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A comprehensive review on the main alkamides in *Piper nigrum* and anti-inflammatory properties of piperine

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Abstract Pepper (*Piper nigrum* Linn) is widely used as a seasoning in the culinary industry, and alkamides are its major active components. Among them, piperine (PIP) is a key natural alkamide known for its diverse pharmacological properties, including anti-inflammatory, antioxidant, anticonvulsant, neuroprotective, anticancer, antibacterial, and antiparasitic effects. In addition, PIP is widely utilized as a bioenhancer. Notably, it has garnered increasing attention for its potential as a natural phytochemical in the treatment of various inflammatory disorders. This review aims to summarize the extraction of alkamides as well as their role in inflammatory diseases by detailing its mechanisms of action and identifying potential anti-inflammatory targets. Following PRISMA guidelines, we comprehensively summarized the regulatory effect of PIP on inflammation-related diseases involve the nervous system, cardiovascular system, gastrointestinal tract and other areas and explained the pharmacological properties and mechanism. These review consolidate the latest research on alkamides and provide a foundation for the potential development of PIP as a natural anti-inflammatory agent in both the food and pharmaceutical industries.

Keywords Pepper · Anti-inflammatory · Bioenhancer · Anti-inflammatory · Health benefits

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Introduction

Inflammation is an innate immune response that protects the body from pathogen infections and cellular stress (Kanneganti 2020). Inflammasomes are large cytoplasmic protein complexes present in various immune cells (Christgen and Kanneganti 2020). Upon detecting pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) (Gong et al. 2020), these complexes self-assemble and oligomerize, releasing pro-inflammatory factors and triggering immune responses as a protective mechanism (Zhou et al. 2016). Although inflammation is generally a beneficial process that promotes the body's recovery, the prolonged activation of immune responses in certain chronic inflammatory conditions can lead to diseases such as neurodegenerative disorders, cardiovascular diseases, diabetes, arthritis, and even cancer (Wang et al. 2015). Current treatments for these chronic diseases often cause adverse effects, including nausea, cramps, loss of appetite, and bradycardia, as well as drug resistance due to long-term use (Oronsky et al. 2018). Therefore, it is crucial to identify safe and effective natural anti-inflammatory drugs. Numerous natural products, such as curcumin (CUR) (Razavi et al. 2021), resveratrol (Lançon et al. 2016), and quercetin (Hou et al. 2019), are not only highly safe with minimal side effects but also exhibit anti-inflammatory properties by inhibiting the expression of inflammatory factors or reducing oxidative stress induced by inflammation.

Pepper (*Piper nigrum*) is widely produced and traded globally, serving as a key natural seasoning in the catering industry for enhancing flavor and preserving food, and it also finds applications in medicine, cosmetics, and insecticides (Mgbeahuruike et al. 2017; Salehi et al. 2019), benefited by the bioactive alkamides. Alkamides, secondary metabolites in plants, possess diverse pharmacological activities (Debnath et al. 2018), and many natural alkamides have been developed into marketed drugs (Pan et al. 2013).

