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Pomolic acid: A short review on its chemistry, plant sources, pharmacological properties, and patents

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ABSTRACT

In this article, the chemistry, plant sources, pharmacological properties, and patents of pomolic acid (PA) are reviewed for the first time. Also known as benthamic acid, PA is a pentacyclic triterpenoid of the ursane type. Its chemical structure has a 30-carbon skeleton comprising five six-membered rings A–E with seven methyl groups and two hydroxyl groups. PA was first isolated from the peels of apples. The compound is commonly reported in species of the families Rosaceae and Lamiaceae. Anti-cancer activities represent the major pharmacological properties of PA with breast cancer and leukemia cells being most susceptible. A wide array of other pharmacological properties of PA have been reported. PA has two patents filed by the same group of scientists from the Federal University of Rio de Janeiro in Brazil. Some areas for further research on PA are suggested. Sources of information were from Google Scholar, PubMed, PubMed Central, Science Direct, J-Stage, and PubChem.

INTRODUCTION

Triterpenoids are oxygen derivatives of triterpenes, often having pentacyclic or tetracyclic structures. Characterized by their five isoprene units, pentacyclic triterpenoids are of the friedelane, lupane, oleanane, and ursane types (Furtado *et al*., 2017; Garg *et al*., 2020; Ghante and Jamkhande, 2019; Woźniak *et al*., 2015). These compounds possess a broad spectrum of pharmacological properties including anti-cancer, antioxidant, antimicrobial, anti-viral, antidiabetic, anti-inflammatory, anti-ulcerogenic, anti-obesity, anti-aging, analgesic, immunomodulatory, anti-hyperglycemia, anti-hypertensive, hypolipidemic, neuroprotective, hepatoprotective, and cardioprotective activities. The molecular mechanisms underlying the anti-cancer activities of triterpenoids range between cytotoxicity, inhibition of tumor cell proliferation, induction of apoptosis, change in signal transduction, and suppression of angiogenesis and metastasis (Ghante and Jamkhande, 2019; Shanmugam *et al*., 2012). These activities are well-documented through *in vitro* and *in vivo* models and chemically induced tumor xenograft models, and they include both naturally occurring triterpenoids and their synthetic derivatives (Patlolla and Rao, 2012). Of the different types of triterpenoids, the ursane-type pentacyclic triterpenoids are a useful source of anti-cancer drugs (Salvador *et al*., 2012). They include asiatic acid, boswellic acid, corosolic acid, pomolic acid (PA), and ursolic acid.

PA was chosen as the compound for review in this short article as there is none in the literature. Only some reviews on pentacyclic triterpenoids such as Salvador *et al*. (2012), Ghante and Jamkhande (2019), and Mioc *et al*. (2022) have included PA. Topics covered in this short review included chemistry, plant sources, synthesis, pharmacological properties, and patents. PA is reported in many plant species and is rich in bioactivities.

CHEMISTRY

PA or 3-β,19α-dihydroxy-urs-12-en-28-oic acid is a pentacyclic triterpenoid of the ursane type. PA is also known as benthamic acid (BA). It has a molecular formula of $C_{30}H_{48}O_4$,

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and molecular weight of 473 g/mol. Its chemical structure has a 30-carbon skeleton comprising five six-membered rings A–E (Fig. 1).

PA has a carboxyl (–COOH) group at C17, and methyl ($–CH_3$) groups are attached to C4, C8, C10, C14, C19, and C20. C4 has two $–CH_3$ groups. There are four oxygen atoms, one at C3, two at C17, and one at C19. At C3, C17, and C19 are the hydroxyl (–OH) groups. Other triterpenoids of the ursane type include ursolic acid, asiatic acid, corosolic acid, and β-boswellic acid. Unlike PA which has –H at C2 and –OH group at C19, ursolic acid has –H at C2 and –H at C19 (Chan *et al*., 2019), and corosolic acid has –OH group at C2 and –H at C19 (Chan *et al*., 2022). The existence of –OH and –COOH groups in the PA molecule enables its intermolecular hydrogen bonding (Hou *et al*., 2022). The ability of PA to self-assemble *via* non-covalent interactions has been attributed to the presence of seven $–CH_3$ groups.

