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ARTICLE

Protocatechualdehyde in Medicine: What We Know and What Lies Ahead

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Abstract

Background: Protocatechualdehyde (PCA) is a naturally-occurring phenolic aldehyde commonly found in many plants and plant-based products. PCA has many possible health benefits. It has shown promising anti-oxidant, anti-inflammatory, anti-bacterial and anti-carcinogenic traits.
Objective: In this study, we aim to explore PCA's potential uses as a therapeutic agent and recommend future research directions.
Methods: PubMed was searched in November 2024. Every article containing "protocatechualdehyde" or "protocatechuic aldehyde" in title or abstract were looked into and relevant studies selected.
Results: PCA has the potential to be effective on a variety of disease. The top five most researched on conditions are: wound healing, atherosclerosis, myocardial ischemia, cerebrovascular disease, Parkinson's disease. Articles mainly focus on cardiovascular, central nervous and urinary systems. Wound-sealant hydrogels containing PCA as a topical agent are an area of focus as well. anti-oxidant, anti-inflammatory, and anti-bacterial properties of PCA appear to give PCA its therapeutic potential. PCA can impact many intracellular pathways including Wnt/β-catenin signaling pathway and induce antiapoptotic proteins like B-cell lymphoma protein**.**
Discussion: In conclusion, studies regarding PCA's therapeutic use have been diverse, but dispersed, and in a few instances contradictory. PCA can have a positive impact on a range of illnesses and conditions *in vitro* and *in vivo*. It appears that PCA owes its therapeutic features to its strong anti-oxidant, anti-inflammatory, and anti-bacterial effects. However, current research lacks in showing PCA's possible systemic effects and interaction with human body. PCA can become a potent pharmacological agent in the future, but still has a long journey ahead.

Keywords: Protocatechualdehyde (PubChem CID: 8768), Anti-oxidant, Anti-inflammatory, Traditional Chinese Medicine, *Salvia miltiorrhiza*

1. INTRODUCTION

3,4-Dihydroxybenzaldehyde, also known as protocatechuic aldehyde or protocatechualdehyde (PCA) is a naturally-occurring compound belonging to the family of phenolic aldehydes [1,2]. PCA appears in liquid or solid form as pale beige acicular crystals, solvable in polar solvents [3]. It has aromatic characteristics with two hydroxyl groups at the 3 and 4 positions, and a functional aldehyde group at the 1 position (Figure 1) [1].

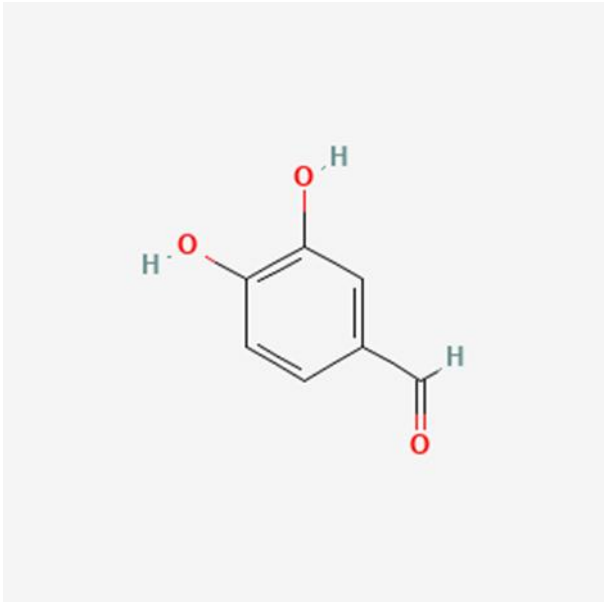


Figure 1. Structure of Protocatechuic aldehyde (source: PubChem)

PCA is found in many plants and plant-based products as a secondary metabolite. fruits, vegetables, and spices such as barley, oat, broad bean sprout, green cavendish banana, grapevine leaf, root of the herb *Salvia miltiorrhiza,* the leaf of *Stenoloma Chusanum Ching* and *Ilex chinensis Sims,* and mushroom *Phellinus gilvus*, all, contain PCA [1-6].

Over the past few decades, PCA has garnered attention because of its potential bioactive properties. PCA can modulate several biochemical pathways, enabling it to affect many biological pathways. As an example, PCA possesses significant antioxidant properties, which can help neutralize free radicals and reduce oxidative stress in the body, this action is important because oxidative stress can lead to various illnesses such as cancers and cardiovascular disease [6].

N*ume*rous studies have been carried out investigating PCA's properties; they have shown its antioxidant, anti-inflammatory, anti-bacterial and anti-carcinogenic attributes [6]. Moreover, PCA has been studied for its relationship with specific diseases as well, such as diabetes, Alzheimer's, melanoma, and so on [7-9].

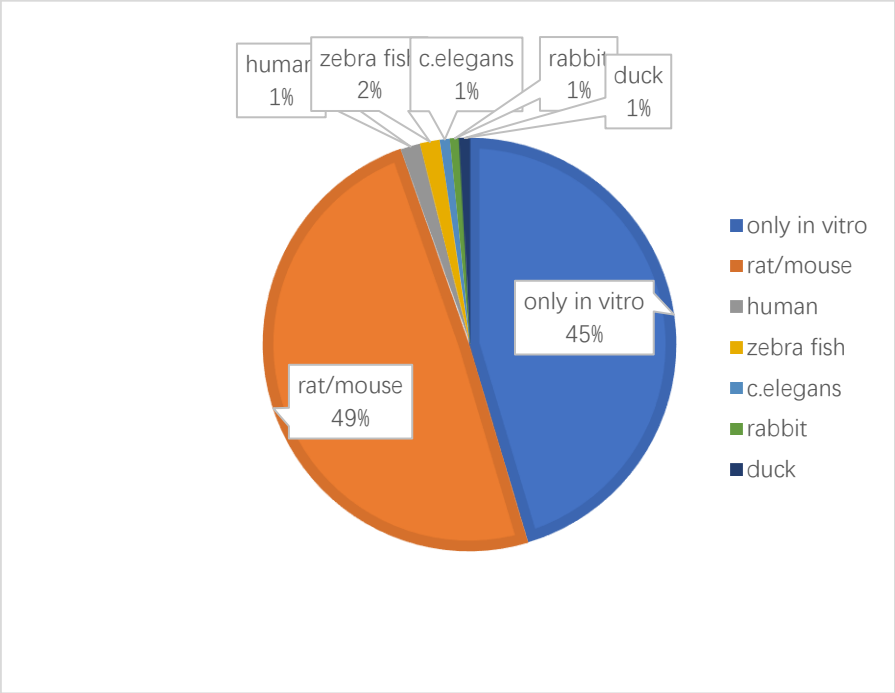
Furthermore, PCA is a main component of *Salvia miltiorrhiza* (Danshen; Danshensu; red sage). *Salvia miltiorrhiza* has been used in many Asian countries for its health benefits since centuries ago. Danshen is used for a variety of health conditions, such as preventing and treating cardiovascular disease, diabetes, and cerebrovascular diseases [10-14]. Needless to say, Danshen is a part of complementary/alternative medicine and not conventional medicine. This review also contains studies on therapeutic properties of Danshen which deemed PCA as an active ingredient of Danshen.