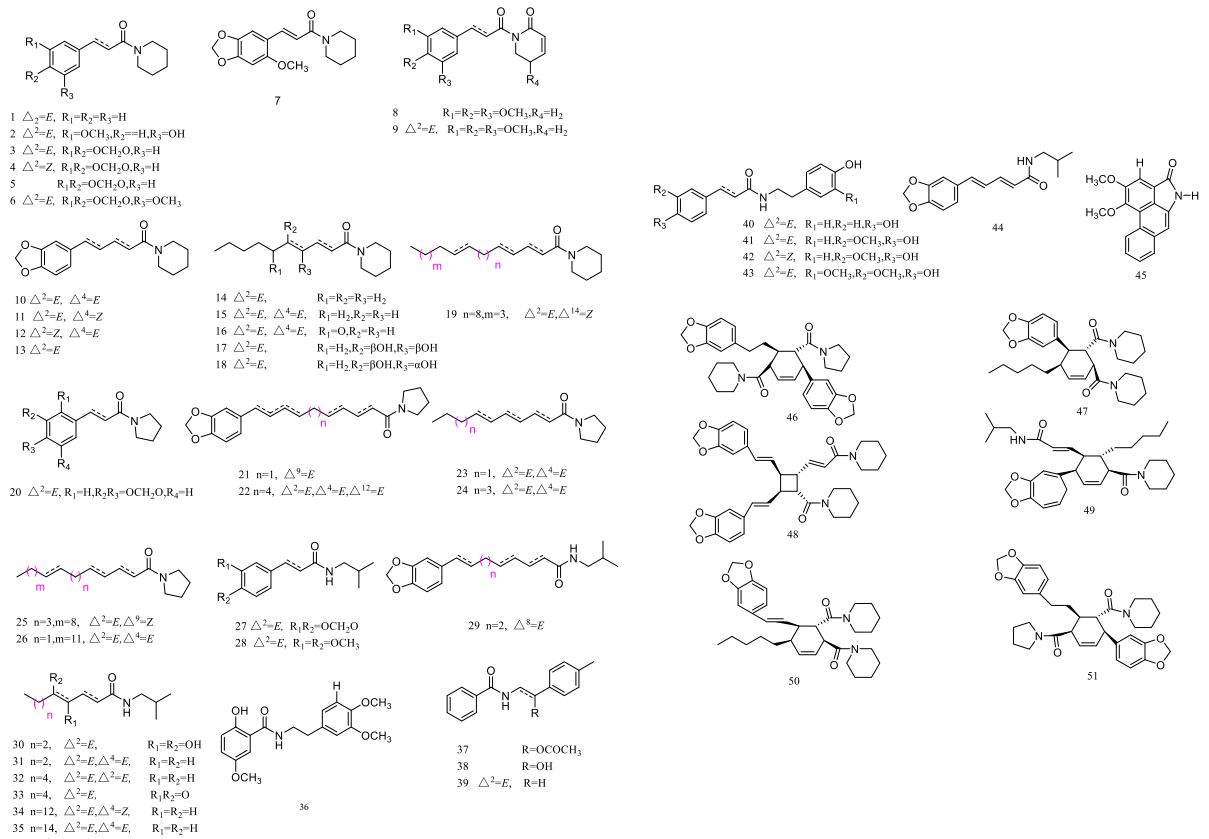

Fig. 1 The chemical structures of the main alkamides from *P. nigrum* L

Table 1 The main alkaloid compounds in *Piper nigrum* L

Number	Compound	Source	References
1	1-(1-oxo-3-phenyl-2E-propenyl)-Piperidine	*P. nigrum* L	Wei et al. (2004)
2	1-[1-oxo-3(3,4-methylenedioxy-5-methoxyphenyl)-2Z-propenyl]-Piperidine	*P. nigrum* L	Gupta et al. (2010)
3	Antiepilepsirine	*P.nigrum* L	Wei et al. (2004)
4	1-[1-oxo-3(3,4-methylenedioxyphenyl)-2Z-propenyl]-Piperidine	*P. nigrum* L	Wei et al. (2004)
5	1-[1-oxo-3(3,4-methylendioxyphenyl)-propan]-Piperidine	*P. nigrum* L	Wei et al. (2004)
6	1-[1-oxo-3(3,4-methylenedioxy-5-methoxyphenyl)-2Z-propenyl]-Piperidine	*P. nigrum* L	Wei et al. (2004)
7	1-[1-oxo-3(3,4-methylenedioxy-6-methoxyphenyl)-2E-propenyl]-Piperidine	*P. nigrum* L	Gupta et al. (1978)
8	1-[3-(3,4,5-trimethoxyphenyl)propanoyl]-5,6-dihydropyridin-2(1H)-one	*P. nigrum* L	Facundo et al. (2005)
9	Piplartine	*P. nigrum* L	Facundo et al. (2005)
10	Piperine	*P. nigrum* L	Wei et al. (2004)
11	Isochavicine	*P. nigrum* L	Wei et al. (2004)
12	Isopiperine	*P. nigrum* L	Wei et al. (2004)
13	Piperanine	*P. nigrum* L	Wei et al. (2004)
14	1-(1-oxo-2E-decaenyl)-Piperidine	*P. nigrum* L	Wei et al. (2004)
15	Neopellitorine B	*P. nigrum* L	Wei et al. (2004)
16	1-(1,6-dioxo-2E,4E-decadienyl)-Piperidine	*P. nigrum* L	Wei et al. (2004)
17	(±)-threo-1-(1-oxo-4,5-dihydroxy-2E-decaenyl)-Piperidine	*P. nigrum* L	Wei et al. (2004)
18	(±)-erythro-1-(1-oxo-4,5-dihydroxy-2E-decaenyl)-Piperidine	*P. nigrum* L	Wei et al. (2004)
19	1-(1-oxo-3-phenyl-2E-propenyl)-Pyrrolidine	*P. nigrum* L	Wei et al. (2004)
20	1-[1-oxo-3(3,4-methylenedioxyphenyl)-2E-propenyl]-Pyrrolidine	*P. nigrum* L	Wei et al. (2004)
21	Isopiperoleine B	*P. nigrum* L	Balakrishnan et al. (2023)
22	Brachyamide A	*P. nigrum* L	Koul et al. (1988)
23	Sarmentine, Iyeremide A	*P. nigrum* L	Wei et al. (2004)
24	1-(1-oxo-2E,4E-dodecadienyl)-Pyrrolidine	*P. nigrum* L	Wei et al. (2004)
25	Brachystine	*P. nigrum* L	Ding et al. (2016)
26	Trichonine	*P. nigrum* L	Moriyama et al. (1986)
27	Fagaramide	*P. nigrum* L	Wei et al. (2004)
28	N-isobutyl-3-(3,4-dimethoxyphenyl)-2E-trienamide	*P. nigrum* L	Kim et al. (2013)
29	N-isobutyl-7-(3,4-methylenedioxyphenyl)-2E-heptenamide	*P. nigrum* L	Rho et al. (2007)
30	(±)-threo-N-isobutyl-4,5-dihydroxy-2E-octaenamide	*P. nigrum* L	Wei et al. (2004)
31	N-isobutyl-2E,4E-octadienamide	*P. nigrum* L	Wei et al. (2004)
32	Pellitorin	*P. nigrum* L	Wei et al. (2004)
33	N-isobutyl-4,5-epoxy-2E-deccaenamide	*P. nigrum* L	Wei et al. (2004)
34	Pipericine	*P. nigrum* L	Shityakov et al. (2019)
35	N-isobutyl-2E,4E-eicosadienamide	*P. nigrum* L	Jiang et al. (2009)
36	Aduncamide	*P. nigrum* L	Chen et al. (2007)
37	Tembamide acetate	*P. nigrum* L	Chen et al. (2017a)
38	Tembamide	*P. nigrum* L	Da Silva et al. (2018)
39	Alatamide	*P. nigrum* L	Da Silva et al. (2018)
40	N-p-coumaroyltyramine	*P. nigrum* L	Chen et al. (2017a)
41	N-trans-feruloyltyramine	*P. nigrum* L	Masi et al. (2021)
42	N-cis-feruloyltyramine	*P. nigrum* L	Kanada et al. (2012)
43	N-(4-hydroxy-3-methoxyphenethyl)-3-(4-hydroxy-3-methoxyphenyl)-2E-propenamide	*P. nigrum* L	Kanada et al. (2012)

Table 1 continued

Number	Compound	Source	References
44	Piperlongumamide C	*P. nigrum* L	Yu et al. (2022)
45	Cepharanone B	*P. nigrum* L	Tran et al. (2023)
46	Nigramide G	*P. nigrum* L	Ikhlas et al. (2023)
47	Nigramide J	*P. nigrum* L	Ikhlas et al. (2023)
48	Dipipermide D	*P. nigrum* L	Ikhlas et al. (2023)
49	Pipernigramide C	*P. nigrum* L	Xu et al. (2023)
50	Pipernigramide D	*P. nigrum* L	Xu et al. (2023)
51	Pipernigramide H	*P. nigrum* L	Xu et al. (2023)

Nascimento et al. (2012) reported on 277 alkamides from *Piper* species and their associated biological activities. The study illustrated the structures of the major alkamides in *P. nigrum* (Fig. 1, Table 1). The differences in these alkamides structures are mainly due to hydrogenation of fatty side chains, modification of MDP rings, substitution of pyrrolidine with alkamides, and differences in configuration (Azam et al. 2022). Among them, pyridine substituted alkylamide compounds have outstanding anti-inflammatory effects (Cai and Wang 2024), and the structure–activity relationship (SAR) analysis of nicotinamide isolated from plant sources is mainly related to irritability, pain relief, and local anesthesia (Lu et al. 2024). Among these pyridine-substituted alkylamides, the most representative compound is piperine (PIP), an alkamide primarily extracted from *P. nigrum*, with its stereoisomeric structure corresponding to the molecular formula $C_{17}H_{19}NO_3$ (Jeon et al. 2019; Liu et al. 2023; Zhang et al. 2024). PIP is commonly used in traditional medicine to prevent infections, improve appetite, and mitigate seizures and depression (Takooree et al. 2019). As research on PIP advances, modern medicine has identified its multiple pharmacological effects, including reducing cardiovascular disease, improving gastrointestinal health, and providing neuroprotection, which are largely attributed to its anti-inflammatory and antioxidant properties (Haq et al. 2021; Tiwari et al. 2020).

In recent years, the reviews on PIP focused more on separation and purification, with less discussion on biological activity, and detailed summarize the pharmacological effects of PIP on cardiovascular system (CVS) (Wang et al. 2021). In addition, Azam et al. (2022) focused more on the pharmacological effects of PIP in the central nervous system, especially in neurodegenerative diseases (Ren and Zuo 2019). However, these reviewers did not establish a comprehensive network linking PIP's role in anti-inflammatory-related diseases and their molecular targets. Given the substantial evidence supporting the regulatory effects of PIP on inflammation, we have summarized current data to identify new therapeutic applications, particularly for inflammatory diseases where existing treatments are either inadequate or associated with significant side effects. Furthermore, our review of PIP may guide the development of novel functional foods or formulations, improving its bioavailability and efficacy as a natural anti-inflammatory agent. The relevant anti-inflammatory activities primarily involve the nervous system, CVS, gastrointestinal tract (GIT), and others, as detailed in Table 2.

Pharmacological applications of anti-inflammatory activity of PIP

Anti-inflammatory effects of PIP on nervous system

Protection against neurodegeneration

Neurodegenerative diseases, such as Parkinson's disease (PD) and Alzheimer's disease (AD), are primarily driven by neuroinflammation. Currently, over 6 million people are affected by PD, with incidence rates steadily rising (Erkkinen et al. 2018) PD patients exhibit symptoms such as tremors, stiffness, cognitive decline, depression, and sleep disturbances (Tolosa