PLANT SOURCES

PA was first isolated by Brieskorn and Wunderer (1967) from the peels of apples. Subsequently, it has been reported in 39 plant species from 19 families (Table 1). Families with more than one species are Rosaceae (10), Lamiaceae (7), Chrysobalanaceae (4), Aquifoliaceae (3), and Styracaceae (2). Species reported more than once are *Diospyros kaki* (Ebenaceae), *Ocimum gratissimum* (Lamiaceae), *Osmanthus fragrans* (Oleaceae), *Weigela subsessilis* (Caprifoliaceae), and *Ziziphus jujuba* (Rhamnaceae).

Although PA has been reported in many plant species, its content is very low. The content of PA in the roots and rhizomes of *Potentilla* species from Poland ranged from 0.09 mg/g in *Potentilla reptans* to 1.63 mg/g in *Potentilla neumanniana* (Jóźwiak *et al*., 2014). In China, the contents of PA in the fruits of different *Chaenomeles* species have been reported to range from 0.10% (*Chaenomeles lagenaria*) to 0.24% (*Chaenomeles sinensis*), 0.17% to 0.36% in *C. sinensis* from different prefectures, and 0.04% in the roots to 0.16% in the fruits of *C. sinensis* (Yang *et al*., 2009).

A practical approach to enhance the availability of PA is to synthesize PA from structurally similar compounds such as tormentic acid and euscaphic acid *via* regioselective acylation followed by Saito photochemical reduction (Kraft *et al*., 2019; Wiemann *et al*., 2016).

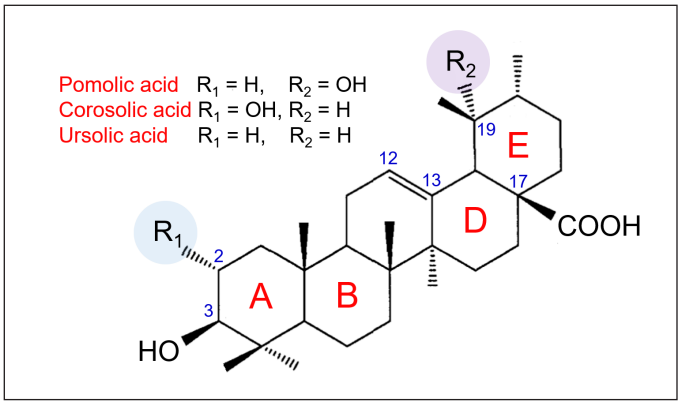

Figure 1. Chemical structure of PA.

PHARMACOLOGICAL PROPERTIES

Anti-cancer properties

Against tumor cells, PA inhibited SK-MEL-28 melanoma, A549 lung, and U-373 MG glioblastoma cancer cells *via* the suppression of NF-κB and HIF-1α pathways (Apaza *et al*., 2021). PA inhibited HIF-1α in the SK-MEL-28 (IC_{50} = 3.0 µM), A549 (IC_{50} = 10 µM), and U-373MG (IC_{50} = 6.3 µM) cancer cells. In addition, PA inhibited NF-κB in SK-MEL-28 (IC_{50} = 1.0 µM), A549 (IC_{50} = 3.6 µM), and U-373 MG (IC_{50} = 2.5 µM) cancer cells.

PA was identified as a potent inhibitor of SUMO-specific protease 1 (SENP1) with an IC_{50} value of 5.1 µM (Wei *et al*., 2022). SENP1 is a member of the SENP family of proteins that can be used to detect bladder, colon, or prostate cancer in a biological sample (Uzoigwe *et al*., 2012). When combined with cisplatin, PA (IC_{50} = 3.7 µM) exhibited potent inhibitory activity compared to cisplatin alone (IC_{50} = 28 µM) against SK-OV-3 ovarian cancer cells.

Against MK-1 squamous, HeLa cervical, and B16F10 melanoma cancer cells, cytotoxicity of PA based on GI_{50} was 55, 59, and 29 µM (Yoshida *et al*., 2005). Against other cancer cells, PA exerted cytotoxic effects on A549 lung cancer cells with IC_{50} values of 5.6 µM (Lei *et al*., 2014) and 10 µM (Yang *et al*., 2022), and on leukemia cells (THP-1) with IC_{50} value of 3.2 µM (Nganteng *et al*., 2022).

