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Potential benefits of patchouli alcohol in prevention of human diseases: A mechanistic review

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ABSTRACT

Patchouli alcohol (PA), a tricyclic sesquiterpene, is a dominant bioactive component in oil extracted from the aerial parts of *Pogostemon cablin* (patchouli). Diverse beneficial activities have been reported, including anti-influenza virus, anti-depressant, anti-nociceptive, vasorelaxation, lung protection, brain protection, anti-ulcerogenic, anti-colitis, pre-biotic-like, anti-inflammatory, anti-cancer and protective activities against metabolic diseases. However, detailed mechanistic studies are required to explore the possibility of developing PA as a functional food material or promising drug for the prevention and treatment of human diseases. This review highlights multiple molecular targets and working mechanisms by which PA mediates health benefits.

1. Introduction

Pogostemon cablin (Blanco) Benth., known as patchouli, is a plant material for the production of essential oil used in the fragrance and cosmetic industries [1]. Patchouli oil has unique characteristics, including a long–lasting, woody, camphoraceous and earthy redolence [2]. It is listed as generally regarded as safe (GRAS) and so approved as a natural food additive by the US Food and Drug Administration [3]. Oil extracted from the whole aerial parts of patchouli consists of patchouli alcohol (PA) (55.7%), α-guaiene (13.1%), α-bulnesene (11.1%) and other compounds. However, oil from the roots consists of mostly pogostone (70.2%), with PA only comprising 4% [4]. In general, PA is higher in leaves and stems than roots. The PA contents in patchouli oil were analyzed in several other literatures (32.3% [5], 37.5–51.0% [6], 40.0% [7], 44.5% [8], and 50.7–54.3% [9]) and the PA contents vary depending on the harvested period, cultivated location and experimental condition. Nonetheless, PA ($C_{15}H_{26}O$), a tricyclic sesquiterpene, is considered to be a major component of patchouli oil and an important indicator for quality control (Fig. 1). Diverse health beneficial activities have been documented for PA, including: anti-influenza virus [10–13], anti-inflammatory [14–17], anti-oxidative [18], anti-ulcerogenic [19,20], anti-colitis [21,22], anti-mucositis [23] and protective activities against brain and lung injuries [24,25]. Most recently, the effects of PA on cancer and metabolic disorders including obesity, fatty

Abbreviations: 3CLpro, 3C-Like Protease; 4E-BP1, Eukaryotic Translation Initiation Factor 4E Binding Protein 1; 5-FU, 5-Fluorouracil; 5-HT, 5-Hydroxytryptamine; 5-HTP, 5-Hydroxytryptophan; ACE2, Angiotensin Converting Enzyme 2; ATF6, Activating Transcription Factor 6; C/EBPα, CCAT/enhancer Binding Protein α; CAT, Catalase; COX2, Cyclooxygenase 2; CUMS, Chronic Unpredictable Mild Stress; CXCL10, C-X-C Motif Chemokine 10; CXCL11, C-X-C Motif Chemokine 11; CXCL9, C-X-C Motif Chemokine 9; DCNB, 2,4-Dinitro-chlorobenzene; DSS, Dextran Sulfate Sodium; DTH, Delayed Type Hypersensitivity; EGFR, Epidermal Growth Factor Receptor; eNOS, Endothelial Nitric Oxide Synthase; ER, Estrogen Receptor; ERK, Extracellular signal-Regulated Kinase; GSH-px, Glutathione Peroxidase; HO-1, Heme Oxidase-1; HPU, *Helicobacter Pylori* Urease; IBD, Inflammatory Bowel Disease; ICAM-1, Intracellular Adhesion Molecule-1; IDO-1, Indoleamine 2,3-dioxygenease-1; IFNγ, Interferon γ; iNOS, Inducible Nitric Oxide Synthase; IP_3R, Inositol Triphosphate Receptor; IR, Ischemia/reperfusion; IRE1, Inositol-requiring Enzyme 1; Kyn, L-Kynurenine; LPS, Lipopolysaccharide; MAPK, Mitogen-Activated Protein Kinase; MCP-1, Monocyte Chemoattractant Protein-1; MDA, Malondialdehyde; MLKL, Mixed Lineage Kinase Domain-Like Pseudokinase; MMP9, Matrix Metalloproteinase 9; mTOR, Mammalian Target of Rapamycin; NF-κB, Nuclear Factor κ-light-chain-enhancer of activated B cells; NLRP3, NOD-, LRR- and Pyrin Domain-containing Protein 3; NO, Nitric Oxide; Nrf2, Nuclear Factor Erythroid 2-Related Factor 2; PA, Patchouli Alcohol; PERK, Protein kinase R-like Endoplasmic Reticulum Kinase; PGE2, Prostaglandin E2; PHE, Phenylephrine; PI3K, Phosphoinositol-3 Kinase; PLpro, Papain-like Protease; PPARγ, Peroxisome Proliferator Activated Receptor γ; PSD-95, Postsynaptic Density Protein 95; PXR, Pregnane X Receptor; RdRp, RNA-Dependent RNA Polymerase; RIP3, Receptor Interacting Serine/Threonine- Protein kinase3; ROCCs, Receptor-operated Ca^{2+} Channels; ROS, Reactive Oxygen Species; RyRs, Ryanodine Receptors; SCFA, Short Chain Fatty Acid; SOD, Superoxide Dismutase; SYN1, Synapsin-1; TLR2, Toll-like Receptor 2; TNFα, Tumor Necrosis Factor α; TPH1, Tryptophan Hydroxylase 1; TXNIP, Thioredoxin Interacting Protein; VCAM-1, Vascular Cell Adhesion Molecule 1; VDCC, Voltage-Dependent Ca^{2+} Channel; VLDL, Very Low Density Lipoprotein; WHO, World Health Organization; ZO-1, Zonula Occludens-1