In this review, we aim to explore the potential and possible hazards of using PCA in medicine as an individual therapeutic agent, and to guide future research. This is the first time an article reviews all aspects of protocatechualdehyde therapeutic uses.

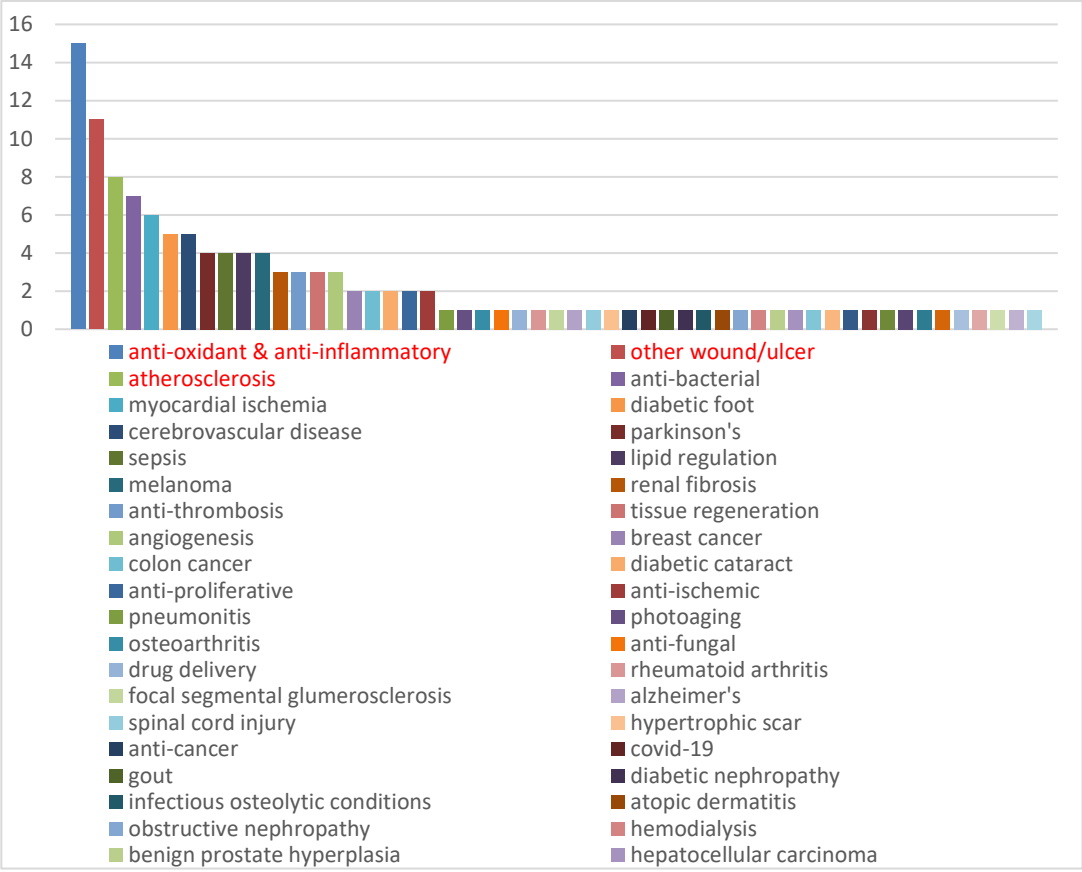
2. METHODS AND MATERIAL

The search was carried out on 15th to 30th of November 2024 through PubMed database. Due to the large number of studies and their dispersion, authors decided to use only one database. In our PubMed search, Studies having the MeSH terms, "protocatechualdehyde" OR "Protocatechuic aldehyde" in title or abstract were inspected. 468 studies were included. Studies not written in English were excluded. Irrelevant studies were excluded. Review articles were excluded. 130 articles met these criteria and were examined in this article.

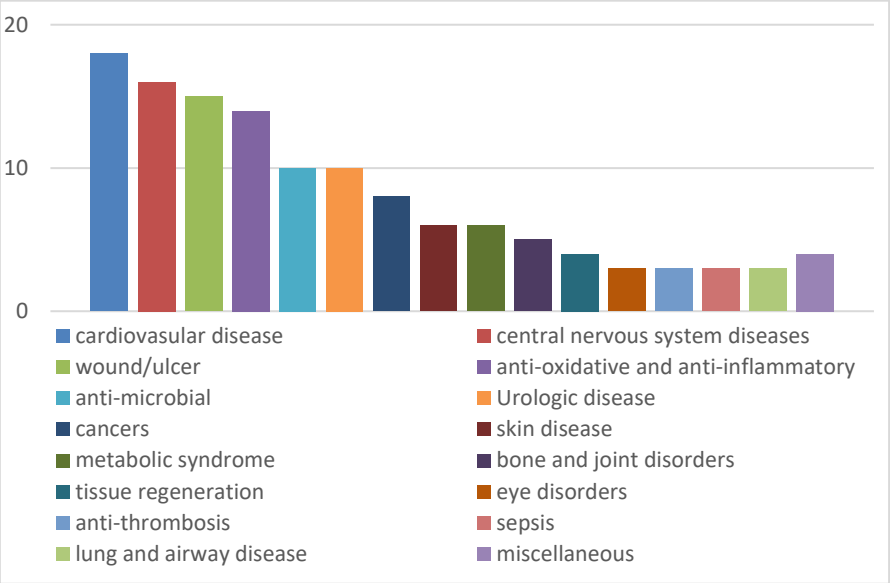
Eligible articles were written down and sorted based on their topic, their respective organ/systems and their test subjects. Diagrams were drawn in Microsoft Office Word 2016 based on this information. Some of eligible articles' features are shown in Graph 1, 2 and 3.



Graph 1. Studies reviewed: *in vitro*/animal models.



Graph 2. Study topics on PCA's therapeutic features and the said topic sorted by the number of carried out research (top 3 marked red)



Graph 3. The most researched topics on PCA's therapeutic features

3. RESULTS

Among the 130 eligible studies, 64 (49.23%) included *in vivo* experiments, of which, only 2 (1.54% of all studies included) were human subject studies, other *in vivo* models were: rats and mice (90.14% of all *in vivo* studies), zebra fish (2.82%), human (2.82%), *Caenorhabditis elegans* (1.41%), rabbit (1.41%) and duck (1.41%). A better demonstration of test subjects is shown in Graph 1.