The anti-cancer effects and molecular mechanisms of PA are listed in Table 2. They involved breast, lung, ovarian, and prostate cancer cells, including leukemia and glioma. Most susceptible are breast cancer and leukemia cells.

Against breast cancer cells, anti-cancer effects include induction of apoptosis and inhibition of cell proliferation, metastasis, angiogenesis, and invasion. Molecular mechanisms against breast cancer cells involve activation of AMP-activated protein kinase (AMPK), poly (ADP-ribose) polymerase (PARP), and caspases-3 and -9; suppression of CXC chemokine receptor type-4 (CXCR4), matrix metalloproteinase-9 (MMP-9), focal adhesion kinase (FAK), and extracellular signal-regulated kinase (ERK); blocking nuclear factor-κB (NF-κB)/ERK/ mammalian target of rapamycin (mTOR) signaling pathways; targeting p38-mitogen-activated protein kinase (MAPK) and mTOR signaling.

Against leukemia cells, anti-cancer effects include inhibition of cell growth, promotion of cell death, and induction of apoptosis. Molecular mechanisms against leukemia cells involve activation of the caspase pathway (caspases-3 and -9) and checking multidrug resistance (MDR) by over-expression of anti-apoptotic Bcl-2 proteins.

Other bioactivities

The other bioactivities of PA are anti-human immunodeficiency virus (HIV), anti-diabetic, anti-fibrosis, anti-human platelet aggregation (HPA), hypotensive, new multi-target cardiovascular agent (MCA), anti-osteoclastogenesis (OCG), anti-aging, anti-inflammatory, new natural product gel (NPG), apoptosis, anti-obesity, and anti-rheumatoid arthritis (RA) properties (Table 3).

Table 1. Plant sources of PA or BA.

