Acta Poloniae Pharmaceutica – Drug Research, Vol. 72 No. 4 pp. 643–650, 2015 ISSN 0001-6837
Polish Pharmaceutical Society

PHARMACOLOGICAL ACTIVITIES OF PROTOCATECHUIC ACID

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Abstract: Protocatechuic acid (3,4-dihydroxybenzoic acid, PCA) is a simple phenolic acid. It is found in a large variety of edible plants and possesses various pharmacological activities. This article aims to review the modern trends in phytochemical isolation and extraction of PCA from plants and other natural resources. Moreover, this article also encompasses pharmacological and biological activities of PCA. It is well known to have anti-inflammatory, antioxidant, anti-hyperglycemia, antibacterial, anticancer, anti-ageing, anti-athrogenic, anti-tumoral, anti-asthma, antiulcer, antispasmodic and neurological properties.

Keywords: protocatechuic acid, phytochemical isolation, extraction, pharmacological activities.

Abbreviations: AHR - hyper-responsiveness, AKT - protein kinase B, BCCAO - bilateral common carotid artery occlusion, BrdU - bromodeoxyuridine, CA - chlorogenic acid, CC R2 - chemokine receptor type 2, COMT - catechol-O-methyl transferase, CP - Chinese quince polyphenols, Cy3G - cyanidin 3-*O*-β-D-glucopyranoside, CyG - cyanidin glucosides, DA - dopamine, DADS - diallyldisulfide, DHBA - 3,4-dihydroxybenzoic acid, DG - D-galactose, DPPH - 2,2-diphenyl-1-picrylhydrazyl, FBS - fetal bovine serum, FRAP - ferric reducing ability of plasma, GSH - glutathione, H_2O_2 - hydrogen peroxide, hADSCs - human adipose tissue-derived stromal cells, HBMEC - human brain microvascular endothelial cell line, IL-1β - interleukin-1β, I/R - intestinal ischemia/reperfusion, JNK - c-Jun N-terminal kinase, LDH - lactate dehydrogenase, LT - luteolin, MAPK - mitogen-activated protein kinase, MIC - minimal inhibitory concentration, MIPS - molecularly imprinted polymer microspheres, MMP-2 - matrix metalloproteinase-2, MTT - (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, $Na_4P_2O_7$ - tetrasodium pyrophosphate, NSC - neural stem cells, OVA - ovalbumin, PCA - protocatechuic acid, PD - Parkinson's disease, ROS - reactive oxygen species, SC-CO_2 - supercritical carbon dioxide, t-BHP - *tert*-butyl hydroperoxide, TCDD - 2,3,7,8-tetracholorodibenzo-p-dioxin, TH - tyrosine hydroxylase, TNF-α - tumor necrosis factor α TPA - 12-*O*-tetradecanoylphorbol-13-acetate, VA - vanillic acid

Phenolic acid compounds occurring naturally in plant kingdom contain distinctive structural similarities, i.e., the presence of carboxylic group, as in caffeic acid, gallic acid, p-coumaric acid, vanillic acid (VA), ferulic acid, and protocatechuic acid (PCA). PCA is one of the widely distributed and common compounds, present not only in human diet like in bran and grain brown rice and onion but also found in many fruits, such as plums, grapes and nuts. Many plants and spices contain PCA such as star anise (*Illicium verum*), melissa (*Melissa officinalis* L.), rosemary (*Rosmarinus officinalis* L.), and cinnamon (*Cinnamomum aromaticum*). This bioactive compound is famous for its biological properties and pharmacological activities such as: antioxidant, antibacterial, anticancer, antiulcer, antidiabetic, antiaging, antifibrotic, antiviral, anti-inflammatory, analgesic, antiatherosclerotic, cardiac, hepatoprotective, neurological and nephroprotective (1).

Flowers of *Hibiscus sabdariffa* contain PCA (2). Type of the food affects the content of PCA, for example 100 mg/kg fresh weight of PCA is present in raspberry where as about 0.22 mg/kg in olive oil. At present, PCA is considered as one of the most important metabolites of polyphenol compounds e.g., anthocyanins and procyanidins present in fruits and vegetables (3).