Graph 2 and Graph 3 demonstrate the number of articles written on the relationship of PCA with a specific topic. They highlight the most used topics which the reviewed articles were based on. Graph 3 sorts topics into 15 broader groups. Graph 2 gives a more detailed and precise view while Graph 3 shows a more comprehensible view of the said topics. Hereinafter, PCA's most important therapeutic features are reviewed (Graphs only include positive effects. adverse effects are discussed separately).

3.1. Pharmacological Properties of Protocatechualdehyde

PCA's antioxidative, anti-inflammatory and anti-bacterial effects seem to be the basis of its application in medicine [15]. To prove PCA's antioxidant abilities five study designs were used:

1. **2,2-Diphenyl-1-picrylhydrazyl antioxidant scavenging assay:** 1,1-diphenyl-2-picrylhydrazil (DPPH) radical scavenging assay is a commonly used technique to determine anti-oxidant activity [16]. Kim, K.-J., et al. investigated PCA's antioxidant activity via DPPH assay in 2008 and observed that PCA is a potent anti-oxidant and reacts with DPPH in a dose-dependent manner. In 2011, Chang, Z.-Q., et al. studied *Phellinus gilvus*'s extract and realized that *Phellinus gilvus* owes a major part of its DPPH radical scavenging activity to PCA. Similarly, in 2021, Chaouche, M., et al. claimed that multiple compounds from *Thymus munbyanus subsp. ciliatus (Desf.) Greuter & Burdet*, including PCA have significant antioxidative abilities. In 2024, Shen, J., et al. stated that PCA, salvianolic acid B and tanshinol were the most potent antioxidant components of *Salvia miltiorrhiza* injection [17-21].
2. **Comparing cell damage after applying Hydrogen peroxide to control group:** in this method oxidative stress is induced by applying Hydrogen Peroxide(H2O2). Pretreatment with more or equal to 2μM of PCA increases survival rate and mitigates damage of Hydrogen Peroxide(H2O2)-induced oxidative stress in both PC12 and SH-SY5Y cells; both of these cell lines are mainly used for studying neurological disease. In PC12 cells treated with PCA, MEG3 was suppressed, as a result, Wnt/β-catenin and PTEN/PI3K/AKT pathways were activated. In PCA applied SH-SY5Y cells, sirtuin-1 and forkhead box O 3a were upregulated and superoxide dismutase 2 and B-cell lymphoma were increased [22,23].

3. **Hydroxyl radical scavenging:** in a study on YuDanshen, Wang, Y.-Q., et al. showed PCA has a good hydroxyl radical scavenging capacity using on-line high-performance liquid chromatography- chemiluminescence detector-diode-quadrupole-time of flight mass spectrometry [24].

4. **Combination of DPPH assay & 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay & Ferric reducing antioxidant power (FRAP) assay:** Burnaz, N. A., et al. developed an on-line high performance liquid chromatography method coupled with three antioxidant assays (DPPH, ABTS, FRAP). They experimented this technique on a few plant-based products, including PCA. PCA was identified as a compound with antioxidant capacity [25].

PCA shows Anti-inflammatory effect as well. Chang, Z.-Q., et al. measured Nitric Oxide (NO) production in RAW246.7 macrophage cell line infected with lipopolysaccharide bacteria with and without pretreatment of PCA. RAW246.7 cells pretreated with PCA produce significantly lower amounts of NO induced by lipopolysaccharide than cells not treated by PCA. PCA might also have an inhibitory effect on the expression of cyclooxygenase-2 messenger RNA. Li, Y., et al. demonstrated that PCA is a potential anti-inflammatory ingredient of *Callicarpa nudiflora*. Li, Y., et al. argue that extracts of *Callicarpa nudiflora* inhibit cyclooxygenase-1 and cyclooxygenase-2 but has a greater inhibition on cyclooxygenase-2. PCA is among the seven anti-inflammatory compounds of Danshen in a study conducted by Ye, T., et al. [17,19,26-28].

Kono, R., et al. studied anti-allergic effects of *Prunus mume* (Japanese apricot; *ume*). Frequency of *ume* intake among 563 age, present illness, medication-adjusted individuals was assessed. It was concluded that women with higher *ume* consumption, were less likely to experience allergy symptoms. Upon further investigation, PCA was among the compounds in *ume* which inhibited Immunoglobulin E-mediated mast cell degranulation. Therefore, PCA might be able to mitigate allergic reaction symptoms [29].

PCA has been described previously as a general anti-bacterial agent. Nonetheless, the following are the documented pathogens PCA is active against:

1. *Candida albicans*: In 2024, Yuan, C., et al. infected a group of *Caenorhabditis elegans*, a nematode, with C. albicans strain SC5314. Under normal circumstances infection with C. albicans significantly reduces C. elegans's life span. However, post-treatment with 10-100μM of PCA could suppress C. albicans's effect on C. elegans's lifespan in a dose-dependent manner, but never to control group's level. PCA and protocatechuic acid could also inhibit hyphal growth and biofilm formation by suppressing virulence genes (ALS3, CaVps34, Vma7, Vac1, and/or HWP1) expression. Nevertheless, in comparison with fluconazole, PCA does not show any fungicidal activity [30].
2. Methicillin-resistant *Staphylococcus aureus (MRSA)*: In 2024, Wang, Y., et al. investigated the impact of PCA on MRSA. Post-treatment of PCA on established MRSA biofilms resulted in remarkable reduction of biomass in a dose-dependent manner *in vitro*, with inhibition rate of 37.4% (4mg/mL PCA). Ampicillin, when used with PCA, achieved better results with lower minimum inhibitory concentration than when used alone. PCA alone has bactericidal properties as well; PCA increases bacterial membrane permeability and causes leakage, encourages intracellular reactive oxygen species production in bacteria [31].
3. *Vibrio parahaemolyticus*: In 2022, Liu, Y. and L. Wang used Crystal violet assay to evaluate PCA's effect on the biofilm of *V. parahaemolyticus*, demonstrating 75 μg/mL of PCA can make *V. parahaemolyticus* biofilm significantly thinner and change structure. PCA can reduce polysaccharide content as well [32].
4. *Yersinia enterocolitica*: In 2022, Meng, X., et al. demonstrated PCA's modest antimicrobial activity against *Y. enterocolitica* infecting HT-29 cells. PCA can inhibit biofilm formation, weaken adhesion of the pathogen to HT-29 cells, suppress pathogen motility. The purposed mechanism of action is similar to previously mentioned Wang, Y., et al.'s study on PCA's effect against MRSA. PCA increases membrane permeability and intracellular reactive oxygen species production in pathogen [33].