No.	Species	Family	Plant part	Reference
1	*Agrimonia pilosa*	Rosaceae	Aerial part	(An *et al*., 2005)
2	*Cecropia pachystachya*	Urticaceae	Leaf	(Schinella *et al*., 2008)
3	*Centella asiatica*	Umbelliferae	Aerial part	(Yoshida *et al*., 2005)
4	*Chaenomeles sinensis*	Rosaceae	Fruit	(Yang *et al*., 2009)
5	*Chamaenerion angustifolium*	Onagraceae	Aerial part	(Frolova *et al*., 2014)
6	*Chrysobalanus icaco*	Chrysobalanaceae	Leaf	(Fernandes *et al*., 2003)
7	*Diospyros kaki*	Ebenaceae	Fruit peel	(Izuchi and Katsuki, 2021)
			Fruit and calyx	(Katsumi *et al*., 2021)
8	*Eriobotrya japonica*	Rosaceae	Leaf	(Tan *et al*., 2015, 2017)
9	*Euscaphis japonica*	Staphyleaceae	Aerial part	(Kim *et al*., 2016a)
10	*Hippophae rhamnoides*	Elaeagnaceae	Leaf	(Yang *et al*., 2013)
11	*Hyptis capitata*	Lamiaceae	Aerial part	(Kashiwada *et al*., 1998)
12	*Ilex asprella*	Aquifoliaceae	Root	(Lei *et al*., 2014)
13	*Ilex pubescens*	Aquifoliaceae	Stem	(Lin *et al*., 2011)
14	*Ilex rotunda*	Aquifoliaceae	Fruit	(Apaza *et al*., 2021)
15	*Jatropha macrantha*	Euphorbiaceae	Aerial part	(Siddiqui *et al*., 1995)
16	*Lantana camara*	Verbenaceae	Aerial part	(Papanov *et al*., 1992)
17	*Lavandula spica*	Lamiaceae	Aerial part	(Ramabulana *et al*., 2022)
18	*Leucosidea sericea*	Rosaceae	Aerial part	(Estrada *et al*., 2009, 2011)
19	*Licania pittieri*	Chrysobalanaceae	Aerial part	(Fernandes *et al*., 2003)
20	*Licania tomentosa*	Chrysobalanaceae	Leaf	(Dzoyem *et al*., 2021)
21	*Ocimum gratissimum*	Lamiaceae	Aerial part	(Nganteng *et al*., 2022)
			Leaf	(Yoo *et al*., 2013)
22	*Osmanthus fragrans*	Oleaceae	Flower	(Le *et al*., 2022)
			Leaf	(Banno *et al*., 2004)
23	*Perilla frutescens*	Lamiaceae	Leaf	(Akihisa *et al*., 2006)
			Leaf	(Tedonkeu *et al*., 2021)
24	*Plectranthus glandulosus*	Lamiaceae	Aerial part	(Eltamany *et al*., 2022)
25	*Plicosepalus curviflorus*	Loranthaceae	Aerial part	(Neto *et al*., 2000)
26	*Polylepis racemosa*	Rosaceae	Bark and stem	(Li *et al*., 2020)
27	*Potentilla fragarioides*	Rosaceae	Aerial part	(Wu *et al*., 2022)
28	*Potentilla freyniana*	Rosaceae	Root	(Hou *et al*., 2022)
29	*Rosa cymosa*	Rosaceae	Root	(Kashiwada *et al*., 1998)
30	*Rosa woodsia*	Rosaceae	Leaf	(Borrás-Linares *et al*., 2014)
31	*Rosmarinus officinalis*	Lamiaceae	Leaf	(Kadioglu and Efferth, 2015)
32	*Salvia officinalis*	Lamiaceae	Leaf	(Cheng and Cao, 1992)
33	*Sanguisorba officinalis*	Rosaceae	Root	(Tra *et al*., 2022)
34	*Styrax annamensis*	Styracaceae	Leaf	(Hu *et al*., 2019)
35	*Styrax tonkinensis*	Styracaceae	Leaf	(Mahmoud *et al*., 2022)
36	*Tabebuia aurea*	Bignoniaceae	Leaf	(Kuete *et al*., 2015)
37	*Uapaca togoensis*	Uapaceae	Fruit	(Thuong *et al*., 2006)
38	*Weigela subsessilis*	Caprifoliaceae	Aerial part	(Lee and Thuong, 2010)
			Leaf	(Fujiwara *et al*., 2011)
39	*Ziziphus jujuba*	Rhamnaceae	Fruit and seed	(Bai *et al*., 2016)
			Fruit	

Table 2. Anti-cancer effects and molecular mechanisms of PA.