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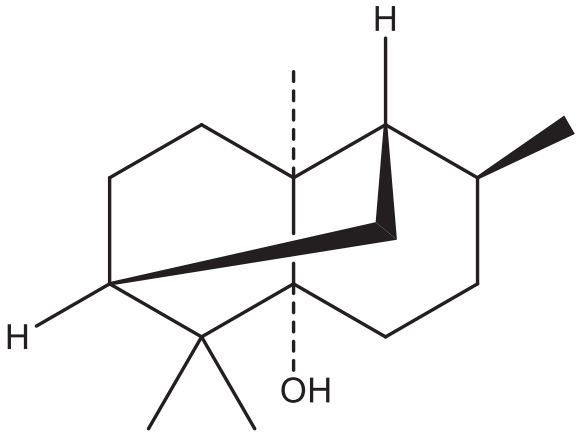

Fig. 1. Structure of patchouli alcohol.

liver and gut microbiota have come under investigation [26–29]. However, despite these diverse beneficial effects, there is a lack of preclinical and clinical studies for the use of PA in the treatment of human diseases. The present review focuses on the health functionalities of PA in diverse disease models to provide evidence and insight for further studies exploring the possibility of using PA in new drug or functional food material development. The present review was carried out using online search engines including Pubmed, Google Scholar and ScienceDirect.

2. Health beneficial effects of PA

2.1. Activities of PA in immune system

2.1.1. Anti-influenza virus activity

Influenza A epidemics include the 1918 Spanish flu (H1N1), 1957 Asian flu (H2N2), 1968 Hong Kong flu (H3N2) and 2009 swine-origin flu (H1N1pdm09) [30]. To combat influenza infections in the future, safe and effective agents without adverse effects need to be developed, for which PA might be a promising candidate. The known anti-influenza virus activity of PA is summarized in Table 1. Wu *et al.* [12] reported that PA showed anti-influenza A virus (A/Leningrad/134/17/1957, H2N2-type) activity (IC_{50} = 4.03 μM) and increased the survival rate of virus-infected mice. Additionally, they suggested that PA may inhibit neuraminidase (NA), one of the viral surface proteins, by binding to NA residues Asp151, Arg152, Glu119, Glu276 and Try406, as identified through a molecular docking study. On the other hand, it has been confirmed that PA has no effect on NA activity in H1N1 type-influenza A viruses (A/FM/1/47 and A/Virginia/ATCC1/2009) [11,31]. A study by Li *et al.* [13] demonstrated that oral administration of PA (20, 40 and 80 mg/kg/day) significantly increased survival in mice infected with lethal doses of influenza A virus (A/FM/1/47). In addition, oral administration of PA in a nonlethal-dose infection model protected from pulmonary injuries through increasing antibodies to the influenza A virus (IgA, IgM and IgG), enhancing CD3+ and CD4+ T cells in blood and decreasing inflammatory cytokines such as TNFα and enhancing immune regulatory cytokines such as IL-10 and IFNγ in blood and the lung. Wu *et al.* [10] likewise investigated the anti-virus activity of PA against influenza A virus (A/FM1/1/47) in human respiratory epithelial cells (16HBE) co-cultured with dendritic cells, macrophages, or monocytes, and found that PA reversed virus-induced increases in cytokine production (IL-4 and IFNγ), indicating that PA attenuated the cellular immune responses. Yu *et al.* [11] found that PA may inhibit influenza A (H1N1 type) infection through interacting directly with viral particles and interfering with viral entry into the host cell and multiplication at early stage via inhibition of the PI3K/Akt pathway and ERK/MAPK signaling, which play roles in viral invasion and the viral life cycle. Moreover, intranasal administration of PA (20 and 40 μg/kg) attenuated infection-induced pneumonia symptoms and infiltration of inflammatory cells in the lung. Most recent review article by Huang *et al.* [32] suggested that PA could be a potential Chinese herbal medicine candidate for targeting three types of proteins (host cell surface protein, ACE2; viral surface protein, Spike protein; viral proteases, 3CLpro and PLpro; viral RNA polymerase, RdRp) of a novel coronavirus (SARS-COV-2), as predicted by *in silico* molecular docking study. Currently, the epidemic disease caused by SARS-COV-2 (known

Table 1
Summary of anti-influenza virus activity of PA.

Function	Study (year published)	Type of study	Model	Dosage & duration of PA	Outcomes of PA treatment
Anti-influenza virus activity	Wu et al. (2011) [12]	*In vitro*	MDCK cell	– 72 h	– IC_{50} to inhibit H2N2 (4.03 μM)
		In vivo	Survival study	– 1 and 5 mg/kg/day (p.o) – 5 days	– Survival rate↑
		In silico	Molecular docking study	– N/A	– PA may interact with residues of NA (Asp151, Arg152, Glu119, Glu276, and Try406)
	Li et al. (2012) [13]	*In vivo*	Survival study at lethal level	– 20, 40, and 80 mg/kg/day (p.o) – 7 days	– Survival rate against H1N1 infection↑
		In vivo	H1N1 infection at non-lethal level	– 20, 40, and 80 mg/kg/day (p.o) – 5 days	– Anti-influenza A virus IgA, IgM, and IgG level in serum↑ – CD3 + and CD4 + T cell in blood↑ – IL-10 and IFN-γ level in serum and lung↑ – TNFα level in serum and lung↓
	Wu et al. (2013) [10]	*In vitro*	Co-culture of 16HBE cells with immune cells	– 10 μg/mL – 24 h	– IL-4 and IFNγ↓
	Yu et al. (2019) [11]	*In vitro*	MDCK cells	– 6.25–50 μg/mL – Pretreatment for 1 h before infection	– IC_{50} for Vir09, NWS, PR8: 6.3 μg/mL, 3.5 μg/mL, 6.1 μg/mL
		In vitro	MDCK cells	– 6.25–50 μg/mL – 2 h (post adsorption)	– PI3K/Akt and ERK activation↓
		In vivo	Influenza A virus (H1N1) infection	– 20 and 40 μg/day (i.n) – 4 days	– Pulmonary viral titer↓ – Survival rate↑ – Pneumonia↓ – IFNγ and IL-2 in lung↑ – Inflammatory cell infiltration↓

IC_{50}, concentration to inhibit viral infection by 50%; NA, neuraminidase; p.o, per os; i.n, intranasal administration.