5. *Pseudomonas aeruginosa:* In 2017, Kong, W.-J., et al. explored the antibacterial properties and bioactive compounds of *Salvia miltiorrhiza. S. miltiorrhiza* has antibacterial effects against *P. aeruginosa* and PCA is one of the 5 bioactive compounds in this plant responsible for its effect against *P. aeruginosa* [34].
6. *Plesiomonas shigelloides:* In 2008, Prachayasittikul, S., et al. studied antioxidant and antibacterial properties of extracts of *Hydnophytum formicarum* Jack., including PCA. In this study, PCA's cytotoxicity was measured by exposing two cell lines, HuCCA-1 and KB, to different doses of PCA. PCA under 10 µg/mL was not toxic for HuCCA-1 and KB cell lines. PCA was applied to 27 strains of microorganisms, it showed antibacterial activity against *P. shigelloides* with minimum inhibitory concentration of less or equal to 60 µg/mL [35].
7. *Severe acute respiratory syndrome coronavirus 2*: PCA is compound of *Sanghuangporus sanghuang*; this fungus and its phenolic compounds decrease angiotensin converting enzyme 2 and transmembrane protease serine 2 expression in cells *in vitro*; therefore, they may have a role in preventing coronavirus disease 2019 infection [36].
8. *Hepatitis B virus*: Hepatitis B virus DNA, e antigen, and s antigen production can be inhibited by PCA dose-dependently in HepG2 2.2.15 cells *in vitro*. DNA of hepatitis B virus was significantly less detectable in serum of ducks infected with Hepatitis B virus and treated with PCA in comparison with ducks infected but not treated [37].

PCA might be helpful in regenerative medicine as well, repairing different kinds of tissue. As discussed earlier, PCA might encourage osteogenesis and suppress osteolysis. In 2023, Zhang et al. utilized PCA as mediator between a cellulose acetate membrane and metal ions to create a membrane which accelerates osteogenesis and mineralization and modulates inflammation and immune response. In the same year, Du et al. developed a sponge made from cross-linking gelatin, PCA, and Zinc ion. When put on site of hepatic injury, it can absorb blood, trigger coagulation, and accelerate tissue repair and recovery [38,39].

Danhong injection might partially owe its angiogenesis abilities to PCA [40,41].

PCA might inhibit the formation of thrombus through different mechanisms. Sun et al. suggest that PCA interacts with cyclooxygenase-1 and synergizes with aspirin, promoting its effect on platelets. Liu et al. state that PCA is involved in influencing intrinsic clotting pathway activity [42-44].

A sum of PCA's pharmacologic properties is shown in figure 2.

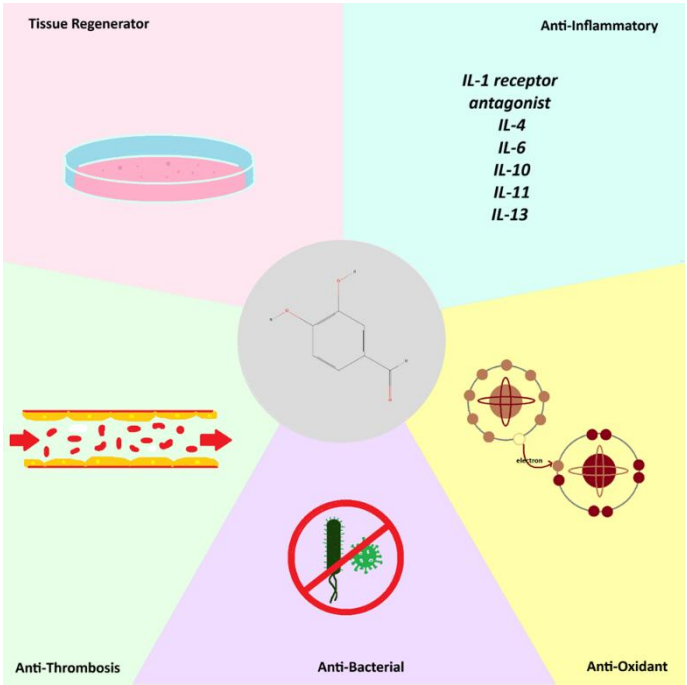


Figure 2. main properties of Protocatechualdehyde

3.2. Therapeutic Applications of Protocatechualdehyde by Disease

The following diseases were the most focused on conditions.

Cardiovascular Disease

Studies indicate that PCA mainly has an effect on atherosclerosis and myocardial ischemic injury (Graph 2). There are 4 general underlying mechanisms known which simultaneously help PCA prevent formation/progression of atherosclerosis:

1. Alleviating endothelial dysfunction: coronary vessels' endothelial cells dysfunction is one of the first steps towards developing atherosclerosis. PCA might be able to reduce endothelial dysfunction through different pathways. Xing et al. discovered that PCA inhibits apoptosis of human umbilical vein endothelial cells by regulating caspase-3 in a dose-dependent manner. Kong et al. stated that PCA affects endothelial cells through G protein-coupled estrogen receptor-1. Zhang et al. stated the possible method which protects endothelial cells from damage is modulating "focal adhesion kinase-phosphatidylinositol 3-kinase-akt" activity. Piezo1 channel is also a possible target.
   Three studies have been executed regarding the relation of mice aortic endothelium functionality and the application of the formula for fufang Danshen, a traditional Chinese medication, which is a combination of Ginsenoside Rg1 (Rg1), Noto ginsenoside R1(R1), and PCA. Cui et al. stated that Rg1-R1-PCA mitigates vascular inflammation and calcification of mice aorta endothelium by increasing the release of Nitric Oxide and inhibiting the TGFβR1-YAP/TAZ pathway. Liu et al. revealed that Rg1-R1-PCA was able to alleviate the process of cell senescence by encouraging autophagy in human aortic endothelial cells and in atherosclerotic mice. However, side effects and systemic effects of administrating PCA were not elucidated in this study [45-50].
2. Preventing/alleviating Dyslipidemia: PCA may be able to lower blood lipids levels and prevent atherosclerosis formation and progression. In a study done by Zhang et al., apolipoprotein E-deficient mice having high-fat diet, were fed Rosuvastatin and PCA (7.24 mM). Blood lipid levels were determined after 8 weeks. PCA and Rosuvastatin lowered mice blood lipids level equally. Moreover, PCA might be able to reduce expression of inflammatory markers such as Toll-like receptor 4, TGF beta-activated kinase 1, nuclear factor kappa-B, interleukin-6, and tumor necrosis factor-α, lowering the chance of plaque formation (more details in "metabolic syndrome" & "anti-oxidant and anti-inflammatory" section) [47,51-55].
3. Preventing accumulation of smooth muscle cells: Moon et al. experienced that PCA mitigates the migration and proliferation of vascular smooth muscle cells through several biological pathways and it is also anti-thrombotic. However, it should be noted that it's only in the beginning of plaque formation that abnormal proliferation and migration of vascular smooth muscle cells form the plaque; after the plaque formation and in advanced plaques, vascular smooth muscle cells do not cause harm instead they help prevent the rupture of the fibrous cap [56,57].
4. Decreasing pericyte damage: pericytes are cells which exist in the wall of both small and large vessels. In an atherosclerotic plaque, lower number of pericytes are associated with lipid accumulation, inflammation, growth and vascularization. Pericyte dysfunction increases lesion instability and intraplaque hemorrhage and calcification. PCA increases pericyte coverage and function resulting in plaque stability in mice with high fat diet-induced atherosclerosis and reduced lipid content and increased collagen accumulation [47,58,59].