Cancer type	Cancer cell line	Anti-cancer effect and mechanism	Reference
Breast	MCF-7	PA inhibited proliferation and promoted apoptosis in breast cancer cells through activation of AMPK, caspases, and PARP.	(Lee *et al*., 2011)
	MCF-7	PA inhibited breast cancer cells by delaying cell progression, promoting apoptosis, and activating AMPK.	(Youn *et al*., 2012)
	MCF-7 and MDA-MB-231	PA inhibited invasion of breast cancer cells through the suppression of CXCR-4 expression.	(Kim *et al*., 2016a)
	SKBR3	PA inhibited metastasis of HER2 over-expressing breast cancer cells through inactivation of the ERK pathway.	(Kim *et al*., 2016b)
	MCF-7 and MDA-MB-231	PA suppressed MMP-9 and FAK expression by blocking NF-κB/ERK/mTOR signaling pathways in growth factor-stimulated breast cancer cells.	(Park *et al*., 2016a)
	MCF-7 and MDA-MB-231	PA suppressed HIF1α/VEGF-mediated angiogenesis in breast cancer cells by targeting p38-MAPK and mTOR signaling.	(Park *et al*., 2016b)
Lung	A549	PA inhibited proliferation of lung carcinoma cells *via* induction of apoptosis and suppression of cell migration and invasion.	(Yang *et al*., 2022)
Ovarian	SK-OV-3	PA-induced apoptosis in ovarian cancer cells *via* the mitochondrial-mediated intrinsic and death receptor-induced extrinsic pathways.	(Yoo *et al*., 2013)
Prostate	PC3 and PC3R	PA exhibited anti-cancer potential against docetaxel-resistant prostate cells by down-regulating transporter proteins and by reverting EMT.	(Martins *et al*., 2019)
Leukemia	P-388	Out of 10 triterpenoids from Goreishi, cytotoxicity of PA (ED_{50} = 2.9 µg/ml) was the strongest.	(Numata *et al*., 1989)
	K562	PA inhibited the growth and induced apoptosis of MDR leukemia cells, with 4.3% and 75% DNA fragmentation at 10 µg/ml and 100 µg/ml.	(Fernandes *et al*., 2003)
	HL-60	PA triggered apoptosis of leukemia cells *via* activation of caspases-3 and -9.	(Fernandes *et al*., 2005)
	K562 and Lucena 1	PA inhibited the growth and promoted the death of chronic myeloid leukemia cells from patients with chronic myeloid leukemia.	(Vasconcelos *et al*., 2005, 2007)
	HL-60	PA checked MDR mediated by over-expression of anti-apoptotic Bcl-2 proteins in leukemia cells.	(Fernandes *et al*., 2007)
	HL-60, U937, and Kasumi-1	PA reduced cell viability, induced cell death, and activated caspases pathway in acute myeloid leukemia cells.	(Pereira *et al*., 2018)
Glioma	U-87 G	PA-induced apoptosis as the basic mechanism of cytotoxic action in glioma cells with IC_{50} value of 50 µM.	(Frolova *et al*., 2017)
	A172, U87, and GBM-1	PA-induced apoptosis, inhibited MDR protein MRP1, and migration in glioblastoma cells.	(Guimarães *et al*., 2017)

Abbreviations: AMPK = AMP-activated protein kinase, CXCR4 = CXC chemokine receptor type-4, DNA = deoxyribonucleic acid, ED_{50} = median effective dose, EMT = epithelial mesenchymal transition, ERK = extracellular signal-regulated kinase, FAK = focal adhesion kinase, GBM = glioblastoma, HIF1α = hypoxia-inducible factor-1 alpha, HER2 = human epidermal growth factor receptor type II, MAPK = mitogen-activated protein kinase, MDR = multidrug resistant, MMP = matrix metalloproteinase, MRP1 = multidrug resistance associated protein 1, mTOR = mammalian target of rapamycin, NF-κB = nuclear factor-κB, PARP = poly (ADP-ribose) polymerase, and VEGF = vascular endothelial growth factor.

Table 3. Other bioactivities of PA.

Bioactivity	Description of effect and mechanism involved	Reference
Anti-HIV	PA inhibited HIV-1 replication in acutely infected H9 cells with an EC50 value of 1.4 µg/ml.	(Kashiwada *et al*., 1998)
Anti-diabetic	PA stimulated glucose uptake by 1.6- and 2.8-fold in basal and insulin-stimulated myotubes.	(Lee and Thuong, 2010)
Anti-fibrosis	PA ameliorated fibroblast activation and renal interstitial fibrosis through inhibition of SMAD3-STAT3 signaling pathways.	(Park *et al*., 2018)
Anti-HPA	PA strongly inhibited HPA induced by ADP and epinephrine with IC_{50} values of 60 and 20 nM, respectively.	(Estrada *et al*., 2009)
	PA was a competitive antagonist in the strong inhibition of HPA induced by ADP.	(Alvarado-Castillo *et al*., 2012)
Hypotensive	PA-induced vasorelaxant effect (IC_{50} = 2.5 µM) by direct activation of endothelial purinergic receptors *via* the NO-cGMP signaling pathway.	(Estrada *et al*., 2011)
New MCA	PA displayed hypotensive, vasorelaxant, and platelet inhibitory effects in rats and has potentials to be a new MCA.	(Lopez *et al*., 2019)