Table 2
Summary of anti-inflammatory activity of PA.

Function	Study (year published)	Type of study	Model	Dosage & duration of PA	Outcomes of PA treatment
Anti-inflammation	Xian et al. (2011) [16]	*In vitro*	LPS-treated RAW264.7 cells	– 10, 20, 40 μM – 24 h	– Production of NO & PGE2↓ – Inflammatory cytokines↓
	Li et al. (2011) [15]	*In vivo*	Xylene-induced ear edema	– 10, 20, 40 mg/kg (p.o) – Single injection (1 h before induction edema)	– Xylene-induced ear edema↓
		In vivo	Carrageenan-induced paw edema	– 10, 20, 40 mg/kg (p.o) – Single injection (1 h before induction edema)	– Hind paw swelling↓ – Production of inflammatory cytokines↓
	Jeong et al. (2013) [14]	*In vitro*	LPS-treated RAW264.7 cells and TNFα-treated HT29 cells	– 50, 75 μM – 21 h	– Inflammatory cytokines↓ – NF-kB activation↓ – ERK activation↓
	Liao et al. (2013) [17]	*In vivo*	PR-treated mice	– 20, 40, 80 mg/kg (p.o) – 7 days	– Phagocytic index↑ – Humoral immunity↑(IgM↑, IgG↑) – Thymus index↑, Spleen index↑
		In vivo	DNCB-induced DTH in mice	– 20, 40, 80 mg/kg (p.o) – 7 days	– DNCB-induced cell-mediated immune response↓
	Raharjo et al. (2014) [34]	*In silico*	Computational docking study	– N/A	– Direct binding of PA to COX-1 protein
	Zhang et al. (2020) [21]	*In vitro*	HEK293T or LS174T cells	– 6.25, 12.5, 25 μM – 24 h	– hPXR-dependant CYP3A4 expression↑ – PXR nuclear translocation↑
		In vitro	LPS/TNFα-stimulated THP-1 cells	– 6.25, 12.5, 25 μM – 24 h	– PXR-mediated inactivation of NFκB pathway↑
		In vivo	DSS-induced colitis	– 40 mg/kg/day (p.o) – 10 days	– DSS-induced colitis symtoms↓ – mPXR activation↑ – DSS-induced colonic inflammation↓
		In vivo	Pharmacological inhibition of mPXR in DSS-induced colitis	– 40 mg/kg/day (p.o) – 10 days	– Attenuating effect of PA was reversed by PXR inhibitor
	Yu et al. (2015) [25]	*In vivo*	LPS-induced acute lung injury (ALI)	– 10, 20, 40 mg/kg (i.p) – For 1 h before ALI induction	– Lung edema↓ – Total cells, Neutrophils, macrophages in BALF↓ – Inflammatory cytokines in BALF↓ – Lung injury observed in H&E staining↓ – NF-κB activity↓

LPS, lipopolysaccharide; NO, nitric oxide; PR, prednisone acetate; DCNB, 2, 4-dinitro-chlorobenzene; DTH, delayed-type hypersensitivity; PXR, pregnane X receptor; DSS, dextran sulfate sodium; BALF, bronchoalveolar lavage fluid; p.o, per os.

as COVID-19) is spreading rapidly and globally, with the World Health Organization (WHO) having declared a global pandemic in March 2020 [33]. Thus, the inhibitory effect and efficacy of PA against SARS-COV-2 and its mechanism of action need to be investigated for use in global healthcare efforts against COVID-19.

2.1.2. Anti-inflammatory activity

The anti-inflammatory activities of PA are summarized in Table 2. In lipopolysaccharide (LPS)-induced RAW264.7 cells, PA attenuated inflammatory response by reducing NO production and inflammatory cytokine production (iNOS, PGE2, COX-2, TNFα, IL-1β and IL6) [16], while it improved xylene/carrageenan-induced edema by reducing production of NO and pro-inflammatory cytokines (TNFα and IL-1β) in a mouse model [15]. Jeong *et al.* [14] demonstrated in LPS-treated RAW264.7 cells and TNFα–treated HT29 cells that PA exerts anti-inflammatory activity through suppressing IκB degradation as well as the nuclear translocation and transcriptional activity of NF-κB via inhibition of ERK activation. According to an *in vivo* study [17], oral administration of PA (80 mg/kg) fortified humoral immunity, as evidenced by increased phagocytic activity and circulating serum IgM and IgG, resulting in improved thymus and spleen indexes. In addition, PA administration suppressed cell-mediated immune responses in a 2,4-dinitro-chlorobenzene (DNCB)-induced delayed-type hypersensitivity (DTH) model using Kunming mice. These findings support that PA can exert an anti-inflammatory effect through suppressing inflammatory response via inactivation of the NF-κB pathway and cell-mediated immune response as well as by enhancing humoral immunity. In the LPS-induced acute lung injury animal model, PA (10, 20 and 40 mg/kg) attenuated histological observation, neutrophil infiltration and inflammatory response through inhibiting NF-kB activation [25]. Furthermore, an *in silico* molecular docking study identified that PA might act as a COX-1 inhibitor [34]. According to this theoretical study, PA can bind to active sites of COX-1, including Leu223B, Asp228B, Leu237B, Arg332B, Trp138A, Glu139A, Ser142A and Asn143A. These bindings can be maintained by hydrogen bonds with Ser142A, Glu139A and Asp228B. However, COX-1 inhibition by PA requires further testing in experimental *in vitro* and *in vivo* models.