Table 2 Molecular mechanisms of anti-inflammatory effects of PIP

Anti-inflammatory activities		Models	Effects	Mechanisms	References
Nervous system	Neurodegenerative diseases	BV2 cell	IL-1β↓, TNF- α↓, IL-6 and PGE2↓	Regulating Nrf2/OH-1 signaling	Chen et al. (2017b)
	Neurodegenerative diseases	Rat model induced by D-Gal	IL-1β↓, TNF- α and Tau↓	Regulating PKC and PI3K/AKT pathways	Wang et al. (2020a)
	PD	Rat model induced by 6-OHDA	Caspase-3↓, caspase-9 and Bax/Bcl-2↓ ADP-ribose↑	Antioxidant, anti-apoptotic and anti-inflammatory m	Shrivastava et al. (2013)
	PD	Rat model induced by 6-OHDA	GSH↑, inflammatory cytokines↓, catecholamines↑, prevents the GABAergic neuronal destruction	Antioxidant, anti-inflammatory and preventing neurotransmitter alteration	Singh and Kumar (2018)
	PD	Rat model induced by MPTP	ROS↑, HO-1 and NQO1↑	Regulating Keap1-Nrf2-ARE signaling	Wang et al. (2020b)
	PD	Rat model induced by SNCA	SNCA↓, olfactory and motor impairments↓	Promoting the fusion of autophagosome and lysosome membranes through P2RX4 activation	Li et al. (2022a)
	PD	Rat model induced by 6-OHDA	α-Synuclein↓, dopaminergic neurons↓, LC3II/LC3I ↑	Regulating PI3K/AKT/mTOR pathways	Yu et al. (2024)
	AD	Rat model induced by administration of artificial cerebrospinal fluid	Memory impairment↑, neurodegeneration in hippocampus↑	Reducing lipid peroxidation and acetylcholinesterase activity	Chonpathompikunlert et al. (2010)
	AD	Rat model induced by STZ	Neurotransmission↓, neuroinflammation↓	Improving oxidative-nitrosative stress	Wang et al. (2019)
	AD	Rat model induced by Aβ1–42	IL-1β↓, TNF- α↓, Bax/Bcl-2↓, memory impairment↑	Regulating Nrf2/TXNIP/NLPR3 pathways and Keap1-Nrf2 pathways	Yang et al. (2021)
	Seizure	Rat model induced by KA	Seizures↓, hippocampal neuron damage↓	Regulating NGF/TrkA/Akt/GSK3β signaling	Hsieh et al. (2022)
	Epilepsy	Rat and zebrafish model induced by pentylenetetrazol	Seizures↓,	/	Ren et al. (2019)
	Neuroprotective Effect	Rat model induced by AKBA	Proinflammatory factor↓, behavioral disorders↓	Regulating Nrf2, NF-κB signaling	Kundu and Singh (2023)
	Neuroprotective Effect	HEK293 cells	Exploring potential targets	Regulating TRPV1 ion channel	Dong et al. (2019)
	SCI	Rat model induced by clamping the spinal cord with a vascular clip	Proinflammatory factor↓, oxidative stress↓	Inhibiting inflammation and activating reactive oxygen species (ROS)-mediated autophagy	Zhang et al. (2023)
	Neuroprotective Effect	Rat model induced by LPS	IL-1β↓, TNF- α↓, neurobehavioral deficits↓	Inhibiting oxidative nitrosative stress and neuroinflammation	Jangra et al. (2016)
	Antidepressant	Rat model in CUMS	Behavioral changes↑	increasing 5-HT and BDNF	Mao et al. (2014)
	Antidepressant	PC12 cell	Glutathione levels↓,SOD↓,BDNF↑	Improving oxidative stress	Mao et al. (2012)
	Antidepressant	Rat model in CMS	Corticosterone levels and behavioral movements↑	upregulating BDNF mRNA levels	Li et al. (2007)
	MS	Rat model induced by lysolecithin	iNOS↓.TNF-α↓, IL-1β↓, Foxp3↑, BDNF↑ and MBP↑, spatial memory↑	Regulating Nrf2, NF-κB signaling	Roshanbakhsh et al. (2020)
	EAE	Rat model in EAE	Demyelination, pro-inflammatory cytokines and caspase-3 ↓, IL-10↑, BDNF↑	Regulating Nrf2/HO-1 signaling	Nasrnezhad et al. (2021)
	Sciatica	Rat model in non-compressive lumbar disc herniation	p65 expression↓, pro-inflammatory factors↓, IL-10 and TGF-β1↑	Targeting P65	Yu et al. (2021)
	Convulsions	Rat model induced by pilocarpine	TNF-α↓, latency to the 1st convulsion↓, GABA, glycine and taurine↑	Regulating amino acids and on the GABAergic system	da Cruz et al. (2013)

Table 2 continued

Anti-inflammatory activities		Models	Effects	Mechanisms	References
	Convulsions	Rat model induced by pentylenetetrazol, strychnine, picroside, and BAYK-8644	Tonic clonic convulsions↓, tonic clonic seizures↓,	Inhibiting sodium ion channels	Mishra et al. (2015)
	Convulsions	Rat model used the two-microelectrode-voltage-clamp technique and fast perfusion	Seizure↓, body temperature↓	Binding site involving only a and b subunits of GABA	Khom et al. (2013)
CVS	Vasculopathy	Rat model induced by STZ	HbA1c↓, serum AGEs↓, TC↓, LDL-C↓, GSH↑, SOD↑	Regulating TXNIP-NLRP3 signaling	Amin et al. (2023)
	Vasculopathy	Rat model	Cardiovascular contraction↓	Regulating calcium ion channel blockade	Taqvi et al. (2008)
	Hypertension	Rat model induced by L-NAME	Blood pressure↓, iNOS↓, aortic cross-sectional area↓, media thickness and elastin↓	Blocking voltage-dependent calcium channels	Hlavačková et al. (2011)
	Hypertension	Rat model induced by L-NAME	NO↓, vasodilation	Inhibiting NO release	Booranasubkajorn et al. (2017)
	Cardiac hypertrophy	Rat model in chronic pressure overload	Pressure overload and isoproterenol↓	Regulating PPAR-γ, AKT/GSK3β pathway	Ma et al. (2017)
	Hyperlipidemia	Rat model in HFD	Metabolic indicators, antioxidant enzymes, and carbohydrate metabolic enzymes↑	Interacting with proteins such as IR, IRS-1, Akt, GLUT4, AS160, and β-arrestin,	Prasad et al. (2023)
	cardiotoxicity	Rat model induced by cyclophosphamide	TC and TG↓, ASTALT and ALP↓ SOD↑	Antioxidant activity and nitric oxide release-enhancing property	Chakraborty et al. (2017)
GIT	Gastric mucosal injury	Rat model induced by ethanol	Keap1, JNK, ERK and p38↓, SOD and GSH-Px↑	Regulating Nrf2/HO-1 and MAPK signaling	Duan et al. (2022b)
	Colitis	Rat model induced by TNBS	Pro-apoptotic protein↑, TJ proteins↑, colon damage and abnormalities↑	Regulating NF-κB pathway	Guo et al. (2020)
	Colitis	SW480 and HT-29 colon cancer cell lines	CXCL8↓, JNK and P38↓	Regulating MAPK signaling pathway	Hou et al. (2015)
Autoimmune disorders	RA	Rat model induced by pristane	COX-2↓, TNF-α↓, IL-1β↓, IL-6↓, CCL5 and CXCL10↓	Regulating NF-κB pathway	Baito et al. (2023)
	GA	Rat model induced by NETosis	Leukocyte extravasation↓, lipid peroxidation↓, and C-reactive protein↓, IL-1β↓, NLRP3↓	Regulating NF-κB, MAPK pathway	Jati et al. (2022)
	LN	HK-2 cells/Rat model induced by phytane	IL-1β↓, pyroptosis↓	Regulating AMPK pathway	Peng et al. (2018)
	SLE	Rat model induced by phytane	IFN-α↓, TNF-α and IL-6↓, lipogranulomas↓	Reducing oxidative stress	Pannu and Bhatnagar, (2020)
	Thymic injury	Primary murine thymocytes	ROS↑, GSH↑, caspase-3↑	Binding affinity to immune cell receptors CD4 and CD8	Kumar et al. (2015)
Endocrine system	Insulin resistance	Rat model in HFD	Weight ↓, plasma insulin and glucose concentration↓	Regulating AMPK and PI3K-Akt signaling	Wang et al. (2022b)
	Insulin resistance	RAW 264.7 cells/Rat model induced by MSG	Gal-3↓, IL-1β↓, CD11c↓	Inhibiting RAW 264.7 cells toward the M1 phenotype	Liu et al. (2020)
	Insulin resistance	pancreatic β-cell	Gal-3↓, IL-1β↓, CD11c↓, Pdx1↓, ALDH1A3↓	Regulating mTOR/S6/4E-BP1 signaling	Yuan et al. (2021)
	Insulin resistance	pancreatic β-cell/Rat model in HFD	MDA↓, cytochrome C↑	Regulating PI3K/AKT signaling	He et al. (2022)
	Metabolic syndrome	Rat model in HFD	IL-1β↓, fat loss	Inhibiting inflammation	Miyazawa et al. (2018)

Table 2 continued

Anti-inflammatory activities		Models	Effects	Mechanisms	References
	DN	Rat model induced by CEP	TXNIP↓, NLRP3↓, NF-κB↓, IL-1βand TNF-α↓, blood glucose↓, urea nitrogen↓, proteinuria↓	Regulating NF-κB pathway	Samra et al. (2016)
	HN	Renal tubular epithelial cells/Rat model induced by adenine and potassium oxonate	mRTEC↓, URAT1/GLUT9↓	Regulating AKT/mTOR pathway	Li et al. (2024)
Skin	Dermatitis	RAW264.7 cells/Rat model induced by IMQ	NO ↓, COX-2↓, IL-1β↓	Regulating NF-κB pathway	Lallo et al. (2023)
	Atopic dermatitis	Rat model induced by TMA	IL-1β↓, TNF- α↓, IL-4↓	Regulating STAT6/GATA3 signaling	Choi et al. (2020)
	Psoriasis	HaCaT cells/Rat model induced by IMQ	β-defensin 2 and CCL20↓	Regulating STAT3 pathway	Lu et al. (2023)
Other	AP	Rat model induced by L-arginine	Endoplasmic reticulum stress↓, ER phagocytosis↓↑	Interacting with FAM134B and CCPG1	Huang et al. (2022)
	CP	Rat model induced by cerulein	Pancreatic fibrosis↓, αSMA↓, TGF-β, chemokines expression↓	Inhibiting pSMAD2/3 activation	Choi et al. (2019)
	ALI	Rat model induced by LPS	TNF-α↓, IL-6 ↓, IL-1β↓, MPO↓	Regulating NF-κB pathway	Lu et al. (2016)
	COPD	Rat model in COPD	IL-1β↓, IL-8↓, MDA↓, MPO↓, MMP-9↓	Repressing infiltration of inflammatory cells and exaggerating oxidative stress	Arora et al. (2022)
	Mastitis	Rat model induced by LPS	TNF-α and IL-1β↓	Regulating PPAR-γ, NF-κB pathway	Yu et al. (2020)