Apart from atherosclerosis, PCA can have cardioprotective effects in ischemic heart disease as well. During a myocardial infarction attack, Pretreatment with PCA can reduce the size of the infarct and lower serum's creatine kinase-MB and cardiac troponin I [60,61]. The underlying mechanism is explained in three studies: PCA is anti-apoptotic. Apoptosis is the known as the main pathophysiologic cause of ischemic heart disease. One explanation is that PCA promotes binding of nuclear pyruvate kinase isoform M2 to β-catenin and promotes T-cell factor 4, leading to transcription of anti-apoptotic proteins; another explanation is that PCA suppresses endoplasmic reticulum stress, by preventing the action of protein kinase R-like endoplasmic reticulum kinase, inositol-requiring enzyme1α, and transcription factor 6α [62-64].

Guo et al. designed a biomimetic nanoparticle containing phenylboronic acid, tissue plasminogen activator and PCA surrounded by platelet membrane. This nanoparticle only targets damaged epithelium- due to the platelet membrane, and is anti-thrombotic. PCA's anti-oxidant properties enable this nanoparticle to neutralize reactive oxygen species released because of reperfusion, thus improving the consequences of reperfusion injury [65].

Other research titles regarding PCA and cardiovascular disease are: cardiomyocyte senescence, myocardial fibrosis, cardiac hypertrophy, and Iron Overload-Induced Cardiac Damage [66-69].

Central Nervous System Disease

PCA may be neuroprotective as shown *in vitro* and *in vivo*. 5μM of PCA was able to alleviate Hydrogen Peroxide-induced cell death and decrease apoptotic proteins in SH-SY5Y cells, a cell line commonly used for studying neurodegenerative disease. PCA might reduce the damage caused by a stroke. Three studies delved into the effect of PCA on cerebral ischemia/reperfusion injury in rat model. All three observed that PCA reduced the volume of infarct and improved neurological score. Time of PCA administration in these studies was heterogenous in 3 studies: before, during, and after middle cerebral artery occlusion [23,70-73].

In rats and mice with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease, PCA's administration, orally or via intraperitoneal injection, is associated with improved behavioral deficits and alleviated cell loss. DJ-1 is a neuroprotective protein encoded by PARK 7 gene which has a significant role in pathogenesis and progression of Parkinson's Disease. DJ-1's absence can lead to a form of hereditary early-onset Parkinson's. PCA might be able to control the symptoms of Parkinson's through increasing DJ-1 and decreasing α-synuclein. The suggested underlying mechanism is by polo-like kinase 2/phosphorylated glycogen synthase kinase 3 β/nuclear factor erythroid-2-related factor 2 [74-78].

Zhao et al. studied the effect of intraperitoneal injection of PCA in rats, attenuates secondary injury after moderate spinal contusion. PCA enhances regeneration of spine and inhibits neuroinflammation and neuron apoptosis. Zhao et al. realized that PCA activates Wnt/β-catenin signaling pathway reducing inflammation. Nonetheless, they observed increased apoptosis-associated factors and apoptosis in microglia and PC-12 cells [79]

In an article studying the effect of Gastrodia elata Blume on Alzheimer's disease, PCA was one of the two active ingredients tested in a *Caenorhabditis elegans* model [80].

In a study including multiple phenols, Wang et al showed that several phenols, including PCA, have anxiolytic effects in mice, tested during an elevated plus maze test [81].

Wound/Ulcer

Oftentimes PCA is used in production of ulcer-healing hydrogels. There has been extensive research regarding the application hydrogels containing PCA compounds on wound closure. Multiple hydrogels comprising PCA have been made, each with different chemical composition and different usage and traits. PCA is often linked with Ferric ion. In 2022, Liang et al. created an injectable hydrogel inspired by mussel and brown algae with temperature-dependent adhesive behavior consisting of ferric ion and PCA complex and sodium alginate and gelatine. Authors claim that PCA and ferric ion complex equips this suture-less wound sealant hydrogel with photothermal antibacterial activity. A test in rat model with full-thickness skin incision showed faster recovery than suture and biomedical glue. In 2021, in another study, Liang et al. created an injectable hydrogel by crosslinking between ferric iron, PCA and quaternate chitosan. Anti-bacterial traits of this hydrogel were studied using an infected full-thickness skin wound model, demonstrating effectiveness. Similar studies, with different chemical constitution of hydrogel, have been executed. In these studies, PCA endows hydrogels with photothermal responsiveness, anti-bacterial and anti-inflammatory properties, and stimulate new blood vessel formation as well. PCA was crosslinked with zinc in one study. PCA- Zn^{2+} with cation guar gum hydrogel was created in Bai et al.'s study. This hydrogel was used to treat burn wound and showed bactericidal effect against Escherichia coli and Staphylococcus aureus. Bai et al.'s hydrogel encouraged faster wound closure than commercial dressings in assessments [82-91].

Another area of research interest is application of PCA in healing diabetic wounds. 25% of Diabetic wounds have impaired self-healing. Since hyperglycemia contributes to formation of a biofilm of

microbes on the surface of ulcer, treating diabetic wounds can prove to be difficult. Applying hydrogels containing PCA can aid treating diabetic wounds. PCA is added to hydrogels specifically designed for diabetic wounds for similar reasons it is added to general wound sealant hydrogels. Fu et al. built an all-natural collagen-based hydrogel which can covert pro-inflammatory macrophages to anti-inflammatory macrophages on its own. diabetic wounds are Intractable partly because of a very long inflammatory phase. Fu et al.'s hydrogel showed immunomodulatory and anti-infective properties *in vitro* and *in vivo*. Geng et al. produced an ultra-small copper nanoparticles-loaded self-healing carboxymethyl chitosan-protocatechualdehyde hydrogel. Geng et al.'s hydrogel accelerates diabetic wound healing *in vitro* and in rat diabetic type I model (86.5% hydrogel vs 68.6% control in one week) [92-97]

Adhesive hydrogel patches incorporating PCA have been proposed for treating oral ulcers. Wang et al. designed an adhesive hydrogel which consists of quaternary ammonium salt of chitosan, aldehyde-functionalized hyaluronic acid, and complex of PCA-Fe3+. This adhesive hydrogel releases PCA-Fe3+ consistently and encourages epithelial-mesenchymal transition. This method was tested on rats and showed great anti-inflammatory and pro-proliferation results. [98]

To meet the demands of treating wounds, artificial skin was born. Xia et al. created a bilayer artificial skin model. The top layer consists of electro-spined poly(l-lactic acid) With cross-linked agents, PCA and gallium ion complexation. This layer has hemostatic and anti-bacterial properties, and absorbs liquids [99].