A recent study identified that PA acts as a pregnane X receptor (PXR) agonist and inhibits inflammatory response through PXR-mediated inactivation of the NF-κB pathway in *in vitro* and *in vivo* models [21]. PXR is highly expressed in the intestinal epithelium and the liver, and it regulates transcription of genes involved in the xenobiotic detoxification and transport pathway [35]. PXR can inhibit NF-kB signaling, which signaling results in pro-inflammatory cytokine production [36]. According to a study by Zhang *et al.* [21] using hPXR-overexpressing human embryonic kidney cells (HEK293T) and endogenously hPXR-expressing human colon cancer cells (LS174T), PA treatment increased the nuclear translocation of PXR, consequently enhancing expression of an hPXR target gene (*CYP3A4*) through activation of *CYP3A4* promoter activity; PA was also shown to induce *CYP3A11* gene expression in mouse primary hepatocytes by activating mPXR signaling. Notably, the suppressive effect of PA on NF-κB activation was enhanced in hPXR-overexpressing LS174T cells and reversed in hPXR-silencing LS174T cells. In a dextran sulfate sodium (DSS)-induced colitis mouse model, PA attenuated colitis symptoms such as body weight loss, bloody diarrhea, colon shortening, immune cell infiltration, and colon injury through suppressing the inflammatory response via inhibition of NF-κB activity as a result of up-regulated mPXR activity. The effects of PA against DSS-induced colitis were reversed by pharmacological mPXR inhibition using the mPXR-specific inhibitor

Table 3
Summary of protective effects of PA against gastric injuries.

Function	Study (year published)	Type of study	Model	Dosage & duration of PA	Outcomes of PA treatment
Gastroprotection	Zheng et al. (2014) [19]	*In vivo*	Ethanol-induced gastric ulcer	– 10, 20, 40 mg/kg (p.o) – Single administration 1 h prior to induction ulcer	– Ulcer area↓ – Pro-inflammatory cytokine↓ – Oxidative stress↓ – NP-SH↑, PGE2↑
		In vivo	Indomethacin-induced gastric ulcer	– 10, 20, 40 mg/kg (p.o) – Single administration 30 min prior to induction ulcer	– Ulcer area↓ – NP-SH↑, PGE2↑
	Xie et al. (2016) [38]	*In vitro*	HPU-induced injury of GES-1 cells	– 5, 10, and 20 μM – Pretreatment for 4 h prior to treatment HPU for 24 h	– GES-1 cell viability↑ – Apoptosis↓ – Mitochondrial damage↓ – Oxidative stress↓ – Inflammation↓
		In silico	Computational docking study		– Binding of PA to active sites of HPU
	Lian et al. (2018) [20]	*In vitro*	*H. pylori*-infected GES-1 cells	– 5, 10, and 20 μg/mL – 24 h	– GES-1 cell viability↑ – Mitochondrial membrane potential↑ – Inflammatory cytokine production↓ – Inflammasome formation↓
		In vivo	*H. Pylori*-induced gastritis	– 5, 10, and 20 mg/kg (p.o) – 2 weeks	– Gastritis↓ – Oxidative stress↓ – Inflammatory cytokine production↓

HPU, *H. pylori* urease; NP-SH, non-protein sulfhydryls; PGE2; prostaglandin E2; p.o, per os; i.p, intraperitoneal injection.

ketoconazole. The authors suggested that the enhancement of PXR by administered PA plays a pivotal role in inhibiting the NF-κB-mediated inflammatory response in DSS-induced colitis, and that PA was proposed as a promising agent for preventing or treating inflammatory bowel disease.

2.2. Activities of PA in digestive system

2.2.1. Protective action of PA against gastritis

Gastric ulcers are considered to be one of the most common diseases in the world, and can be induced by chronic alcohol consumption, anti-inflammatory drugs, smoking and *H. pylori* infection [37]. Several studies demonstrated protective effects of PA against experimental gastric ulcer models (Table 3). Specifically, PA (10, 20 and 40 mg/kg) showed protective effects in ethanol-induced and indomethacin-induced gastric ulcer models through modulating inflammatory cytokine production, suppressing oxidative stress and restoring gastric mucosal integrity [19]. In another study using *in vitro* model [38], PA restored *H. pylori* urease (HPU)-induced injury in a gastric epithelial cell line (GES-1) through attenuating apoptosis, mitochondrial damage and inflammatory cytokine production. Regarding the molecular mechanism, they used docking site identification to elucidate how PA inhibits the enzymatic activity of HPU responsible for gastric injury. The oxygen within the hydroxyl group of PA can interact with Ni atoms of the binickel center of HPU, as well as with the Ala169 and Asn168 residues of HPU via hydrogen bonding. In addition, PA interacts with multiple residues of HPU active sites, including His248, His221, His138, Cys321, Kcx219, Ala365, Asp362, Met366, Gly279 and Arg338. These observations provide strong suggestions for the use of PA as a novel drug in the treatment of gastric injury caused by *H. pylori* infection. Another study investigated the preventive effect of PA on gastritis induced by *H. pylori* infection in GES-1 cells and mice, and found similar gastroprotective effects [20]. In detail, *H. pylori* infection of GES-1 cells induces decreases of cellular anti-oxidative agents such as catalase, non-protein sulfhydryl and the reduced form of glutathione, along with increases of apoptosis and cytokine production. PA counteracted these effects through the inhibition of inflammasome activation, as proved by decreased inflammasome-related factors including IL-1β, TXNIP, pro-caspase-1 and NLRP3. Inflammasome activation plays a critical role in inflammation-related cellular dysfunction and apoptosis [39]. This protective effect of PA against *H. pylori* infection-mediated gastritis may be associated with the binding affinity of PA to HPU.