Continued

Bioactivity	Description of effect and mechanism involved	Reference
Anti-OCG	PA showed stronger inhibition toward osteoclast differentiation with less cytotoxicity compared with oleic acid used as positive control.	(Tan *et al*., 2015)
Anti-aging	The strong activity of PA by stimulating collagen and HA production was 5.8 times that of the control.	(Tan *et al*., 2017)
Anti-inflammatory	PA suppressed TPA-induced inflammation in mice with ID_{50} of 0.12 mg/ear.	(Banno *et al*., 2004)
	PA inhibited NO production in LPS and IFN-γ stimulated RAW 264.7 cells with IC_{50} value of 15 µM.	(Yang *et al*., 2013)
	PA inhibited IFN-γ cytokine and COX enzyme and induced apoptosis in activated RAW 264.7 cells.	(Dzoyem *et al*., 2021)
New NPG	A novel NPG of TCM was developed from PA for drug delivery.	(Hou *et al*., 2022)
Apoptosis	PA inhibited the viability of PMN cells through apoptosis; apoptotic cells increased by 42% at 100 µM and by 71% at 200 µM.	(Schinella *et al*., 2008)
Anti-obesity	PA suppressed GPDH activity in 3T3-L1 adipocytes.	(Izuchi and Katsuki, 2021)
Anti-RA	PA displayed moderate inhibitory activity in RA-FLS cells with IC_{50} value of 25 µM.	(Wu *et al*., 2022)
Anti-complementary	Out of nine triterpenoids, activity of PA (4 µM) was the strongest.	(Thuong *et al*., 2006)
Anti-OCG	PA inhibited RANKL-induced osteoclast differentiation in RAW 264.7 cells with IC_{50} value of 0.6 µM.	(Tan *et al*., 2015)

Abbreviations: ADP = adenosine diphosphate, COX = cyclooxygenase, GPDH = glycerol-3 phosphate dehydrogenase, HA = hyaluronic acid, HIV = human immunodeficiency virus, HPA = human platelet aggregation, ID_{50} = 50% inhibitory dose, IFN-γ = interferon gamma, LPS = lipopolysaccharide, MCA = multi-target cardiovascular agent, NO = nitric oxide, NPG = natural product gel, OCG = osteoclastogenesis, PMN = polymorphonuclear, PA = pomolic acid, RA = rheumatoid arthritis, RANKL = receptor activator of NF-κB ligand, SMAD3 = mothers against decapentaplegic homolog 3, STAT3 = signal transducer and activator of transcription 3, TCM = traditional Chinese medicine, and TPA = 12-*O*-tetradecanoyl phorbol-13-acetate.

PATENTS

PA has two patents filed by the same group of scientists from the Federal University of Rio de Janeiro in Brazil (Gattass et al., 2004, 2008). The two patents are entitled, 'PA, its isomers, derivatives and their uses, pharmaceutical composition, method to prepare the pharmaceutical composition, and method for treating MDR tumors' and 'PA for treating MDR tumors'. The former (WO 2004/030682 A1) was a World Intellectual Property Organization (WIPO) Patent published in April 2004, while the latter (EP 1 549 330 B1) was a European Patent (EP) published in January 2008. The WIPO invention was specifically related to the identification of PA, its isomers, and derivatives as anti-neoplastic drugs, to be used in the treatment of patients suffering from tumors intrinsically MDR or tumors that acquired this resistance as a result of chemotherapy treatment (Gattass *et al*., 2004). The EP invention was related to the use of PA for the preparation of medicaments for the treatment of cancer with MDR (Gattass *et al*., 2008).

CONCLUSION

PA is an ursane-type pentacyclic triterpenoid. It is commonly reported in species of the families Rosaceae and Lamiaceae. Anti-cancer activities are the major pharmacological properties of PA with breast cancer and leukemia cells being most susceptible. A wide array of other pharmacological properties of PA have been reported. In view of the very low content of PA in plant species, more research on the synthesis of PA from structurally similar compounds is recommended to enhance its availability. The correlation of the bioactivities of PA with its structural properties, i.e., structure-activity relationship studies, is worthy of more in-depth investigation. Analysis of the bioactivities and drug delivery of PA-gel holds great promise especially when its bioactivity is equal to or stronger than that of non-gel PA. Greater effort deserves to be accorded to strengthening the MDR potential of PA.

AUTHORS' CONTRIBUTIONS

All the authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revised it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; agreed to be accountable for all aspects of the work.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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