et al. 2022; Vijiaratnam et al. 2021). Studies have demonstrated that PIP showed significant therapeutic potential for PD by modulating neuroinflammatory. 6-Hydroxydopamine (6-OHDA) initiates an oxylysis reaction, which produces ROS and free radicals that directly damage mitochondria, thereby triggering the release of inflammatory factors (Luo et al. 2020; Wang et al. 2022a). In 6-OHDA-induced Parkinson's disease (PD) models, rats treated with 10 mg/kg of PIP displayed normalized movement and behavior and decreased inflammatory markers such as tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) (Shrivastava et al. 2013). In addition, Shrivastava et al. (2013) demonstrated PIP's anti-apoptotic properties in PD by showing that it inhibited neuronal apoptosis through the downregulation of pro-apoptotic proteins bcl2-associated x (Bax) and upregulation of the anti-apoptotic protein Bcl-2.

Furthermore, modification of PIP where a methoxy group was introduced at the 2-position of the phenyl ring improved its efficacy in treating PD. Wang et al. (2020b) evaluated the neuroprotective effects of PIP analogues, administered orally at 100 mg/kg, which significantly reduced 1-Methyl-4-pheny1-1,2,3,6-tetrahydropyridine (MPTP)-induced PD-related behavioral deficits in rat models and rescued dopaminergic neuron cell death. This cytoprotective effect was likely mediated by covalent binding to Cys288 within Keap1, leading to the activation of the Nrf2-ARE signaling pathway and upregulation of phase II antioxidant enzymes, including heme oxygenase-1 (HO-1) and NQO1.

Previous reports indicated that early symptoms of PD include olfactory impairment and slow movement. Li et al. (2022a) confirmed that PIP could alleviate olfactory impairment and improve movement disorders caused by SNCA overexpression in a PD rat model. The mechanism involved PIP activating P2RX4, which enhanced the membrane fusion of autophagosomes and lysosomes, promoting the autophagic degradation of SNCA. Yu et al. (2024) demonstrated that PIP significantly improved voluntary motility and gastrointestinal dysfunction, reduced α-Syn aggregation, and alleviated the loss of dopaminergic neurons in a PD rat model. The mechanism involved PIP activating autophagy to degrade α-Syn in the substantia nigra (SN) and colon, protecting neurons by inhibiting the activation of the PI3K/AKT/mTOR signaling pathway.

AD is another major neurodegenerative disorder, primarily characterized by the accumulation of amyloid β, which triggers the spread of tau pathology and leads to dementia symptoms (Scheltens et al. 2021). PIP has been shown to effectively improve memory loss and neurodegeneration in AD by reducing lipid peroxidation, lowering acetylcholinesterase activity, mitigating hippocampal neurodegeneration, and increasing neuronal density (Chonpathompikunlert et al. 2010). Wang et al. (2019) investigated the therapeutic effect of PIP in a streptozotocin (STZ)-induced intracerebroventricular (ICV) sporadic Alzheimer's disease (sAD) mouse model. These findings revealed that PIP inhibited oxidative-nitrosative stress, restored neurotransmission, reduced hippocampal neuroinflammation, and alleviated cognitive deficits. Similarly, Yang et al. (2021) synthesized a novel piperine derivative HJ105, an effective oral small-molecule inhibitor of Keap1. HJ105 demonstrated enhanced therapeutic effects in sAD by reducing apoptosis, oxidative stress, and neuroinflammation through the inhibition of Keap1-Nrf2 complex formation. PIP consists of a methylenedioxyphenyl ring, an aliphatic chain and a piperidine ring (Afreen et al. 2021). This unique molecular architecture enables its interaction MAOs, which exist as two functionally distinct isoforms. MAO-B inhibition has shown particular efficacy in neurodegenerative disorders, such as AD and PD. In contrast, MAO-A is beneficial for treating depression and anxiety. Mu et al. (2012) found that the SAR of PIP derivatives, formed by replacing the pyridine ring, resulted in a non-selective inhibitory effect on both MAO-A and MAO-B. Substituting pyridine with small-molecule amines enhanced selectivity for MAO-B but has minimal impact on MAO-A. The pyridine moiety played a crucial role in PIP-mediated neuropharmacology; however, catalytic hydrogenation or carbonyl removal weakened its inhibitory activity against MAO. Furthermore, substituting the MDP ring with phenolic hydroxylation increased selectivity for MAO-A while reducing its effect on MAO-B (Azam et al. 2022).

In addition, PIP significantly suppressed the production of inflammatory factors and PGE_2 in Lipopolysaccharide (LPS)-induced BV2 cells, inhibited nuclear factor kappa-B (NF-κB) activation, and promoted HO-1 expression through the Nrf2 signaling pathway (Chen et al. 2017b). Similarly, dementia in AD has garnered considerable attention, primarily due to neuritis and aging (Luca et al. 2015). Wang's study demonstrated that continuous administration of PIP for four weeks improved memory and cognitive impairment induced by D-galactose (D-Gal). The findings revealed that PIP reduced neuroinflammation, prevented hippocampal tau protein hyperphosphorylation, decreased oxidative stress levels, and enhanced cholinergic function by regulating glycogen synthase kinase-3β (GSK-3β) through the protein kinase C (PKC) and PI3K/Akt pathways in the hippocampus (Wang et al. 2020a) (Fig. 2).

Protection against chronic inflammatory nervous system

Multiple sclerosis (MS) is a chronic central nervous system disorder characterized by hippocampal demyelination, inflammation, and memory deficits (Lassmann et al. 2012; Gilgun-Sherki et al. 2004). PIP has been shown to inhibit mRNA expression of inducible nitric oxide synthase (iNOS), TNF-α, IL-1β, and NF-κB, while reducing glial activation and upregulating the expression of Nrf2, HO-1, and BDNF, thereby promoting memory improvement and myelin repair (Roshanbakhsh et al. 2020). Nasrnezhad et al. (2021) confirmed the anti-inflammatory and antioxidant properties of PIP in MS. In the EAE model, a widely accepted MS model, PIP demonstrated neuroprotective and anti-apoptotic effects by lowering pro-inflammatory cytokines, oxidative stress, and caspase-3 levels, while increasing IL-10, Nrf2, HO-1, and brain-derived neurotrophic factor (BDNF) expression (Nasrnezhad et al. 2021). In sciatica, primarily caused by lumbar disc herniation and nerve compression, PIP provided a safer alternative to traditional analgesics by inhibiting p65 expression, reducing pro-inflammatory factors, increasing IL-10 and transforming growth factor-β1 (TGF-β1), and promoting nerve fiber repair, thus offering both analgesic and therapeutic benefits (Yu et al. 2021) (Fig. 2).