2.2.2. Protective effects of PA in intestinal disease and microbiota

The prevalence of intestinal bowel disease (IBD) is continuously increasing in Western countries, and the incidence of IBD is also rapidly increasing in newly industrialized countries. In addition, it is well known that the intestinal microbiome plays an important role in the pathogenesis of IBD [40]. PA has abilities to attenuate inflammatory intestinal injury and maintain gut microbiota homeostasis (Table 4). Liu *et al.* [18] demonstrated that PA has a protective effect against heat shock-induced injury in a rat intestinal epithelial cell line (IEC-6) through its anti-oxidative properties, as evidenced by downregulated oxidative stress markers (ROS and MDA) and upregulated anti-oxidative enzymes (SOD, CAT and GSH-px) and survival signaling regulators (Nrf2, Keap1 and HO-1). In an animal study, PA administration (10, 20 and 40 mg/kg) prevented 5-fluorouracil (5-FU)-induced intestinal mucositis via suppression of TLR2/MyD88-mediated NF-B pathway activation [23]. Treatment with PA attenuated body weight loss, diarrhea and intestinal mucous tissue injury induced by 5-FU treatment. Significant inhibition of inflammatory response was detected with reduced cytokine production (TNFα, IL-1β and IL-6), along with nuclear translocation of NF-κB and I-κB degradation through TLR2 downregulation. In addition, PA rescued 5-FU-induced intestinal mucosal barrier dysfunction, as evidenced by inhibited MLC phosphorylation and loss of tight junction proteins (ZO-1, occluding and claudin-1), which are good indications of improved intestinal permeability. Another interesting finding in this study is the improvement of 5-FU-induced microbiota dysbiosis with PA administration. At phylum level, PA treatment reversed both 5-FU-induced decrease in *Firmicutes* and increase in *Proteobacteria*. Particularly, probiotics (*Bifidobacterium* and *Lactobacillus*) were increased in abundance with PA treatment, but pathogenic bacteria (*Bacteroides*, *Escherichia, Helicobacter*, and *Parabacteroides*) were significantly decreased. *Bifidobacterium* and *Lactobacilli* are known as having beneficial effects in terms of inhibiting NF-κB activation, upregulating tight junction proteins and decreasing intestinal permeability

Table 4
Summary of protective effect of PA on intestinal disease and microbiota.

Function	Study (year published)	Type of study	Model	Dosage & duration of PA	Outcomes of PA treatment
Intestinal protection	Liu et al. (2016) [18]	*In vitro*	Heat shock-induced IEC-6 cells	– 10, 40, 80 ng/mL – 3 h before heat shock	– Heat shock stress↓ – Oxidative stress↓ – Survival signal↑
	Wu et al. (2020) [23]	*In vivo*	5-FU-induced intestinal mucositis	– 10, 20, 40 mg/kg/day (p.o) – 7 days	– Intestinal epithelium damage↓ – Inflammatory cytokines↓ – TLR2-MyD88-NF-κB pathway↓ – Intestinal mucosal barrier dysfunction↓ – Mucin-2 synthesis and secretion↑ – Gut microbiota dysbiosis↓
	Qu et al. (2017) [22]	*In vivo*	DSS-induced colitis	– 10, 20, 40 mg/kg/day (p.o) – 7 days	– Colitis symptoms↓ – Inflammatory response↓ – Gut epithelial barrier function↑ – Colonic apoptosis and necroptosis↓ – Tryptophan catabolism and metabolite↓
Prebiotics-like effect	Leong et al. (2019) [28]	*In vivo*	Mice	– 20 mg/kg/day (p.o) – 15 days	– Gut epithelial barrier function↑ – Lactic acid producing bacteria↑ – SCFAs producing bacteria↑ – SCFAs receptors in mucus↑

5-FU, 5-flurouracil; DSS, dextran sulfate sodium; LPS, lipopolysaccharide; p.o, per os; i.p, intraperitoneal injection; SCFAs, short-chain fatty acids.

[41,42]. Meanwhile, *Bacteroides*, *Escherichia*, *Helicobacter*, and *Parabacteroides* are closely associated with intestinal inflammation and disease severity [43]. The positive effects of PA on intestinal barrier function and gut microbiota were further supported by a study investigating the prebiotic activity of PA in mice of normal condition [28]. Oral administration of PA (20 mg/kg) for 15 consecutive days improved intestinal epithelial barrier function, evidenced in increased E-cadherin/N-cadherin ratio and tight junction markers (ZO-1 and occludin). Reduction of the E-cadherin/N-cadherin ratio is generally detected in patients suffering from colitis, Crohn's disease and colorectal cancer [44], while the loss of major tight junction proteins ZO-1 and occludin is closely associated with increases of gut permeability and intestinal inflammation [45]. Moreover, PA showed intestinal immunosuppressive activity in terms of down-regulation of immune cell adhesion molecules (ICAM-1 and VCAM-1) and pro-inflammatory cytokines (IL-18 and TNFα) and upregulation of anti-inflammatory cytokines (IL-4 and IL-10). Interestingly, the immunosuppressive properties of PA might result from inactivation of polarization to M1-type macrophages, evidenced by down-regulation of the proinflammatory M1-type macrophage marker (iNOS and CXCL10); PA showed no effect on the anti-inflammatory M2-type macrophage marker (Arginase 1 and mannose receptor) [28]. Moreover, the effect of PA on intestinal barrier function might result from gut microbiota modulating activity of PA. PA increased the abundance of lactic acid-producing bacteria (*L. johnsoni* and *L. reuteri*) and short chain fatty acid (SCFA)-producing bacteria (*Prevotella* spp., *C. jejunese*, and *C. populeti*), along with enhancing SCFA-sensing receptors (GPR41 and GRP43) in intestinal tissue [28]. Lactic acid producing-bacteria in the host gut can improve intestinal barrier function, host digestion and nutrient absorption, and lactic acid maintains the intestinal PH balance [46]. Meanwhile, SCFAs are a major energy source for colon cells and stimulate intestinal cell growth; they also exert immunomodulatory, anti-inflammatory, pro-apoptotic and anti-cancer activity through SCFA receptors, especially in the case of butyrate [47]. Thus, the prebiotic-like activity of PA on gut microbiota homeostasis contributes to enhancing intestinal barrier function and modulating inflammatory response by increasing lactic acid- and SCFA-producing bacteria.