As far as chemical structure is concerned, PCA is a carboxy-derivative of catechol and reacts with reactive compounds of oxygen. Its wide variety is

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found in natural products like fruits and plants. Its bioactivities include anti-radical, anti-oxidant [scavenger of hydrogen peroxide (H_2O_2)], and anti-cancer. Anti-cancerous activity of PCA could be due to its activity as free radical scavenger. It is also useful for treating oxidative stress-induced neurodegenerative diseases (4).

A well-known Chinese herbal medicine, named as Danshen, is used for angina pectoris and myocardial infarction. The effectiveness of Danshen injection (adanshen prescription) as anti-angina might primarily be due to the presence of these phenolic compounds in more than 90% of the constituents. Contrary to this, one of the most active phenolic acids present in Danshen is PCA that has shown apparent anti-angina effect. Metabolism study shows that PCA generally undergo phase II reactions such as methylation, glucuronidation, and sulfonation (5).

Newly, PCA has been confirmed as an effective agent against carcinogenesis in different tissues including in liver diethylnitrosamine, 4-nitroquinoline-1-oxide in the oral cavity, azoxymethane in the colon, *N*-methyl-*N*-nitrosourea in glandular stomach tissue, and *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine in the bladder (6-10).

This article aims to review the modern trends in phytochemical isolation and extraction of PCA from plants and other natural resources. Moreover, this article also encompasses pharmacological and biological activities of PCA.

OCCURRENCE

Phytochemically, PCA is a phenolic compound, extracted from flowers of *Hibiscus sabdariffa* L. (7). It occurs naturally in multiple plant species. It is found in *Allium cepa* (8), carrot (*Daucus carota*), mushrooms, loquat fruit, wine, honey, soybean, and fruits of Ficus species (1).

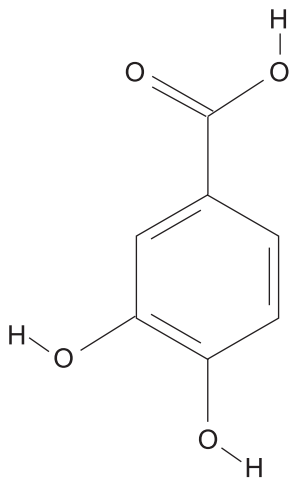

Figure 1. Chemical structure of protocatechuic acid

CHEMICAL AND PHYSICAL PROPERTIES

Various plants contain phenolic compounds that are considered as secondary metabolites. Shikimic acid pathway is used to derive these phenolic compounds from phenylalanine. PCA is also known as simple phenolic acid, and is chemically known as 3,4-dihydroxybenzoic acid. Various kinds of phenolic derivatives e.g., benzoic and cinnamic acid derivatives, flavonoids and isoflavonoids are present in plants (1). The chemical structure of PCA is given in Figure 1.

At 760 mm of Hg, boiling and melting points of PCA are 410°C and 221°C, respectively. It is gray to tan solid crystalline powder. Solubility studies of PCA indicate that it is soluble in alcohol, ether and scarcely soluble in water with the ratio of 1 : 50 (1).

EXTRACTION AND ISOLATION

Initially PCA was isolated from pigmented scales of bulb onion (*Allium cepa*). Extraction was done in plenty of water and alcohol and the extracts were crystallized. These crystals of PCA were found to be effective in a disease, called oil smudge (9). This phenolic acid was isolated from culture of vibrio growing on p-hydroxybenzoic acid. It was found that PCA is formed during p-hydroxbenzoic acid oxidation by pseudomonas flourescens (10).

Another method for the extraction of PCA is from soil with 0.1 M $Na_4P_2O_7$ and acetone. Acidic, neutral and basic fractions were obtained from phosphate extracts of ether soluble substances by paper chromatography. Resultantly, three phenolic acids i.e., PCA, vanillic acid and p-hydroxybenzoic acids were isolated (11). PCA, along with eight other phenolic compounds including: 3‘-*O*-methylquercetin 3-*O*-β-D-glucopyranoside (1); 3‘-*O*-methylquercetin 3-*O*-β-D-galactopyranoside (2); 3‘-*O*-methylquercetin 3-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (3); kaempferol 3-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (4); naringenin 7-*O*-β-D-glucopyranoside (5); catechin (6); PCA (7); VA (8); and *p*-hydroxybenzoic acid (9) were isolated from ethyl acetate and n-butanol fractions of almond (*Prunusamy galus*) skins and identified on the basis of NMR and MS data. Moreover, 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity was observed for PCA (12).