Neuroprotective effect

PIP has demonstrated neuroprotective effects in various models of neuronal damage. In a kainic acid-induced rat model of epilepsy, Hsieh et al. (2022) reported that PIP (10 or 50 mg/kg) mitigated seizures and hippocampal neuron damage by downregulating

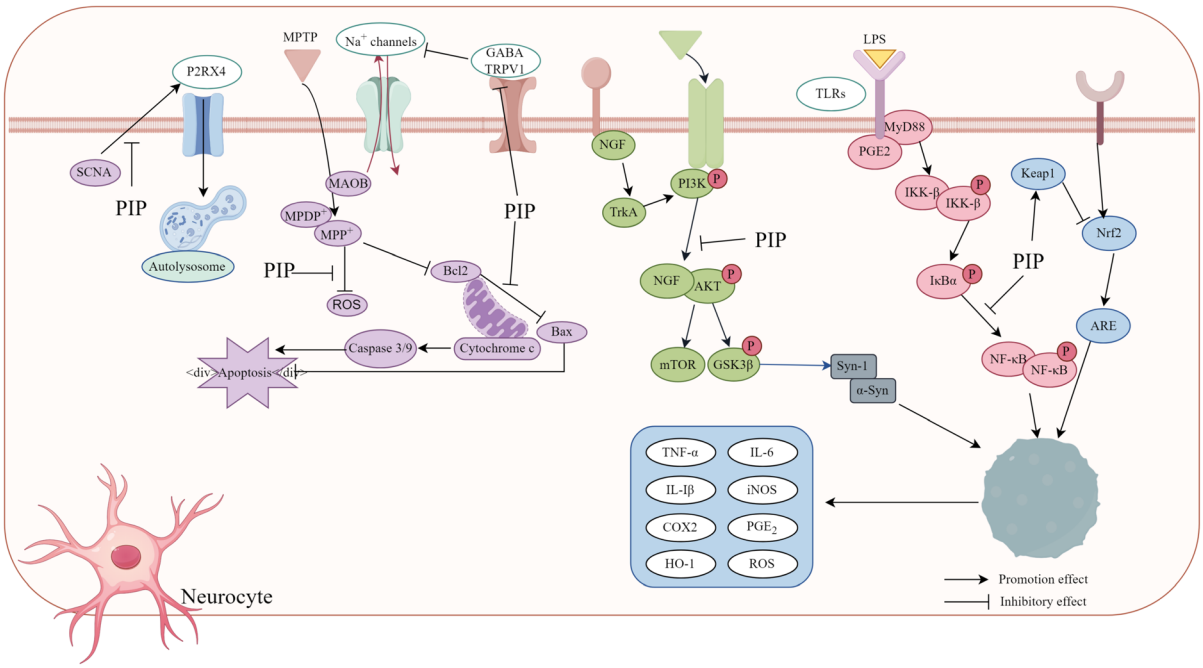

Fig. 2 Molecular pathways involved in the anti-inflammatory effects of PIP on nervous system. All figures in the article were created using Chemdraw and Figdraw 2.0

pro nerve growth factor (NGF) and matrix metalloproteinase-9 while upregulating matrix metalloproteinase-7, NGF, and TrkA. Kundu and Singh (2023) further further explored PIP's neuroprotective potential in combination with 3-acetyl-11-keto-β-boswellic acid (AKBA), demonstrating that the combination exerted anti-inflammatory effects by modulating Nrf2 and NF-κB expression and reducing oxidative stress to prevent neuronal injury. Importantly, previous studies have confirmed that the capsaicin receptor transient receptor potential vanilloid 1 (TRPV1), a non-selective cation channel in the peripheral nervous system, mediated PIP's neuroprotective effects (Lu et al. 2022). Dong et al. (2019) found that PIP interacted with multiple amino acids within the TRPV1 binding pocket, with a mutation at T671 on the pore-forming S6 fragment significantly reducing its pharmacological action. Additionally, PIP promoted functional recovery following spinal cord injury (SCI) by alleviating oxidative stress and pyroptosis through the inhibition of inflammation and activation of ROS-mediated autophagy (Zhang et al. 2023).

Depression is associated with hormonal imbalances and hippocampal neurodegeneration, resulting in self-harm or suicidal ideation due to low mood and cognitive deficits. Traditional antidepressants are slow-acting, have prolonged efficacy, and exhibit drug resistance, with limited effects in over 30% of patients (Peng et al. 2020). In clinical practice, Majeed et al. (2024) found that daily use of PIP (500 mg) for 30–90 days in patients with mild to moderate depression and anxiety can increase serum serotonin levels demonstrated that daily administration of PIP at 500 mg dosage for 30–90 days significantly increased serum serotonin concentrations in patients diagnosed with mild to moderate depressive and anxiety disorders. Moreover, Mao et al. (2014) found that PIP treatment in chronic unpredictable mild stress (CUMS) animal models increased serotonin (5-HT) levels in the hippocampus and frontal cortex, elevated BDNF, and alleviated behavioral changes. Additionally, Mao et al. (2012) demonstrated that PIP mitigated corticosterone-induced neurotoxicity in PC12 cells, even at a low concentration of 1 μM, enhancing BDNF gene expression and significantly reducing oxidative stress by increasing total glutathione and superoxide dismutase (SOD) activity. Furthermore, PIP treatment improved depression-like symptoms in

chronic mild stress (CMS) models, such as elevated corticosterone levels and behavioral deficits (Li et al. 2007). Simultaneously, previous studies have shown that PIP increased the proliferation of hippocampal progenitor cells in depressed mice, potentially exerting antidepressant effects by upregulating BDNF mRNA levels in hippocampal neurons (Fig. 2).

Anticonvulsant effect

The anticonvulsant effects of PIP were likely mediated through a combination of mechanisms, including the modulation of neurotransmitter systems, reduction of inflammation and oxidative stress, and regulation of ion channel activity (Quijia and Chorilli 2020). PIP's anticonvulsant properties stem resulted from its anti-inflammatory and antioxidant effects, which significantly reduced brain nitrite and TNF-α levels while increasing γ-aminobutyric acid (GABA), glycine, and taurine in the striatum, thereby alleviating convulsions (Da Cruz et al. 2013). In addition, Khom et al. (2013) studied PIP's activation of TRPV1, revealing that the regulation of GABA-induced chloride current (IGABA) by PIP did not require the presence of the γ2S subunit, indicating that the binding site involved only the α and β subunits. Concurrently, PIP improved the efficacy of GABAA receptor regulation and inhibited TRPV1 activation to avoid proconvulsant phenomena. SAR analysis of piperine analogues revealed that shortening the fatty chain significantly reduced their modulation of GABAA receptor activity, whereas replacing the aromatic ring with thiophene markedly enhanced IGABA (Li et al. 2022b). Mishra et al. (2015) focused more on PIP's regulation of ion channels, showing that PIP reduced the mortality rate in the MES-induced epilepsy model and decreased the incidence of tonic–clonic seizures induced by pentylenetetrazol, strychnine, picroside, and BAYK-8644. In particular, whole-cell patch clamp analysis demonstrated that the anticonvulsant effect of PIP was dependent on the inhibition of sodium ion channels. Ren et al. (2019) prepared PIP nanoparticles using nanoprecipitation, which enhanced PIP's bioavailability by 16-fold after 10 h of oral administration, resulting in improved control of epilepsy. In summary, PIP could serve as a valuable adjunctive therapy in the management of seizure disorders (Fig. 2).

Anti-inflammatory effects of PIP on CVS

Vasculoprotective effect

Diabetes increased the production of advanced glycation end products (AGEs) in blood and tissues, which triggered thioredoxin-interacting protein (TXNIP), elevating ROS and NF-κB levels (Rhee and Kim 2018). This process promoted the production of inflammatory factors and activation of the nod-like receptor protein 3 (NLRP3) inflammasome, leading to a chronic inflammatory response. Amin et al. (2023) demonstrated that PIP treatment in diabetic rats significantly reduced blood glucose levels, HbA1c, AGEs, total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), while enhancing antioxidant levels such as glutathione (GSH) and SOD, and eNOS expression. PIP also downregulated NF-κB, NLRP3, IL-1β, caspase-3, and TNF-α, improving vasculopathy by targeting the TXNIP-NLRP3 signaling pathway, reducing endothelial damage, and enhancing aortic relaxation (Amin et al. 2023). Taqvi et al. (2008) found that PIP's cardiovascular benefits may be mediated by calcium channel blockade (CCB). In a rat model of hypertension induced by NG-nitro-L-arginine methyl ester hydrochloride (L-NAME), PIP alleviated symptoms such as high blood pressure, reduced iNOS levels, aortic cross-sectional area, media thickness, and elastin degradation (Hlavačková et al. 2011). Booranasubkajorn et al. (2017) further studied the vascular protective effects of herbal formula (Sahatsatara) with main active component, PIP, on hypertension, finding that at its maximum plasma concentration (T_{max}) of 3.9 h, PIP repaired NO damage and promoted vasodilation in the thoracic aorta (Fig. 3).