In a study that performed metabolomics analysis using a DSS-induced colitis animal model, PA attenuated acute colitis through inhibition of tryptophan metabolism [22]. Treatment with PA (10, 20 and 40 mg/kg) attenuated DSS-induced colitis symptoms including body weight loss, colon length shortening, histological observation and immune cell infiltration. In addition, PA counteracted DSS-induced increases inflammatory cytokines (TNFα, IFNγ, IL-1β, IL-6, IL-4, IL-10 and IL-12), colonic apoptosis (up-regulated Bax/Bcl-2 ratio) and necroptosis (up-regulated RIP3 and MLKL) and decrease of gut epithelial barrier functions (up-regulated tight junction proteins such as claudin-1, occluding, ZO-1 and ZO-2) in colon tissue. The authors suggested that these protective activities of PA against DSS-induced colitis resulted from inhibition of two key rate-limiting enzymes in tryptophan catabolism, indoleamine 2,3-dioxygenase-1 (IDO-1) and tryptophan hydroxylase-1 (TPH1). Plasma metabolite profiling revealed that the increase of tryptophan metabolites, L-kynurenine (Kyn) and 5-hydroxytryptophan (5-HTP), in the colons of DSS-treated mice were reversed by PA administration as a result of suppressed IDO-1 and TPH1 activity. IDO-1 catalyzes the oxidative cleavage of tryptophan to Kyn, while TPH1 catalyzes tryptophan to 5-HTP, which subsequently creates 5-hydroxytryptamine (5-HT) by decarboxylation [48]. Notably, Kyn is highly increased in the inflamed colon tissue of mice [49]. The effect of PA on these enzymes was further supported by the co-administration of PA with Kyn for seven days, which reversed the protective effect of PA on colitis symptoms including body weight loss, colon length shortening and an increase of disease activity. More broadly, pharmacological inhibition of IDO-1 attenuates DSS-induced colitis [50], while deletion of *TPH1* in mice ameliorates colitis symptoms; supplementation of *TPH1* (-/-) mice with 5-HTP results in more severe colitis [51]. These findings indicate that inhibition of TPH1 and IDO-1 and suppression of 5-HTP synthesis by PA administration contributed to improving DSS-induced colitis; however, it remains to be elucidated how PA regulates the tryptophan metabolism-mediated inflammatory response and cell death pathway.

2.3. Activities of PA in nervous system

2.3.1. Anti-depressant-like activity

According to a report released by the WHO, approximately 4.4% of people worldwide live with depression, and regulating the depression is essential for their mental health [52]. Essential oils extracted from plant materials have been used in aromatherapy for the purpose of releasing depression [53]. In an experimental depressant animal model PA, a major component in patchouli essential oil, has anti-depressant-like activity via mTOR pathway activation (Table 5) [54]. Specifically, this study found PA to attenuate chronic unpredictable mild stress (CUMS)-induced depressant-like behaviors through phosphorylation of mTOR and its downstream regulators (4E-BP1 and p70S6K), consequently upregulating synaptic proteins (PSD-95 and SYN-1) and down-regulating autophagy marker proteins (LC3-II and p62) in the hippocampus. In addition, these activities were reversed by treatment with

Table 5
Summary of potent effects of PA in nervous system.

Function	Study (year published)	Type of study	Model	Dosage & duration of PA	Outcomes of PA treatment
Anti-depressant activity	Zhuo et al. (2020) [54]	*In vivo*	CUMS-treated SD rat	– 10, 20, 40 mg/kg – 4 weeks	– Depressant-like behavior↓ – mTOR pathway activation in hippocampus↑ – Autophagy in hippocampus↓ – Synaptic protein↑
Anti-nocieptive effect	Yu et al. (2019) [57]	*In vitro*	C17.2 and PC12 cells	– 5 μg/mL – 3 h	– Intracellular Ca^{2+}↓
		In vivo	Acetic acid-induced writhing test in mice	– 200 mg/kg (s.c) – 30 min	– Writhing frequency↓ – Latency time of visceral pain↑ – Inflammatory cytokines↓
		In vivo	Intraplantar formalin-induced allodynia test in mice	– 200 mg/kg (s.c) – 30 min	– Planar licking frequency↓ – COX2↓
Brain protection	Wei et al. (2018) [24]	*In vivo*	Ischemia/reperfusion-induced brain injury	– 10, 20, 40 mg/kg (i.p) – Twice (0 h after reperfusion and 12 h later)	– Infarct volume & neurological deficit score↓ – Blood brain barrier dysfunction↓ – Brain edema↓ – MMP9 in brain tissue↓ – Inflammatory cytokines↓ – MAPK activation↓

CUMS, Chronic unpredictable mild stress; s.c, subcutaneous injection; i.p, intraperitoneal injection.

mTOR inhibitor (rapamycin), thus it is reasonable to speculate that activated mTOR mediates the anti-depressant-like activity of PA. This conclusion is further supported by evidence that the mTOR signaling pathway contributes to synapse formation and inhibition of hippocampal autophagy, and is inactivated in CUMS-treated mice [55]. In addition, the anti-depressant-like activity of PA is supported by an animal study demonstrating the PA-enriched dichloromethane extract of *Valeriana wallichii* to have anti-depressant-like activity evidenced by the increased neurotransmitters (norepinephrine and dopamine) level in forebrain [56].

2.3.2. Anti-nociceptive activity

Only one study has investigated the anti-nociceptive activity of PA, using both *in vivo* and *in vitro* models (Table 5) [57]. In acetic acid-induced writhing tests using mice, PA (200 mg/kg for 30 min) prolonged the writhing period and decreased the frequency of writhing action, indicating that PA reduced the response to visceral pain. This was accompanied by reduced production of inflammatory cytokines (TNFα, IL-1β, COX2 and NF-κB) in the brains of the treated mice. In plantar formalin-induced allodynia tests, PA reduced plantar licking time, indicating that treatment of PA reduced response to plantar pain. In addition, PA significantly reduced Ca^{2+} influx in mouse cerebellum stem cells (C17.2) and pheochromocytoma cells (PC12) derived from rat adrenal glands. Further support comes from a report that Ca^{2+} influx is closely associated with neurotransmitter release and cell membrane excitability modulation [58]. Finally, a study demonstrated that the essential oil extracted from *Valeriana wallichii* DC showed anti-analgesic activity with the decreased writhing time in acetic acid-induced writhing test; PA was identified a main component of this essential oil, supporting the anti-nociceptive activity of PA [59].