Cyathenosin A, a spiro-pyranosyl derivative of PCA, was isolated from *Cyathea phalerata* Mar. Repeated silica gel chromatography was used for its isolation, while structure elucidation was done by MS, 1D and 2D NMR spectroscopic techniques and confirmation was done by single crystal X-ray analysis. This derivative showed antioxidant and hypoglycemic activity (13).

In addition, PCA along with: isorhamnetin 3-O-β-D-glucoside, isorhamnetin 3-*O*-β-rutinoside, quercetin 3-*O*-β-D-glucoside, and syringetin 3-*O*-β-D-glucoside were isolated from sea buckthorn juice concentrate by high-speed counter-current chromatography (HSCCC) in two phase solvent system of n-hexane–n-butanol–water in mode of head to-tail phase. The characterization of the compounds was done by HPLC–ESI–MS–MS, 1D-NMR and 2D-NMR (14).

Scutellaria barbata D. Don (herb) has been used to extract PCA by using supercritical carbon dioxide (SC-CO_2) combined with HPLC. Water was used as solvent in SC-CO_2 extraction, so this was found to be environment friendly method, and PCA extracted from the above herb can be used as an anti-tumor treatment (15).

Molecularly imprinted polymer microspheres (MIPS), characterized by FTIR spectroscopy and scanning electron microscopy (SEM), have been used to assess their functionality against non-imprinted polymers by equilibrium binding experiments. To extract PCA from *Rhizomaho malomenae*, MIPS was used as solid phase extraction absorbent and found to be very effective, so PCA can have good traditional applications as medicines (16). Furthermore, cytotoxic activity of methanolic extract of *Veronica americana* was observed after extraction of PCA along with other aromatic acids. Additionally, spectroscopic analysis was used to determine structures of isolated compounds (17).

PHARMACOLOGICAL PROPERTIES

A lot of work has been done in order to determine biological and pharmacological effects of PCA such as antioxidant (18, 19), antiviral (20), antiatherosclerotic and hyperlipidemic (2), nephroprotective (21), and neurological effects (22). In this review, some of major and important biological activities of PCA have been summarized and discussed in Tables 1 and 2.

Different properties of PCA have been studied for its protective effects against oxidative breakdown done by *tert*-butyl hydroperoxide (t-BHP) in a culture of rat hepatocytes. It was found that PCA has protective effects against cytotoxicity and genotoxicity of hepatocytes induced by t-BHP through scavenging free radicals (23). Moreover, PCA inhibited 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced skin tumors of female CD-1 mice showing its anti-tumor effect (24). Moreover, PCA was found effective against pulmonary cancer (25).

After inhibition of o-methyltranslation of PCA to form VA in rat liver cytosol, the prepared hepatocytes were characterized by activity of flavinoids

Table 1. Pharmacological activities of protocatechuic acid.

No.	Biological activities	Inhibitory effects of PCA (1)
1.	Antibacterial	Membrane lysis of bacteria Decreases murine cytochrome P450 and phase II enzymes leading to diminished lipid oxidation levels
2.	Anti-viral	Down-regulates the secretion of HBsAg and decreases the release of the HBV DNA from HepG2
3.	Neurological effect	PCA inhibited the cytotoxicity, apoptotic morphology, reduction of TH expression and abnormal oligomerization of α-synuclein in PC12 cells
4.	Anti-atherosclerotic	Inhibits monocyte adhesion to TNF-α activated mouse aortic endothelial cells VCAM-1 ICAM-1 expression and reduces NF-Xb binding activity
5.	Antifibrotic	Inhibits the levels of TGF-β1, CTGF and inhibits HSCs proliferation.
6.	Anti-ageing	Increases activity of glutathione peroxidase, catalase and decreases the malondialdehyde level.
7.	Anti-ulcer	Cytoprotective action and strengthening of the gastric mucosa; it enhances mucosal defense.
8.	Anticancer	Inhibition of generation of free radicals, influences in phases 1 and 2 of the metabolism of certain carcinogens, directly blocks the binding site of carcinogens with DNA molecules.