Anti-cardiac fibrotic effect

Long-term high blood pressure induces the overexpression of TGF-β, leading to cardiomyocyte hypertrophy and the activation of cardiac fibroblasts, which secrete hypertrophic and fibrogenic factors. AMPKα/TGF-β/ Smads/MAPK play crucial roles in myocardial fibrosis (Tian et al. 2021; Dobaczewski et al. 2011; Zhang et al. 2008). Smads influence MAPK and NF-κB pathways, and they regulate inflammation and fibrosis either positively or negatively (Lan 2011). Previous findings have demonstrated that PIP has

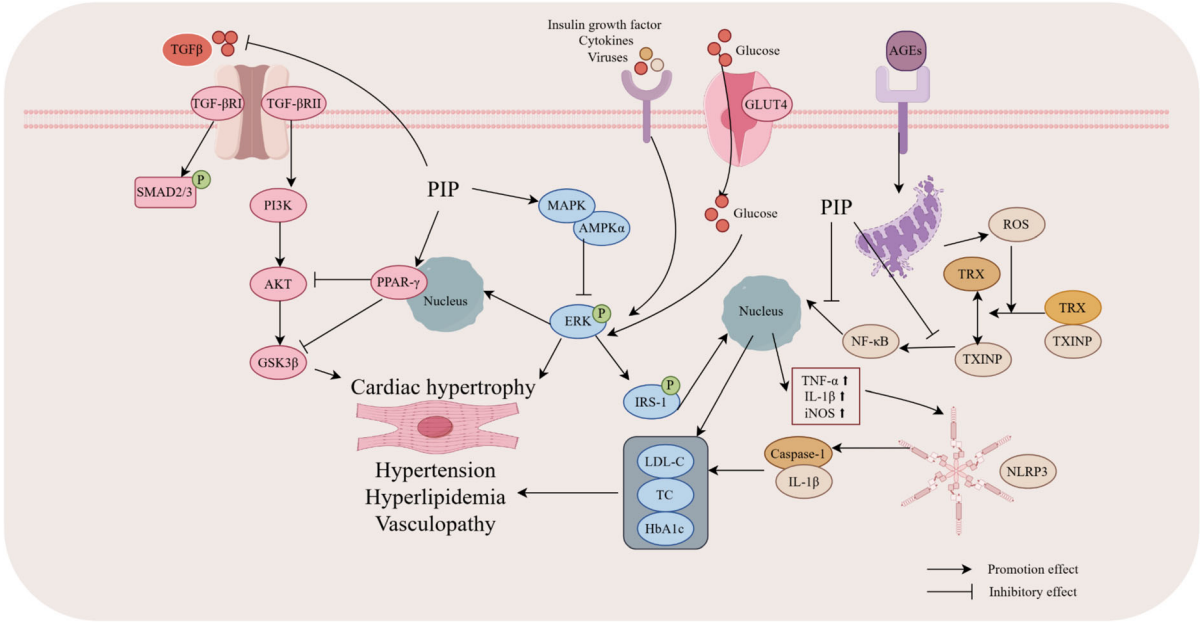

Fig. 3 Molecular pathways involved in anti-inflammatory effects of PIP on CVS

potential in preventing cardiac hypertrophy by activating AMPKα and reducing the phosphorylation of ERK to alleviate inflammation (Kim et al. 2011; Hwang et al. 2011). PIP inhibited cardiac hypertrophy induced by pressure overload or isoproterenol in mice by inhibiting TGF-β, activating PPAR-γ, and blocking the Akt/GSK3β pathway, thereby reducing myocardial fibrosis (Ma et al. 2017) (Fig. 3).

Antihypertensive effect

Prasad et al. (2023) found that PIP exerted an antilipidemic effect in a high-fat diet (HFD) rat model through insulin signaling pathway. This regulation helped alleviate diabetes and reduced the impact of adipose tissue on blood lipids. Molecular docking studies suggested that the mechanism of action of PIP may involve the modulation of glucose metabolism through interactions with proteins such as IR, IRS-1, Akt, GLUT4, AS160, and β-arrestin. These interactions lead to significant anti-lipidemic and antioxidant effects, reducing the expression of diabetes-induced inflammatory factors and mitigating diabetes-related complications (Fig. 3).

Anti-inflammatory effects of PIP on GIT

Chronic alcohol abuse can lead to severe gastric mucosal damage, resulting in gastric ulcers (Yu et al. 2018). Common treatments, such as rabeprazole, omeprazole, and lansoprazole, are associated with significant side effects (Da Luz et al. 2021). In a rat model, PIP demonstrated protective effects against ethanol-induced gastric mucosal injury by upregulating Nrf2 and HO-1 expression and modulating the Nrf2/HO-1 and MAPK signaling pathways, offering a safer alternative for gastrointestinal protection (Duan et al. 2022b). Similarly, PIP has shown promise in mitigating colitis, a chronic inflammatory condition, in rat models. In a trinitrobenzene sulfonic acid (TNBS)-induced colitis model, PIP significantly reduced colon damage, oxidative-nitrosative stress, and pro-inflammatory markers. It also downregulated pro-apoptotic proteins, such as caspase-1, while enhancing the expression of tight junction (TJ) proteins, including claudin-1, occludin, and zonula occludens-1, through regulation of the B-cell inhibitor-α and NF-κB signaling pathways (Guo et al. 2020). Moreover, Hou et al. (2015) reported that in colon cancer cell lines SW480 and HT-29 stimulated with

LPS, PIP reduced inflammatory responses by downregulating the MAPK signaling pathway and inhibiting CXCL8 expression. These findings suggest that PIP holds potential as a natural therapeutic agent for treating gastrointestinal disorders, including gastric ulcers and colitis (Fig. 4).

Anti-inflammatory effects of PIP on autoimmune disorders

Rheumatoid arthritis (RA) is chronic inflammatory diseases with distinct pathophysiologies but shared underlying inflammatory mechanisms (Huang and Zhang 2024). RA is characterized by excessive proliferation of fibroblast-like synoviocytes (FLS), leading to cartilage destruction and inflammation, primarily via the activation of the NF-κB signaling pathway (Bartok and Firestein 2010). PIP has demonstrated anti-inflammatory effects in RA by downregulating phosphorylation of NF-κB and reducing the expression of COX-2, TNF-α, IL-1β, IL-6, and chemokines such as CCL5 and CXCL10 (Baito et al. 2023). Lupus nephritis (LN), a complication of systemic lupus erythematosus (SLE), resulted from immune system misrecognition, leading to the production of autoantibodies, immune complex deposition, and inflammation, particularly affecting proximal renal tubular epithelial cells via overexpression of priming stage of NLRP3 (Li et al. 2018; Lu et al. 2017). Current immunosuppressants often face challenges related to drug resistance and adverse reactions (Kalloo et al. 2013). Peng et al. (2018) found that PIP significantly suppressed NLRP3 inflammasome activation and reduced IL-1β by decreasing AMPK activation in a rat model injected with pristane, as well as in LPS and nigericin-stimulated HK-2 cells. This inhibition of pyroptosis in renal tubular epithelial cells improved the progression of LN. Additionally, Kumar et al. (2015) found that PIP significantly reduced caspase-3 activation in a deltamethrin (DLM)-induced mouse primary thymocyte apoptosis model, prevented GSH depletion, increased ROS levels, and restored cell viability. Notably, PIP has a high binding affinity for immune cell receptors CD4 and CD8, providing both biological and chemical protection to the immune system (Fig. 4).

Anti-inflammatory effects of PIP on endocrine system

HFD-induce obesity is often accompanied by insulin resistance which along with oxidative stress and inflammation, a major metabolic complication (Panahi

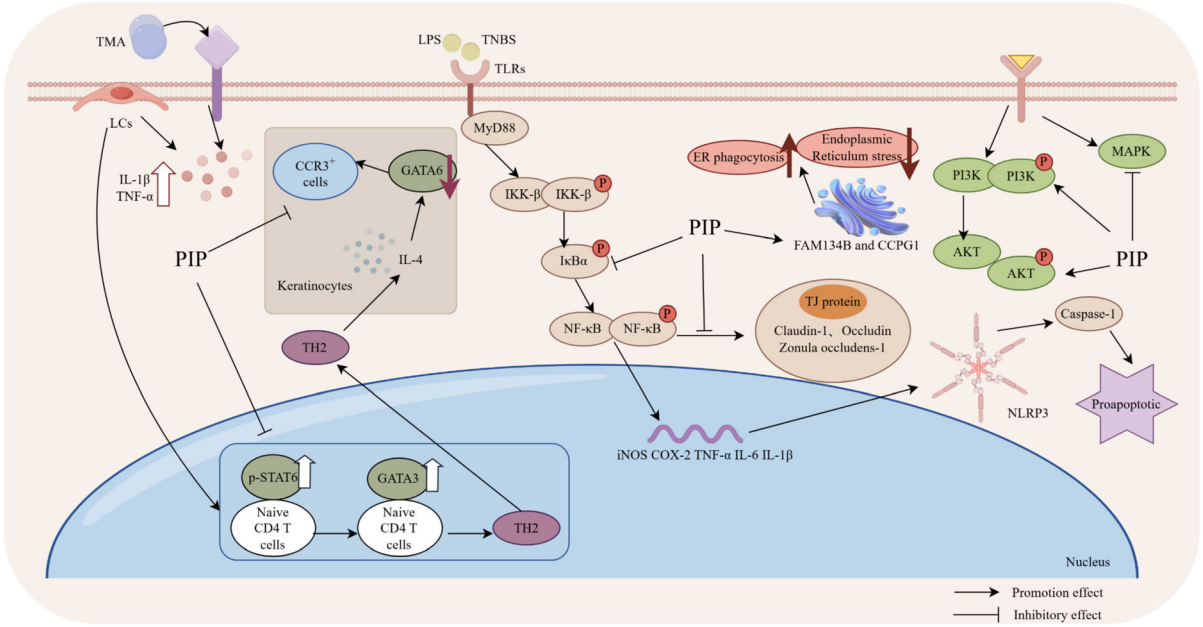

Fig. 4 Molecular pathways involved in the anti-inflammatory effects of PIP on related mechanisms