2.3.3. Protective effect against acute brain injury

In an ischemia/reperfusion (IR)-induced cerebral injury animal model, PA not only improved brain edema, blood-brain barrier dysfunction and MMP-9 expression in brain tissue, but also suppressed inflammatory cytokine production via inhibition of MAPK activation [24].

2.4. Vasorelaxation activity

Ichikawa K *et al.* [60] found that PA showed vasorelaxation activity for the first time. In the study, PA exhibited inhibitory activity on Ca^{2+}-induced contraction of rat aorta with IC_{50} of 4.7×10^{-5} M. Hu *et al.* [61] demonstrated PA to have vasorelaxant activity through blocking extracellular Ca^{2+} influx via voltage-dependent Ca^{2+} channels (VDCCs) and receptor-operated Ca^{2+} channels (ROCCs) into vascular smooth muscle cells, and also blocking intracellular Ca^{2+} release from the sarcoplasmic reticulum via inositol triphosphate receptor (IP_3R)- and ryanodine receptor (RyR)-mediated Ca^{2+} channels (Table 6). Two different vasocontractants, KCl and phenylephrine (PHE), were used in this study; these molecules induce membrane polarization [62] and extracellular Ca^{2+} influx via activating ROCCs [63]. PA inhibited both KCl-and PHE-induced aorta contraction, indicating that PA might be a vasorelaxant due to its role as a Ca^{2+} channel antagonist. Notably, vascular smooth muscle cells widely have α and β receptors that play opposite roles in vasocontraction (α-receptor, vasocontraction; β-receptor, vasorelaxation) [64]. The β-receptor inhibitor propranolol did not affect the relaxant effect of PA, indicating that β-receptors are not involved in PA-induced vasorelaxation. This effect of PA on the vascular muscle cell contractile response could be a promising treatment option for hypertension or cardiovascular disease; however, a follow-up study is required to elucidate such beneficial effect in an animal disease model.

2.5. Anti-cancer activity of PA

The anti-cancer activities of PA are summarized in Table 6. PA inhibited the growth of non-small-cell lung cancer cells (A549) by inducing cell cycle arrest (G1/S phase arrest) and apoptosis through suppression of the EGFR-ERK signaling pathway [26]. In this study, the IC_{50} value of PA with respect to the proliferation of A549 cells was 79.8 μg/mL, however, that in normal human cells (L02, liver; HEK293T, embryonic kidney; HFL-1, lung) was more than 300 μg/mL, indicating that PA might be a safe anti-cancer agent with specific activity against non-small-cell lung cancer. In non-small-cell lung cancer, EGFR and its downstream signaling pathway play crucial roles in cell proliferation and oncogenesis [65]. PA-induced apoptosis and suppression of the EGFR pathway in A549 cells was reversed by treatment with exogenous EGF [26], indicating that the anti-proliferative activity of PA is dependent on blocking the EGFR-ERK signaling pathway. In another study, Yang *et al.* [66] reported that PA-induced A549 cell death was resulted from increased autophagosome formation and activity; however, neither molecular target nor mechanism was identified, and so both remain unclear. Anti-proliferative activity of PA was

Table 6
Summary of vasorelaxation, anti-cancer and preventive effect of PA on metabolic diseases.

Function	Study (year published)	Type of study	Model	Dosage & duration of PA	Outcomes of PA treatment
Vasorelaxation	Hu et al. (2018) [61]	*Ex vivo*	Isolated rat thoracic aorta	– 100 μM	– KCl- and PHE-induced contraction↓ – Exctracellular Ca^{2+}-induced contraction↓ – Endogenous Ca^{2+} release-induced contraction↓
Anti-cancer	Lu et al. (2016) [26]	*In vitro*	A549 cell	– 50, 75, 100 μg/mL – For 48 h	– A549 cell growth↓ – Mitochondiral membrane permeability↑ – Apoptosis↑ – Cell cycle arrest↑ – EGFR downstream signaling↓
		In vivo	Xenograft model using A549 cells	– 5, 10, 15 mg/kg (i.p.) – Once every 3 days for 21 days	– A549 xenograft tumor weight↓ – Cell proliferation↓ – Apoptosis↑
	Yang et al. (2019) [66]	*In vitro*	A549 cells	– 150, 300 μM – For 24 h	– A549 cell growth↓ – Autophagosome formation↑ – Autophagosome activity↑
	Jeong et al. (2013) [67]	*In vitro*	Colon cancer cells	– 50, 75, 100 μM – For 24 h	– Growth of cancer cells (HCT116, SW480, MCF7, BxPC3, PC3)↓ – Cell cycle inhibition↑ – NF-κB-mediated cell death↑
Anti-atherosclerosis	Wang et al. (2016) [69]	*In vivo*	Atherogenic diet-induced atherosclerosis	– 40 mg/kg/day (p.o) – 10 weeks	– Plaque burden in aorta and aortic root↓ – Macrophage infiltration in atherosclerotic plaque in aortic root↓ (Muc2-positive area↓) – Macrophage recruitment↓ – Inflammatory response↓
Anti-obesity	Lee et al. (2020) [27]	*In vitro*	3 T3-L1 cells	– 12, 25, 50, 75, 100 μM – 10 days	– Lipid accumulation in mature adipocyte↓ – Adipogenesis↓
		In vivo	High fat diet-induced obesity	– 25, 50 mg/kg (p.o) – 3 times/week for 8 weeks	– Body weight gain↓, WAT weight↓
Anti-steatosis	Wu et al. (2019) [29]	*In vivo*	High fat diet-induced steatosis	– 10, 20, 40 mg/kg/day (p.o) – 4 weeks	– Hepatic lipid accumulation↓ – Hepatic oxidative stress↓ – Hepatic ER stress↓ – Hepatic VLDL uptake↓ – VLDL export ↑

PHE, Phenylephrine; EGFR, epidermal growth factor receptor; WAT, white adipose tissue; BAT, brown adipose tusse; ER, endoplasmic reticulum; VLDL, very low density lipoprotein; i.p, intraperitoneal injection; p.o, per os.

observed in other types of human cancer cell lines, such as colorectal cancer (HCT116 and SW480), breast cancer (MCF-7), pancreatic cancer (BxPC3) and prostate cancer (PC3) [67].