and gallic acid esters. The inhibitory phenomenon of catechin gallates and gallic acid esters on cellular PCA o-methylation was due to the direct response of catechol-O-methyl transferase (COMT) activity (26). The inhibitory effect of PCA and roselle calyx was studied on growth of various bacteria and PCA was found to have greater antibacterial activity than roselle calyx but less inhibitory effect in human plasma than in broth (27). Different extracts like PCA diallyldisulfide (DADS), roselle calyx, and diallyltrisulfide (DAT extract) were found to have *in vitro* inhibitory effects on the growth of *Helicobacter pylori (H. pylori)* (15 susceptible, 11 clarithromycin-resistant and 9 metronidazole-resistant strains). Tube dilution assay was used to find the minimal inhibitory concentration (MIC) of every agent. Urease activity of resistant and susceptible *H. pylori* was decreased by PCA (28). In addition, PCA produced by ferulic acid through bioconversion was studied in plant-growth-promoting *Pseudomonas putida* WCS358 and it was found that the strongest induction of genes was done by PCA (29) that was used to find growth of Azotobacter in chemically defined media containing p-hydroxybenzoic acid (30).

The anti-aerobic and anti-oxidative effects of PCA and *roselle calyx* in ground beef were determined revealing that growth of various bacteria and lipid oxidation was decreased in ground beef. So it was also found that PCA could be used for the prevention of microbial growth in foods (28).

Antibacterial activity

Roselle calyx and PCA extracts (both aqueous and ethanolic) were found to have antibacterial activities on some food spoiling bacteria, where PCA and *roselle calyx* had inhibitory effects on test bacteria present on ground beef and apple juice. This concept can be used to prevent contamination from bacteria, as an additive industry (31). The influence of PCA on murine cytochrome P450 and phase II

Table 2. Sources of protocatechuic acid and their activities.

No.	Sources	Activities	References
1.	*Vitis vinifera*	Antioxidant	(6)
2.	*Ciboti umbarometz*	Antioxidant	(19)
3.	*Hibiscus sabdariffa*	Antihypertensive, hepatoprotective, and anti-inflammatory	(23)
4.	*Hedera helix*	Bronchodilatory, antispasmodic activity	(24)
5.	Fruit of *Phyllanthus emblica*	Anti-inflammatory, analgesic activity	(27)
6.	*Saliva miltiorrhiza*	Antiviral, antiatherosclerotic, Hyperlipidenic and ischemic heart disease protective	(25, 26)
7.	*Alpiniao xyphylla*	Antiageing	(28)
8.	Human metabolite of Cyanidin glycosides	Antioxidant	(14)
9.	Euterpeoleracea	Antioxidant, anti-inflammatory, antiproliferative and cardioprotective	(20)
10.	*Allium cepa*	Antifungal	(4, 21)
11.	*Oryza sativa*	Cancer chemopreventive	(3)
12.	*Cinnamomum aromaticum*	Antioxidant	(4)
13.	*Ginkgo biloba* L.	Antioxidant	(12)
14.	*Prunusa mygdalus*	Antioxidant	(7)
15.	*Prunus domestica* L.	Antioxidant	(5)
16.	*Agaricus bisporus* or *Phellinus linteus*	Chemopreventive	(24)
17.	*Hibiscus sabdariffa*	Antibacterial, nephroprotective activity	(10, 11, 15)
18.	*Boswelli adalzielii*	Antispasmodic	(22)
19.	*Hypericum perforatum* L.	Antioxidant	(13)
20.	*Ribesuva crispa* L.	Antioxidant	(6)

enzymes was examined and mutagenicity and/or carcinogenicity of amine derivatives and polycyclic aromatic hydrocarbons were found to be decreased by injecting PCA into rodents. This effect was found to be dose- and tissue-dependent (32).

The antibacterial activity of PCA was determined against Gram-positive and Gram-negative bacteria by microdilution assay. It was noticed that PCA successfully inhibited its growth due to membrane lysis of bacteria, so PCA can be used as natural preservative (33).

Neuroprotective effects

The neuroprotective effects of PCA, extracted from *Alpinia oxyphylla*, on H_2O_2 resulted in apoptosis and oxidative stress in cultured PC12 cells. Apoptotic cell death by H_2O_2 was dose-dependent. Enhanced effect of PCA on protecting PC12 cells against apoptosis, augmented glutathione (GSH) level and an increase in catalytic activity was investigated by flow cytometric analysis (34).