et al. 2015). PIP has been shown to improve obesity, reduce insulin resistance, and regulate plasma insulin and glucose levels by inhibiting AMPK activation and enhancing phosphorylation of PI3K-Akt, suggesting its potential as a natural weight loss agent (Wang et al. 2022b). A double-blind experiment by Panahi et al. (2015) also confirmed these results. Liu et al. (2020) recognized the therapeutic effects of PIP on insulin resistance and obesity, noting that PIP significantly reduced serum levels of LPS and pro-inflammatory cytokines, such as galectin-3 (Gal-3) and IL-1β, while downregulating mRNA levels of pro-inflammatory cytokines in adipose tissue and M1-like macrophage markers. These findings highlighted PIP's potential as an immunomodulator for obesity and diabetes-related diseases through its anti-inflammatory effects.

Yuan et al. (2021) similarly found that PIP upregulated pancreatic and duodenal homeobox 1 (Pdx1) and aldehyde dehydrogenase 1 family, member A3 (ALDH1A3) via the mTOR/S6/4E-BP1 signaling pathway. Additionally, PIP reduced pancreatic β-cell apoptosis in diabetic mice by downregulating the expression of PI3K and AKT, increasing SOD levels, reducing multiple desiccation analyses (MDA) levels, and lowering the Bax/Bcl-2 ratio (He et al. 2022). Hyperglycemia worsens the immune response by increasing the release of pro-inflammatory factors, contributing to the development of diabetic nephropathy (DN), which begins with hypertension and proteinuria and can progress to renal dysfunction and end-stage renal failure (Umanath and Lewis 2018). Current therapeutic strategies for DN focus on controlling blood glucose and blood pressure, but many patients still experience terminal renal impairment, underscoring the need for novel treatments to halt disease progression (Opazo-Ríos et al. 2020). Samra et al. (2016) found that PIP prevented DN by reducing TXNIP, NLRP3, NF-κB, IL-1β and TNF-α expression levels, while also lowering MDA, blood glucose, urea nitrogen, proteinuria, and the kidney weight-to-body weight ratio in diabetic rats. These findings suggest that further research into PIP for clinical trials aimed at treating diabetes and restoring pancreatic β-cell function is of significant value. Hyperuricemic nephropathy (HN), a complication of hyperuricemia and diabetes, is characterized by kidney damage from elevated uric acid levels (Li et al. 2021). Treatment aims to reduce inflammation and oxidative stress to protect renal function and prevent kidney failure (Yang et al. 2022). Li et al. (2024) demonstrated that PIP's anti-inflammatory properties inhibited the AKT/mTOR pathway, alleviated uric acid-induced renal tubular epithelial cell (mRTEC) damage, and reduced the risk of renal injury by inhibiting URAT1/GLUT9 transporters in a dose-dependent manner. This resulted in lowered serum uric acid levels and improved renal health in HN mice. In gouty arthritis (GA), acute inflammation is triggered by the deposition of monosodium urate crystals, primarily mediated by the NLRP3 inflammasome and overexpression of IL-1β (Lin et al. 2020). PIP alleviated inflammatory symptoms by inhibiting NLRP3 activation, reducing NETosis-induced tophi formation, and decreasing leukocyte extravasation, lipid peroxidation, and C-reactive protein levels. Molecular docking studies suggested that PIP competitively inhibited JNK-1 and the NF-κB kinase β subunit to regulate the NF-κB pathway (Jati et al. 2022) (Fig. 4).

Anti-inflammatory effects of PIP on skin

Piper retrofractum extract, with PIP as its primary active component, has shown potential in alleviating dermatitis and psoriasis through its anti-inflammatory properties. According to Lallo et al. (2023), PIP inhibited the NF-κB pathway and significantly reduced the expression of inflammatory factors, including iNOS, COX-2, and IL-6, thus protecting mice from imiquimod (IMQ)-induced dermatitis. In the context of atopic dermatitis, a condition linked to autoimmune dysfunction and characterized by a type 2 helper T-cell (Th2) inflammatory response (Czarnowicki et al. 2015), PIP has been shown to alleviate symptoms in atopic dermatitis-like mice induced by trimellitic anhydride (TMA). PIP downregulated pro-inflammatory cytokines, inhibited IL-4 secretion, and reduced GATA3 mRNA levels, thereby preventing Th2-mediated immune responses by inhibiting the STAT6/GATA3 signaling pathway (Choi et al. 2020).

Similarly, psoriasis, a chronic inflammatory skin condition driven by genetic and environmental factors (Ghoreschi et al. 2021), has also been a focus of PIP research due to the high costs associated with first-line biologic therapies (Armstrong and Read 2020). Lu et al. (2023) investigated PIP's therapeutic effects on psoriasis-like dermatitis induced by M5 and imiquimod (IMQ), demonstrating that PIP reduces the

severity of psoriasis lesions and the expression of key cytokines such as β-defensin 2 and CCL20 by inhibiting STAT3 phosphorylation. Overall, PIP showed promise as a candidate for the treatment of both dermatitis and psoriasis, offering a potential alternative to current therapies (Fig. 4).

Anti-inflammatory effect of PIP on other inflammations

Acute pancreatitis (AP) is characterized by acute abdominal pain, pancreatic acinar cell death, and a local and systemic inflammatory response, potentially leading to pancreatic injury (Ren et al. 2021). PIP has been found to act on endoplasmic reticulum (ER)-phagocytosis receptors, FAM134B and CCPG1, enhancing ER-phagocytosis to alleviate ER stress and, thereby, reducing pancreatic injury (Huang et al. 2022). The SAR analysis indicated that PIP's cyclohexylamino analogs also alleviated ER stress by reducing the expression of GRP78 and CHOP in renal cells (Hammad et al. 2017). Chronic pancreatitis (CP), an irreversible inflammatory disease, caused glandular necrosis and fibrosis, impairing both the exocrine and endocrine functions of the pancreas, and may progress to pancreatic cancer (Apte et al. 2011). Choi et al. (2019) demonstrated that PIP treatment significantly inhibited pancreatic fibrosis, decreased the expression of α-SMA, TGF-β, and pro-inflammatory cytokines and chemokines, while also inhibiting pSMAD2/3 activation and increasing pancreatic acinar cell proliferation.

Acute lung injury (ALI) is associated with the overproduction of inflammatory cytokines (Goodman et al. 2003), which plays a crucial role in disease progression. Lu et al. (2016) found that PIP attenuated the production of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β was well as decreased myeloperoxidase (MPO) activity and pulmonary edema by inhibiting LPS-induced NF-κB activation. Arora et al. (2022) further explored the therapeutic effect of PIP on chronic obstructive pulmonary disease (COPD), a condition exacerbated by long-term smoking and cigarette smoke (CS), which induced oxidative stress and inflammatory responses. Their findings revealed that PIP reduced oxidative stress by down-regulating CS-induced proinflammatory factors. Molecular docking revealed potential targets such as human neutrophil elastase, MMP-9, MPO, and related receptors, indicating PIP's protective effects on lung function.