2.6. Preventive effect of PA on metabolic diseases

Metabolic diseases are a leading cause of death around the world and are closely associated with cancer [68]. There are several reports demonstrating the effect of PA against metabolic diseases (Table 6). In an atherosclerosis animal model fed an atherogenic diet for ten weeks, PA administration reversed plaque burden, macrophage infiltration and production of inflammatory cytokines such as IL-1β, IL-6, iNOS, CXCL9 and CXCL11 [69]. This anti-atherogenic activity seems to be due to downregulation of the chemoattractant molecule MCP-1; however, the molecular mechanism of action of PA in pathophysiological aspects of atherogenesis requires further elucidation. Lee *et al.* [27] reported that PA suppressed adipogenesis and lipid accumulation in 3T3-L1 cells through suppressing PPARγ and C/EBPα and activating β-catenin. In mice fed a high-fat diet for 12 weeks, oral administration of PA (25 and 50 mg/kg body weight) decreased the weight of abdominal white adipose tissues (epididymal and retroperitoneal adipose tissue). In a fatty liver animal model using Sprague Dawley rats, oral administration of PA (10, 20 and 40 mg/kg body weight) for four weeks attenuated hepatic steatosis through not only suppressing endoplasmic reticulum (ER) stress by inactivating ER stress mediators (PERK, IRE1 and ATF6) but also regulating hepatic VLDL uptake by reducing VLDL receptor expression and elevating VLDL secretion [29]. These reports imply that PA can be used for the prevention or treatment of metabolic diseases as a dietary supplement or functional food material.

3. Conclusion

Emerging evidences concerning the bioactivity of PA in diverse experimental disease models supports that PA could be a promising therapeutic or preventive agent for a variety of acute and chronic human diseases, including influenza, depression, gastric disorder, inflammatory intestinal diseases, cancer and metabolic diseases (Fig. 2). Recently, molecular targets of PA have been reported in diverse experimental *in vitro* and *in vivo* models; however, there is as of yet no application in clinical study or acute/chronic toxicological assessment using upper-class experimental animals. Based on the diverse identified bioactivities and proposed mechanisms, PA could be a promising multipotent drug and thus a safe natural compound for preventing or treating human diseases.

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Author contributions

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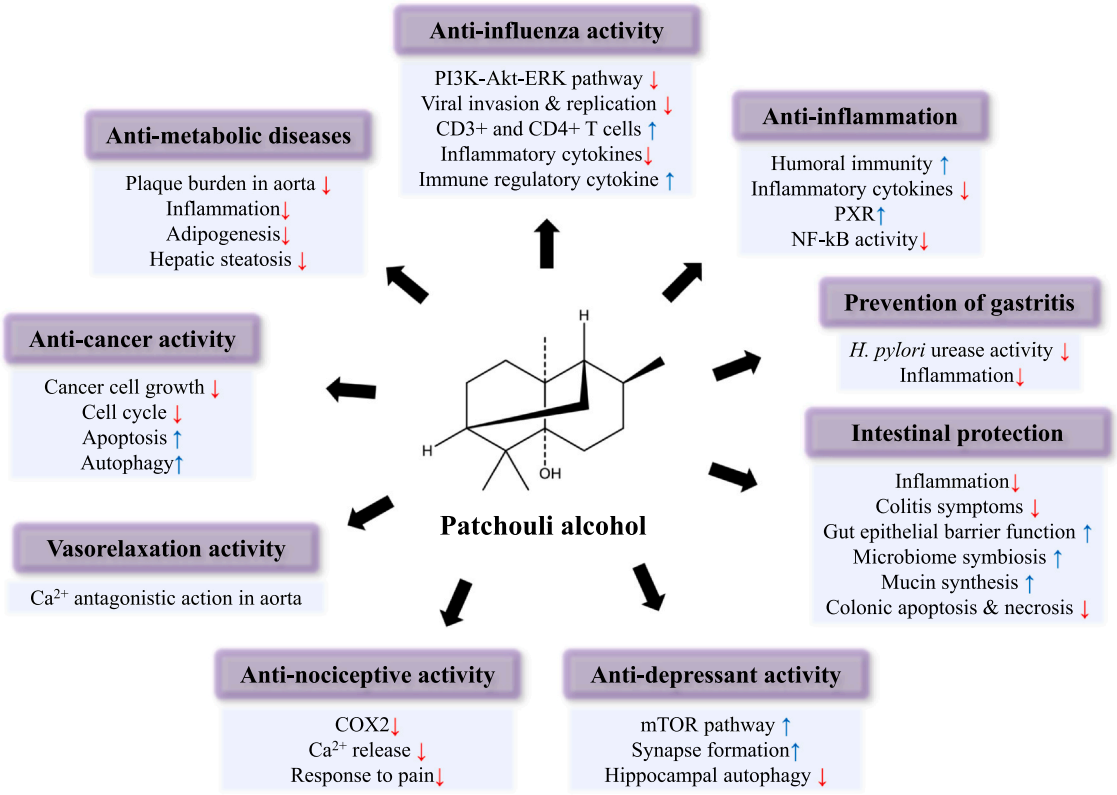

Fig. 2. Schematic diagram showing multiple biological activities of PA.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2020.107056.

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