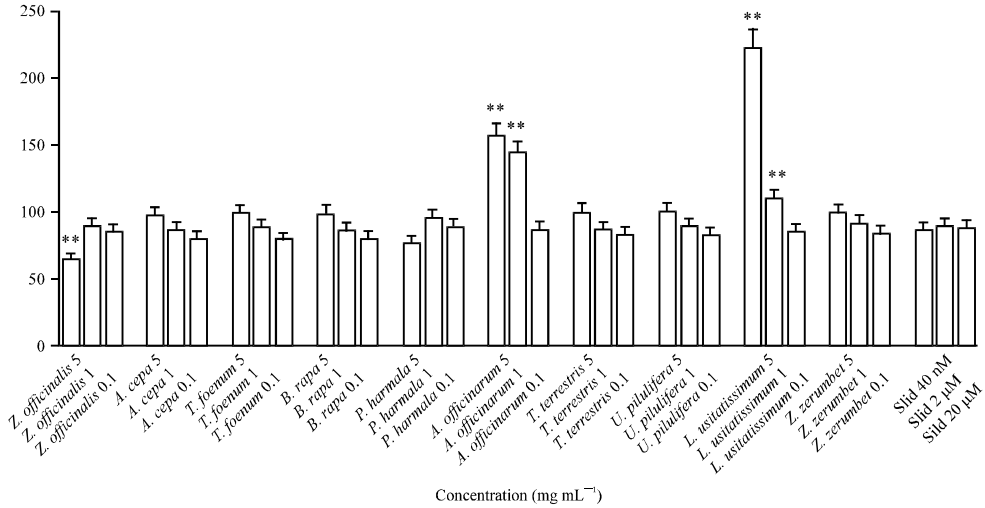

Fig. 1: Inhibitory effects of 10 extracts on cAMP-PDE activity *in vitro*. Values are expressed as Mean±SE. **Significantly different from Sildenafil (Sild) groups at ($p<0.01$)

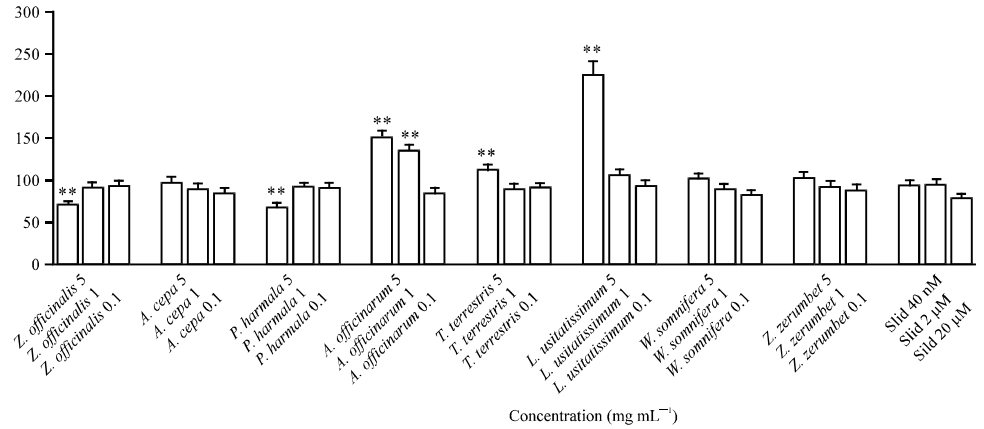

Fig. 2: Inhibitory effects of 8 extracts on cGMP-PDE activity *in vitro*. Values are expressed as Mean±SE. **Significantly different from Sildenafil (Sild) groups at ($p<0.01$)

Z. zerumbet have shown antithrombotic and antiplatelet aggregation effects (Im *et al*., 2009; Thomson *et al*., 2002; Guh *et al*., 1995; Yob *et al*., 2011). *A. officinarum* and *U. pilulifera* increase motility and count of sperm (DerMarderosian, 2008; Irshaid and Mansi, 2009). *T. terrestris* is currently used in management of ED (Gauthaman and Ganesan, 2008). All of these therapeutic effects could be relevant to PDEI properties (Rahimi *et al*., 2010). In our previous paper, it was indicated that main components of the plants with PDEI effects are flavonoids, alkaloids, saponins, lignans and coumarins (Rahimi *et al*., 2010) that are seen in all 19 plants tested here (Table 1). Among tested herbs, *Z. officinalis* and *P. harmala* at 5 mg mL^{-1} showed better cGMP-PDEI in comparison to sildenafil. *Z. officinalis* includes volatile oils, alkaloid and oleoresins (DerMarderosian, 2008; Gruenwald *et al*., 2007; Syamkumar *et al*., 2003) while *P. harmala* contains alkaloid (Hemmateenejad *et al*., 2006; Pulpati *et al*., 2008).

CONCLUSION

The present study for the first time reports PDEI activities of TIM plants that is notable in the field of drug discovery for ED or other relevant diseases. It is required to complete animal and then clinical profile of these extracts. Also, combinative use of these plants may reveal more efficiency in ED with respect to synergetic effect of constituents.

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