Neuroprotective mechanism of PCA was studied by finding the activities of endogenous antioxidants and the content of lipid peroxide in brain by calculating cell viability through (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and lactate dehydrogenase (LDH) assays. As a result, PCA promoted cell growth by quenching H_2O_2 (35). It can encourage the neuronal demarcation combined with fetal bovine serum (FBS) *in vitro*, neuronal maturation and neurite outgrowth. In addition, PCA-induced viability was also mediated with endogenous antioxidant enzymes activation. Furthermore, PCA can serve as a tool to help in brain recovery, and thus may be responsible for neurodegenerative disease repair (36).

Ethyl ester of PCA, silymarin and piracetam were found to be neuroprotective towards cerebral global ischemic/reperfusion in rat model by performing a bilateral common carotid artery occlusion (BCCAO) on rat models using a traumatic clamp followed by reperfusion. Treatment with PCA has ability to enhance the endogenous defense functions. Silymarin was found to have better neuroprotection so can be clinically assessed for human use (37). Neurotrophic effects of PCA on cultured cortical neurons were investigated by real time PCR and the signaling pathways activated by PCA were studied by antagonists. PCA-induced neurite outgrowth and neuronal survival in cultured cortical neurons were blocked by LY294002 (a PI3K inhibitor) and ZM241385 (an A2A receptor antagonist) but phosphorylation of AKT (associated with neurotrophic activity) was enhanced by PCA (38).

Anticancer activity

In cytotoxic assays, PCA causes cell death in HepG2 cancerous cell line of liver showing that PCA stimulates the c-Jun N-terminal kinase (JNK) and p38 subgroups of the mitogen-activated protein kinase (MAPK) family (39). The effect of PCA on apoptotic cell death in PC12 cells and on MPP-induced mitochondrial dysfunction was studied. The loss of mitochondrial membrane potential and reactive oxygen species (ROS) was the cause of apoptosis in MPP-induced PC12 cells. Mitochondrial dysfunctioning was significantly reduced when PC12 cells were treated with PCA (40).

The effects of PCA on H_2O_2 or MPP-induced apoptosis in *in vitro* rotenone model were observed through treatment of PC12 cells with PCA. PCA had the capacity to block the retinone induced apoptotic death of cells (41). Neural stem cells (NSC) obtained from the embryos of old rats were propagated and then cultured with and without PCA. Cell proliferation was detected by bromodeoxyuridine (BrdU) labeling. In fact, PCA also reduces apoptotic activity and ROS level in NSC (42).

Evaluation of PCA as a degradation product of cyanidin 3-O-β-D-glucopyranoside (Cy-3-G) in plasma of rats was done by high performance liquid chromatography (HPLC) but formation of PCA was not detected in rats revealing that PCA was not the major metabolite in liver of rats (43). Major human metabolite of cyanidin glucosides (CyG) is PCA. It was found by analysis of blood, fecal and urine samples of healthy people who consumed 6 liters of blood orange (a variety of orange with crimson having blood like color) juice. Native CyG were evaluated by HPLC/MS/MS and the found major metabolite was PCA out of 73% injected CyG (43).

It has been observed that PCA derived from Alpinia was found to enhance migration capacity of human adipose tissue-derived stromal cells (hADSCs), used in transplantation for regeneration of injured tissues. The presence of PCA increased the rate of migration of hADSCs, dependent on dose and time. It also enhanced the movement of hADSCs *in vitro* because of expression of MT1-MMP and the increase of matrix metalloproteinase-2 (MMP-2) zymogen activation. Thermophillic bacteria were used as a degrading agent for naphthalene and the pathway for naphthalene formation passes through the PCA production. The metabolites were determined by GC-MS, protocatechuic intermediates detected in supernatant culture showed that the degradation of naphthalene by *Geobacillus* sp. G27 occurred through PCA by ortho-cleavage pathway (44).

Moreover, PCA was found to be beneficial against reproductive toxicity due to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a pollutant of environment. The study was done on rats by biochemical assay. Toxic effects of TCDD were reduced by treating rats with PCA (21). Action of PCA in hADSCs was found to increase the cell proliferation in dose dependent manner and elevation in expression of cyclin D1. When DNA content was analyzed by flow cytometric analysis, the cell cycle progressed from G_0/G_1 phase to the S phase showing retention of functional characteristics of cells (45).