Urologic Disease

PCA might be able to delay the progression of unilateral ureteral obstruction surgery-induced renal fibrosis and hydronephrosis in rats. In mice with unilateral ureteral obstruction surgery, intraperitoneal injection of PCA modulates and suppresses expression of long non-coding RNA 9884 and inflammatory cytokines in primary renal tubular epithelial cells. In 2022, Chang et al. purposed that PCA suppresses renal fibrosis by lowering the concentration of Transforming Growth Factor Beta-1. Transforming Growth Factor Beta-1 can induce renal fibrosis by upregulating epithelial mesenchymal transition. PCA interferes with this process, suppresses expression of Vimentin, Collagen IV, and α-smooth muscle actin and enhances E-cadherin expression in NRK-52E cells. In 2021, Chang et al. described a very similar pathway regarding PCA's impact on diabetic nephropathy. In this study, diabetic mice were orally treated with PCA for 16 weeks, PCA could partially preserve kidney function. Diabetic mice treated with PCA had lower urinary albumin-to-creatinine ratio and blood creatinine than the control group in 16th week [100-104]

PCA is the main active component of *Phellinus linteus* responsible for modulating Thrombospondin 1 and Transforming growth factor beta-1 signaling pathway in rats with focal segmental glomerulosclerosis, in a similar manner to studies on renal fibrosis previously mentioned. post treatment with *Phellinus linteus* might be able to stop the progression of focal segmental glomerulosclerosis. Thrombospondin 1 gene is a potential target for PCA [105].

PCA can attenuate acute kidney injury induced by cisplatin. In a study conducted in 2016, Gao et al. applied cisplatin to a group of HK-2 cells, continued by PCA post-treatment; similar study design was applied to mice *in vivo*. Blood urea nitrogen and creatinine of mice in group cisplatin + PCA was lower than the group only receiving cisplatin. PCA attenuated HK-2 cell inflammation and death *in vitro* through inhibiting Nicotinamide adenine dinucleotide phosphate oxidase 4 [106].

Danhong injection, a traditional Chinese medicine, might be able to help with the clearance of protein-bound uremic toxins, Indoxyl sulfate and p-cresyl sulfate, during hemodialysis. PCA is among the active compounds of Danhong injection responsible for the removal of Indoxyl Sulfate and P-cresyl Sulfate [107].

Cynomorium songaricum Rupr is a plant containing PCA commonly used in traditional Chinese medicine for treating benign prostatic hyperplasia. Tao et al. investigated *C. songaricum* Rupr and its components' effect on benign prostatic hyperplasia *in vitro* and *in vivo*. this study showed *C. songaricum* Rupr ameliorates benign prostatic hyperplasia in rats and BPH-1 cells. Compounds were tested on BPH-1 cell line, PCA inhibited cell proliferation by interfering with 17β-estradiol and dihydrotestosterone [108].

PCA can be used cross-linked with small intestinal submucosa to create a promising multifunctional urethral patch graft suitable for male urethral regeneration [109].

Cancers

PCA might be able to induce apoptosis in cancer cells. PCA's effect on multiple cancer type cells have been recorded: breast, colorectal, and hepatocellular cancers. Lee et al. revealed that *Polyporus parvovarius*-derived PCA can cause S-phase arrest and induce apoptosis in HeLa, BEAS-2B, NCI-H1299, HCC15, HCC95, A549, PC-9, NCI-H2009 cell lines. The extract of 3 Polyporus species was tested on multiple cancer cell lines and compared to cisplatin and control group. In this study *Polyporus parvovarius* could lower proliferation of abnormal cells higher than control group but lower than cisplatin group. The main active component of *P. parvovarius* was determined and it was PCA. Unlike cisplatin, *P. parvovarius*-derived PCA did not induce chemoresistance by increasing the proportion of side population of cancer cells. In other studies, PCA could induce apoptosis in MCF-7, CTLL-2, 293T, MDA-MB-231, HCT116, SW480 and V79 cell lines as well. The suggested underlying mechanisms inducing S-phase arrest are binding and inhibiting C-terminal binding protein 1 in breast cancer cell lines (293T, MDA-MB-231 and MCF-7) and β-catenin suppression. PCA downregulates Cyclin D1 and Histone Deacetylase 1 gene expression in colorectal cancer cells. At the time of writing this review, there is no evidence of PCA's anti-tumor activity *in vivo*, all reviewed articles and experiments happened *in vitro* [18,110-116].

PCA might help suppress metastases as well. Wang et al. studied *Salvia chinensia* Benth-derived PCA hepatocellular carcinoma cells in the liver of mice and its metastases in lung tissue. PCA repressed cancer cells in both tissue samples. The suggested underlying pathway was modulating Wnt/β-catenin pathway [117].

(Melanoma is discussed in "skin disease" section.)

Skin Disease

PCA could repress melanoma cells *in vitro* as tested in A375, SK-MEL-28, and B16-F10 cell lines. PCA can induce apoptosis in melanoma cells. It is suggested that PCA gives rise to G0/G1 cell cycle arrest. Apoptosis is encouraged in PCA treated cells through activation of complement cascade and downregulation of DNA replication and repairment genes. PCA can synergize with dacarbazine, a chemotherapy agent used for melanoma, in causing apoptosis. Melanoma cells escape dacarbazine-induced death by expressing O(6)-methylguanine DNA methyltransferase (MGMT). PCA causes degradation of MGMT. Therefore, PCA may be complementary to dacarbazine. Moreover, PCA can inhibit melanogenesis in B16-F10 murine melanoma cells [118-120].

PCA might have cosmeceutical application as well, especially in photoaging and hypertrophic scars. A main cause of photoaging and DNA damage is ultraviolet radiation. Ding et al. exposed human dermal fibroblasts to 20 J/cm^2 ultraviolet radiation and treated them with 0-2 μg/mL of PCA afterwards. Concentration 3 μg/mL and higher of PCA was evaluated to be cytotoxic to human dermal fibroblasts. Cellular reactive oxygen species were measured with Dichloro-dihydro-fluorescein diacetate assay, and Nitric oxide production was determined utilizing Griess reagent, both were significantly decreased in the PCA treated group. PCA might be able to increase collagen synthesis in ultraviolet-induced damaged human dermal fibroblasts; as opposed to PCA's impact on renal fibrosis mentioned in previous articles. These effects can be associated to regulating underlying signaling pathways: activator protein 1, nuclear factor-kappa B, and p38. Hao et al. designed microneedle containing PCA, hyaluronic acid, and gelatin for preventing or healing hypertrophic scar. This injection was tested *in vitro* on hypertrophic scar-derived fibroblasts and vascular endothelial growth factor-stimulated human umbilical vein endothelial cells and *in vivo* on rabbit ear. PCA/hyaluronic acid/gelatin microinjection modulates angiogenesis in vascular endothelial growth factor-stimulated human umbilical vein endothelial cells and reduces collagen build up in hypertrophic scar-derived fibroblasts [121,122].