LPS can induce breast inflammation, or mastitis by stimulating the release of inflammatory mediators through the toll-like receptors4 (TLR4) signaling pathway (Fu et al. 2014; Gonen et al. 2007). Yu et al. (2020) demonstrated that PIP attenuated LPS-induced inflammatory cytokines, including TNF-α and IL-1β, by activating PPAR-γ and inhibiting NF-κB activation. The findings indicated that PIP alleviated the pathological changes of breast tissue and reduced MPO activity, demonstrating a therapeutic effect on mastitis. Duan et al. (2022a) and Ying et al. (2013) further investigated the molecular mechanism of PIP in LPS-induced inflammatory response in RAW264.7 cells. The results showed that PIP reduced the production of NO and ROS and downregulated the expression of pro-inflammatory factors. PIP also inhibited the phosphorylation of ERK, JNK, p38, and p65 proteins. Furthermore, PIP inhibited the production of PGE_2, iNOS and COX-2, exerting its anti-inflammatory effects by preventing the degradation of IκB and inhibiting the translocation of NF-κB into the nucleus (Fig. 4).

Combination therapy using PIP in anti-inflammatory effects

PIP can be used as a bioenhancer in combination therapies with natural compounds, such as CUR (Patel et al. 2020), resveratrol (Johnson et al. 2011), and quercetin (Sharma et al. 2020), significantly enhancing the anti-inflammatory effects of individual treatments (Haq et al. 2021). Pannu and Bhatnagar (2020) demonstrated that in a pristane-induced SLE mouse model, administering only 1/10 of the standard dose of resveratrol combined with PIP (25 mg/kg) produced the same absence of fat granulomas as the high-dose resveratrol group (50 mg/kg). Furthermore, this combination reduced the release of IFN-α, IL-6, and TNF-α, alleviating symptoms such as proteinuria and elevated creatinine levels. The combination of PIP with CUR has been more extensively researched (Heidari et al. 2023), demonstrating that PIP enhances CUR's neuroprotective effects by inhibiting oxidative and nitrosative stress as well as neuroinflammation (Jangra et al. 2016). Co-treatment with CUR and PIP promotes fat loss and suppresses high-fat diet (HFD)-

induced inflammation (Miyazawa et al. 2018). The combination therapy of PIP and CUR has been promoted in clinical practice. Hosseini et al (2024) explored the therapeutic effect of 500 mg CUR and 5 mg PIP as supplements on patients with type 2 diabetes. The results of a double-blind experiment showed that PIP and CUR improved triglyceride and glucose levels in patients. Sharifi et al. (2023b) also investigated the therapeutic effect of PIP and CUR in patients with moderate to high hepatic steatosis. Double-blind randomized trials demonstrated that 500 mg CUR and 5 mg PIP improved blood pressure, blood glucose, cholesterol, and liver function. Moreover, the co-administration of PIP (20 mg/kg) and CUR (50 mg/kg) effectively mitigates cyclophosphamide-induced cardiotoxicity, with effects significantly greater than those of CUR or PIP alone (Chakraborty et al. 2017). Singh and Kumar (2018) observed that using PIP as a bioenhancer with quercetin significantly enhanced its antioxidant and anti-inflammatory effects, thereby restoring neurotransmitter function and promoting neuroprotection. Moreover, PIP has been shown to significantly enhance the bioavailability of clinical drugs such as carbamazepine, metronidazole, oxytetracycline, ibuprofen, and omeprazole (Azam et al. 2022; Haq et al. 2021).

Conclusion and prospect

PIP, an alkamide derived from *P. nigrum*, has shown significant potential as an anti-inflammatory agent. This review highlighted the preventive and therapeutic effects of PIP via various systems, including the nervous system, cardiovascular system, gastrointestinal tract, and other inflammatory conditions. In autoimmune diseases such as RA and SLE, chronic inflammation can lead to tissue damage. Similarly, in neurodegenerative diseases like AD and PD, sustained inflammation resulted in neuroinflammation and neuronal damage. In cardiovascular diseases, inflammation contributed to the progression of conditions such as atherosclerosis and cardiac hypertrophy. Moreover, chronic inflammation can lead to metabolic disorders, including insulin resistance and dysregulated metabolic processes in syndromes such as obesity and type 2 diabetes. PIP exerted its anti-inflammatory effects by inhibiting key signaling pathways and cascade reactions, including PI3K/Akt/mTOR, NF-κB, Keap1/Nrf2 and MAPKs. This inhibition alleviated inflammation or activated the expression of related target genes, such as SOD HO-1 and NQO1 (Wang et al. 2020b). The feedback regulation of IL-1β released after the activation of NLRP3 further activated NF-κB, which led to the expansion of the degree and time of inflammatory reaction and caused many diseases as mentioned like RA, SLE and IBD. However, PIP could influence downstream signaling pathways by targeting multiple molecules, such as TRPV1 or Keap1, inhibiting the release of inflammatory factors and improving oxidative stress levels to maintain mitochondrial homeostasis. Furthermore, PIP regulated caspase family proteins and prevents cell apoptosis (Yadav et al. 2023). In addition, PIP enhanced the bioavailability and therapeutic efficacy of drugs when combined with other anti-inflammatory agents, such as CUR, quercetin, resveratrol.

Although PIP has shown significant anti-inflammatory effects in various diseases, its clinical efficacy remains uncertain. The hydrophobicity of PIP led to poor absorption and bioavailability, becoming a major obstacle in the process from research to clinical application (Smilkov et al. 2019). To address this, Ren et al (2019) prepared PIP nanoparticles to improve dissolution rate and oral bioavailability and has better epilepsy control effect than oral PIP administration. Elnaggar et al. (2015a) designed PIP-loaded chitosan nanoparticles (CS-NPs) to address dissolution challenges through nasal delivery. Etman et al. (2018) employed Tween 80 as a surfactant to emulsify PIP nanoparticles to minimize potential toxicity. Elnaggar et al. (2015b) also utilized Tween-modified PIP-loaded monoolein cubes (T-cubs), which demonstrated enhanced therapeutic effects on cognitive recovery in AD. Similarly, in order to improve the solubility of PIP and its targeted delivery to the brain in AD, Ahmad and Hafeez (2023) developed and optimized CUR-PIP solid self-emulsifying drug delivery system. Ezawa et al. (2016) combined the hydrophilic excipient cyclodextrin with PIP for supramolecular formulation to improve solubility. In addition, several PIP analogues have been synthesized to enhance efficacy and provide new insights into whether PIP's bioavailability can be increased through chemical modifications. Generally, as a natural product, PIP did not produce negative effects on the human body when administered orally or

intravenously at a dose of 100 mg/kg or with an intake of 5 mg/kg/day and is considered highly safe (Azam et al. 2022). However, PIP contains an MDP ring, which is also present in the chemical structures of many carcinogens. Chonpathompikunlert et al. (2010) suggested that PIP may have reproductive toxicity. In their study, male albino rats given 10 mg/kg of PIP orally exhibited increased serum gonadotropin levels and decreased testosterone. Despite this, piperine is generally used as a supplement in clinical practice, and no safety issues have been reported. Shityakov et al. (2019) proposed a novel approach to analyze the absorption, distribution, and metabolism of PIP using the QSAR paradigm to further study the safe dosage of PIP. Therefore, confirming the optimal dosage of PIP within its safe usage range for specific disease conditions requires further research and verification.

Currently, there are few studies on the targets of PIP, which limits our understanding of the pharmacological mechanisms by which PIP exerts its anti-inflammatory effects. Related target research focuses on PIP's role in activating TRPV1 receptors and GABA receptors. Subsequent studies have also employed molecular docking methods to identify targets, utilizing AutoDock and Molegro software to explore potential targets of PIP (Jati et al. 2022; Sharifi et al. 2023a). Shaheer et al. (2024) used Schrodinger software to perform pharmacophore analysis and protein–ligand interaction profiler (PLIP) on PIP and discovered that PIP regulated estrogen receptor β. Nayana et al. (2024) predicted that AKT1 was a potential target of PIP through molecular docking. Their further analysis found that there was a stable hydrogen bond between Lys268 and Ser205 amino acid residues by PLIP and molecular dynamics. In subsequent research, emerging technologies such as spatial single-cell mass spectrometry (Wienke et al. 2024), artificial intelligence (Drake et al. 2022), and target identification in pharmacological studies of natural products will provide valuable insights for identifying molecular targets of PIP (Noor et al. 2023).

In summary, to effectively accelerate the anti-inflammatory effects of PIP in clinical practice, it is essential to enhance its solubility or develop derivatives based on pharmacophores. Further elucidation of the pharmacological mechanisms is necessary, along with the identification of its targets, optimal dosage, and treatment duration. Therefore, additional experimental studies should be conducted at effective doses to evaluate the clinical safety of PIP.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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