Anti-anginal effect

It is observed that when rat heart perfusion with PCA was performed, it undergoes methylation in microsomes and cytosol. It is followed by diffusion of methylated metabolite into mitochondria that ultimately lead to conversion into acetyl-CoA thioester. The decrease in fatty acid oxidation (FAO) lead to conversion of fatty acid to glucose, which is beneficial for ischemic heart thereby giving anti-anginal effect (46).

Anti-aging potential

In a study, PCA showed anti-inflammatory and anti-glycative effects on mice brain when treated with D-galactose (DG). PCA could reduce level of ROS, sorbitol and fructose produced by increased levels of DG reducing the ageing phenomenon (47). Intraperitoneal injection of PCA was given to young and aged rats at a single dose. It was found that PCA raised weights of spleen, raised the activities of GSH-PX (glutathione peroxidase) and CAT (catalase) and lowered MDA level of aged rats; it revealed the scope of PCA in age associated disorders (48). PCA, isolated from *Veronica peregrina*, was found to decrease the aging in wild type worms and increase the progeny production due to decrease in ROS. So PCA can be studied as an anti-aging agent for human (49).

Anti-athrogenic effect

It was found that cyanide-3-*O*-β-glucoside (Cy-3-G) and its metabolites have anti-athrogenic property and PCA efficiently increases Cy-3-G level in apolipoprotein E deficient mouse model (50).

Anti-inflammatory, antioxidant and antitumoral activities

In vivo protective effect on acute lung injury was investigated. In fact, PCA inhibited inflammatory cytokinins tumor necrosis factor α (TNF-α), interleukin-1 β (IL-1β), and IL-6 in mice having lipolysaccharide induced lung injury through NF-κB inhibition pathway (51).

Effect of PCA on histological injury caused by intestinal ischemia/reperfusion (I/R) was studied in murine intestinal I/R model. After pretreatment with PCA, I/R induced lung injury was reduced by decrease in tumor necrosis factor, interleukin 6, and caspase-3 expression level and by down-regulation of p66shc expression and phosphorylation (52). From the result of heat-treated Chinese quince polyphenols (CP) on plasma antioxidant action and the plasma levels of aromatic acids after oral application to rats, significant increase in antioxidant activity was observed by the ferric reducing ability of plasma (FRAP) method when heat treatment is given to CP for 2 hours (CPT-2) (49).

Outcome of PCA pretreatment of defending intestinal I/R-induced local intestine and distant liver injury in mice was investigated. Intestinal I/R was established and PCA-induced adaptor protein p66shc inhibition was the main phenomenon that protects intestine from I/R injury. These defensive result of PCA might be credited to the repression of p66shc and the regulation of p66shc-related antioxidative and antiapoptotic phenomenon (53).

Toxic effects of TCDD and preventive effects of PCA on heart tissues of rats were investigated revealing that toxic effects caused by TCDD were partially prevented by PCA treatment. This treatment improved the histopathological alterations e.g., necrosis through its antioxidant effect (54). The role of PCA on human brain microvascular endothelial cell line (HBMEC) proliferation, invasion and tube formation *in vitro* was studied and MTT was used to test proliferation of HBMEC by scratch adhesion tests. Resultantly, PCA enhanced angiogenesis *in vitro* by enhancing proliferation, invasion and tube formation (55).

Anti-asthma activity

Anti-asthma activity of PCA in mice sensitized to ovalbumin (OVA) was studied. Treatment with PCA decreased OVA-induced airway hyper-responsiveness to inhaled methacholine. Cell inflammation and mucus hypersecretion was also decreased by PCA. Thus, PCA can be useful for treating the asthma (56).

CONCLUSION

As a conclusion, PCA is an excellent natural compound which possesses anti-inflammatory, antioxidant, anti-hyperglycemia, antibacterial, anticancer, anti-ageing, anti-athrogenic, anti-tumoral,

anti-asthma, antiulcer, antispasmodic and neurological properties. It can further be explored for its potential to be assessed with other compounds for any possible synergestic effect.

Conflict of interests

There is no conflict of interests among authors over the contents of this manuscript.

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Received: 28. 10. 2014