PCA might have a role in 2,4-dinitrofluorobenzene-induced atopic dermatitis amelioration by Qingxue jiedu Formulation [123].

Metabolic syndrome

PCA might be able to improve blood lipid profile, and it is reported to be as effective as Rosuvastatin under certain circumstances. In a study conducted by Lin et al. in 2024, zebrafish were fed a high cholesterol diet for 48 hours, coupled with nothing, PCA, or other test agents. The PCA + high cholesterol diet group had longer total distance moved, higher mean velocity, lower total cholesterol, lower low-

density lipoprotein, lower triglyceride, and higher high-density lipoprotein compared to only high cholesterol diet group. This implies that PCA can improve lipid deposition and some dyslipidemia complications in zebrafish in a dose dependent manner. Similar study was performed on hyperlipidemic rats, in which PCA induced higher plasma clearance rates in rats with hyperlipidemia. PCA might prevent differentiation of preadipocytes in 3T3-L1 cell line [47,51-53,124].

In one study, PCA alleviated endothelial dysfunction in streptozotocin-induced diabetic rats, by decreasing p47phox and p22phox production and augmenting Copper-Zinc Superoxide Dismutase expression, without any significant improvement in rats' body weight or fasting plasma glucose. No hypoglycemic effect was seen in streptozotocin-induced diabetic mice in another study as well [15,125].

Salvia miltiorrhiza-derived PCA in combination with other active *Salvia miltiorrhiza* ingredients might be able to lower systolic blood pressure in hypertensive rats by inhibiting vascular remodeling in thoracic aorta and alleviating oxidative stress [126].

Diseases with Main Presentation in Bone or Joint

PCA be used to help delay or alleviate osteoarthritis. Jie et al. simulated post-traumatic osteoarthritis in mouse model by destabilizing the medial meniscus in a study conducted in 2024. Mice treated orally with PCA had less pathological changes in micro-CT scanning indicative of post-traumatic osteoarthritis. Moreover, PCA attenuates chondrocyte senescence marked by decreased P21 and PINK1 protein expression and modulating senescence-associated secretory phenotype-related molecules. In another article, Huang et al. introduced an injection: a hydrogel consisting of PCA combined with decellularized porcine knee joints matrix tested on rats' knee joints after inducing osteoarthritis by medical meniscus and anterior cruciate ligament excision surgery. However, these two studies do not measure symptoms; pain caused by osteoarthritis oftentimes does not correlate with imaging evidence [127-129].

In 2023, Li et al. conducted a small clinical trial on patients with rheumatoid arthritis comparing Jishe Qushi capsules and methotrexate combination with Glucosidorum Tripterygll Totorum and methotrexate combination's effect on rheumatoid arthritis. Glucosidorum Tripterygll Totorum and Jishe Qushi are both traditional Chinese medicines. The Jishe Qushi group was more successful in suppressing symptoms (pain and morning stiffness) and lowering pro-inflammatory cytokines. PCA is an active component of Jishe Qushi capsules, modulating pathways related to rheumatoid arthritis. Nevertheless, the trial consists of only ninety-nine patients and the results might not be accurate [130].

PCA might inhibit osteoclast activity by repressing nuclear factor-kappa B ligand. This may lead to controlling of a variety of osteolytic conditions including osteolysis caused by long-term nearby infection. In mice with lipopolysaccharide infection of calvaria, administration of PCA could suppress osteolysis in a dose dependent manner [131].

PCA might be able to increase bone density in iron-overload-induced bone loss and remodeling in aged iron-overload rats. PCA can lessen the expression of pro-inflammatory cytokines for example, tumor necrosis factor alpha, and encourage osteogenic differentiation [132].

Phellinus igniarius, an edible fungus, might have a positive effect on hyperuricaemia and acute gout arthritis attacks in hyperurecemic and gouty rats by reducing swelling in joint and uric acid in blood and urine. PCA is an active ingredient of *Phellinus igniarius* [133].

Eye disorders

PCA might protect against and delay the progression of diabetic cataract in diabetic patients as tested *in vitro*, on human lens epithelial cells, and in streptozotocin-induced diabetic rats. PCA might act by impacting receptors of advanced glycation end products, which are linked to the development of diabetic cataract. Kim et al. formed advanced glycation end products using bovine serum albumin, fructose and glucose in a sodium azide solution as a part of their research in 2007. After 14 days of incubation, PCA or aminoguanidine were added to this mixture and incubated for another 14 days. As a result, PCA was considerably more effective in preventing glycation end products formation than aminoguanidine. In 2014, Wang et al. compared cell morphology and viability between two groups of SRA01/04 cells incubated with methylglyoxal, one pre-treated with PCA and one untreated. Methylglyoxal is a cytotoxic agent, and a precursor of advanced glycation end products. Group of SRA01/04 cells pre-treated with PCA and incubated with methylglyoxal showed less mitochondrial

dysfunction, morphological changes, apoptosis and higher cell viability. The effect of PCA on streptozotocin-induced diabetic rats' lens opacity was also inspected in Kim et al.'s study [134,135].

Accumulation of hyaluronan in orbital fibroblasts and subsequent volume increase of adipose tissue in orbit, which happens during Graves' orbitopathy, might be inhibited by the application of PCA [136].

Sepsis

In 2012, Xu et al. tested anti-septic abilities of PCA on RAW 264.7 cells and on cecal ligation and puncture-induced septic rats. PCA decreased Interleukin-6 and tumor necrosis factor-alpha and increases Interleukin-10 in RAW 264.7 cells. PCA synergizes with imipenem in lowering the level of Myeloperoxidase in lung, liver, and small intestine of septic rats. PCA with and without Imipenem decreased mortality in septic rats. Both this work and Jiang et al.'s work in 2013 suggest that PCA attenuates phosphorylation of nuclear factor-kappa B in septic situation [137,138].

In 2024, Cao et al. created a nanoparticle using Polymyxin B and PCA designed for managing sepsis, which lowered bacterial survival *in vitro* and *in vivo* [139].

Lung and Airway Disease

PCA might have a role in modulating inflammation, fibrosis and remodeling in lung. Pretreatment with extracts of *Phellinus gilvus* and Phellinus baumii, two mushroom species containing PCA, in healthy rats challenged with polysaccharides intratracheally, attenuates the level of total white cells, neutrophiles and Interleukin-1beta in their bronchoalveolar lavage fluid. PCA lavage reduced the eosinophile count of bronchoalveolar lavage fluid in ovalbumin-induced asthmatic mice. Continuous gavage of PCA to ovalbumin-induced asthmatic mice, interrupts and controls their airway remodeling compared to asthmatic mice not exposed to PCA; asthmatic mice treated with PCA had lesser epithelial lamina and smooth muscle layer thickness of left main bronchus with lower collagen deposition and goblet cells count. Lower collagen deposition is also seen in bleomycin-induced lung fibrosis in rats treated with PCA and in A549 cells, suggesting PCA can lower the severity of lung fibrosis through downregulating high mobility group box 1 and upregulating receptor for advanced glycation end-product [140-142].

3.3. Safety and Toxicity

PCA is cardiotoxic and lethal to zebrafish in doses equal or higher than 70 μg/mL. acute exposure to PCA can cause deformities such as spine curvature, swim bladder closure and pericardial edema. Similar cardiotoxicity might be seen in human as well [143].

PCA was deemed not suitable for clinical application in bone healing in a study by Liu et al. Tested on rat bone marrow culture, PCA suppressed bone marrow cells and caused morphological changes in a dose-dependent manner [144].

4. DISCUSSION AND FUTURE DIRECTIONS

The collective body of evidence reviewed in this article positions PCA as a pleiotropic phenolic compound with broad biological activity across multiple organ systems. Mechanistically, PCA appears to exert its effects primarily through redox modulation, inflammation suppression, and regulation of cell survival and differentiation pathways. These core actions provide a unifying explanation for PCA's seemingly diverse therapeutic indications, ranging from cardiovascular and neurodegenerative diseases to wound healing, fibrosis, and infection.

At the molecular level, PCA consistently demonstrates antioxidant capacity through direct free-radical scavenging and indirect upregulation of endogenous antioxidant defenses, including superoxide dismutase, sirtuin-1, and nuclear factor erythroid 2-related factor 2 (Nrf2) signaling [22,23,74]. Unlike some phenolic acids that act predominantly as chemical antioxidants (e.g., gallic acid), PCA repeatedly shows pathway-level modulation, influencing Wnt/β-catenin, PI3K/Akt, NF-κB, and endoplasmic reticulum stress responses across different disease models [23,62-64,79]. This signaling plasticity likely underlies its anti-apoptotic effects in ischemic heart and brain injury, as well as its context-dependent pro-apoptotic activity in cancer cells.

When compared with structurally related phenolic compounds, PCA occupies an intermediate mechanistic niche. Protocatechuic acid (PC), for example, shares antioxidant and anti-inflammatory properties but lacks the reactive aldehyde moiety that may confer PCA's stronger protein-interaction

potential and bioadhesive capabilities [2]. Curcumin, another extensively studied phenol, exhibits wide-ranging anti-inflammatory and anti-cancer effects but is limited by poor bioavailability and rapid metabolism [6]. Resveratrol, while cardioprotective and neuroprotective, acts predominantly through sirtuin activation and estrogen receptor modulation and shows inconsistent efficacy in clinical trials [10]. In contrast, PCA combines redox activity with chemical reactivity, enabling cross-linking with metals and polymers—an advantage that has been exploited in wound sealants, hydrogels, and tissue-engineered scaffolds [82-99]. This dual biochemical-material functionality distinguishes PCA from many other dietary phenols and may explain its disproportionate success in regenerative and biomaterial-based applications.

Notably, PCA's biological effects are highly context- and dose-dependent. In cardiovascular and neurological disease models, PCA predominantly preserves cell viability and suppresses apoptosis, whereas in malignant cells it induces cell-cycle arrest and programmed cell death [18,110-117]. This bidirectional behavior mirrors that of other polyphenols, such as quercetin and epigallocatechin gallate, which exert cytoprotective or cytotoxic effects depending on cellular redox state and proliferative capacity [6]. However, PCA's selectivity mechanisms remain poorly defined, and few studies have systematically explored its therapeutic window across different tissues.

Despite the breadth of preclinical evidence, substantial translational gaps remain. First, human data are strikingly scarce: only two studies among 130 eligible articles included human participants, and neither evaluated PCA as an isolated pharmacological agent. Consequently, its pharmacokinetics, bioavailability, metabolic fate, and interindividual variability in humans are largely unknown. Second, most *in vivo* studies rely on acute or short-term disease models in rodents or zebrafish, limiting insight into long-term efficacy, cumulative toxicity, and chronic exposure outcomes. This limitation is particularly relevant given PCA's reported cardiotoxicity at higher concentrations in zebrafish and its suppressive effects on bone marrow cells *in vitro* [143,144].

Another translational challenge lies in formulation and dosing. Many promising results derive from PCA-containing extracts (e.g., *Salvia miltiorrhiza*, Danhong injection) or from complex biomaterials in which PCA is immobilized or released locally [10-14,82-99]. While these approaches may mitigate systemic toxicity, they obscure PCA's independent contribution and complicate regulatory approval pathways. Furthermore, interactions between PCA and conventional drugs, suggested by its synergism with aspirin, ampicillin, imipenem, and dacarbazine, remain insufficiently characterized and may pose both opportunities and risks in clinical settings [31,42,65,118].

In sum, PCA represents a biologically versatile molecule with mechanistic overlap across oxidative stress, inflammation, apoptosis, and tissue remodeling. However, the field remains predominantly discovery-driven rather than translationally oriented. Bridging this gap will require standardized dosing studies, rigorous toxicological profiling, and well-designed early-phase clinical trials focusing on indications where local delivery or short-term administration is feasible, such as wound healing, oral ulcers, or adjunctive antimicrobial therapy.

5. CONCLUSION

PCA is a potential pharmacological agent owing to its phenolic nature with its anti-bacterial, anti-inflammatory, and anti-oxidant features. PCA can be highly efficient and have a wide range of applications. However, an extensive amount of research is still needed and some possible setbacks might be encountered along the way. Recommended future research directions are written below.

Only 2 studies out of 130 eligible articles had human subjects. Research inspecting PCA's effect as a solitary agent on human test subject is minimal and almost non-existent. Therefore, our knowledge of PCA's interaction with human body is extremely limited. Prior to the time PCA can be accessed as an individual medication, it should undergo a considerable number of human-subject researches.

The long-term effect of PCA is unclear. Most test subjects experimented on, such as mice, rats, and zebrafish are rather short-lived, hence not suitable for inspecting long-term effects. Studying long-term effects can be difficult and time-consuming.

There were only 2 articles written on the possible adverse effects or side effects of PCA among 130 articles. Possible side effects, systemic effects, and toxicity of PCA is heavily underreported. PCA's

exact pharmacokinetics and safety profile is still unknown. Similarly, information on drug-drug, drug-food, and drug-condition interaction of PCA is merely notional.

Overall, the current evidence on PCA remains heavily preclinical, fragmented, and methodologically heterogeneous. Critical gaps persist regarding PCA's safety profile, pharmacokinetics, long-term effects, and clinical efficacy as a standalone agent in humans. Until these gaps are addressed through systematic translational research, PCA's role will likely remain confined to experimental therapeutics and complementary formulations.

Future investigations should prioritize controlled human studies, standardized formulations, and mechanistic clarification of dose-dependent and tissue-specific effects. With careful progression from bench to bedside, PCA may ultimately transition from a promising bioactive compound to a clinically relevant therapeutic agent.

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