Tormentic Acid

Subjects: Chemistry, Medicinal
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Tormentic acid, also known as 2α,3β,19α-trihydroxyurs-2-en-28-oic acid (IUPAC Name: (1R,2R,4aS,6aR,6aS,6bR,8aR,10R,11R,12aR,14bS)-1,10,11-trihydroxy-1,2,6a,6b,9,9,12a-heptamethyl-2,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydropicene-4a-carboxylic acid), is a pentacyclic triterpene. Its biological activity e.g. anti-inflammatory, antidiabetic, antihyperlipidemic, hepatoprotective, cardioprotective, neuroprotective, anti-cancer, anti-osteoarthritic, antinociceptive, antioxidative, anti-melanogenic, cytotoxic, antimicrobial, and antiparasitic has been confirmed in in vitro and in vivo studies. This molecule and its derivatives can be found in various plant species and families (e.g. Rosaceae, Lamiaceae, Myrtaceae, Oleaceae, Urticaceae, Boraginaceae), including edibles and herbs.

Keywords: tormentic acid ; triterpenes ; pentacyclic triterpene ; CAS 13850-16-3 ; bioactivity ; plant metabolite ; tormentic acid derivatives

1. Introduction

Given the constantly growing number of diseases and the common phenomenon of drug resistance, scientists are forced to seek for more potent and less toxic treatments. Pentacyclic triterpenes represent a valuable group of compounds among natural metabolites. They are abundant in the plant kingdom and are found in various plant parts, including edibles (olive, strawberries, mango, rose fruits, apples, mulberry, quince), herbs, and herbal products. Therefore, the quantities of these compounds in human diet can be quite significant. The individual average human intake of triterpenes was determined to be approximately 250 mg per day in the Western world, and even 400 mg per day in the Mediterranean countries [1].

Pentacyclic triterpenes have been repeatedly proven to possess a broad spectrum of pharmacological activities. The health-beneficial properties of these compounds have been shown to include anti-inflammatory, anticancer, antidiabetic, cardio- and hepato-protective, antimicrobial, antiviral, antiparasitic, and other activities [2][3][4][5][6]. The affinity and spectrum of biological activity is associated with the diverse triterpene skeleton structure and connected substituents. Even structurally quite similar triterpenes may have different pharmacological potential, polarity, solubility, and bioavailability and can occur in unrelated plant species [1][7][8][9]. One of the pentacyclic triterpenes is 2α,3β,19α-trihydroxyurs-2-en-28-oic acid known as tormentic acid (TA).

2. Structure, Function, and Occurrence of TA

Tormentic acid, also known as 2α,3β,19α-trihydroxyurs-2-en-28-oic acid (IUPAC Name: (1*R*,2*R*,4a*S*,6a*R*,6a*S*,6b*R*,8a*R*,10*R*,11*R*,12a*R*,14b*S*)-1,10,11-trihydroxy-1,2,6a,6b,9,9,12a-heptamethyl-2,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydropicene-4a-carboxylic acid), is a compound classified as a pentacyclic triterpene. Triterpenes are synthesized via the mevalonic acid (MVA) pathway in cytosol by cyclization of the squalene molecule. Their skeleton is composed of six isoprene units (C_5). Owing to the number of cyclic structures making up such compounds, there is a wide variety of triterpenes, including pentacyclic triterpenes. These can be further categorized into the oleanane, ursane, lupine, and hopane groups. Tormentic acid belongs to ursane-type pentacyclic triterpenes [10][11].

Tormentic acid has been found in various species and plant families (**Table 1**). Based on the collected data, it can be assumed that this compound is typical of the Rosaceae family. However, several species from Lamiaceae and Urticaceae were also reported to be sources of this compound. Moreover, TA was also found in nineteen other families including, e.g., Betulaceae, Boraginaceae, Compositae, Caryophyllaceae, Ericaceae, Oleaceae, Polygonaceae, Urticaceae, and Saxifragaceae. The presence of this triterpene was revealed in different aerial and underground plant organs [3][12][13][14][15][16][17][18][19][20][21][22].

Table 1. Confirmed botanical sources of tormentic acid (currently accepted botanical names (where applicable) according to www.theplantlist.org (accessed on 12 April 2021) are given in square brackets) and initial extrahent type used for

elution of TA from plant material.

Plant Family	Species and Organ Investigated	Extraction Solvent	Ref.
Acanthaceae	*Rostellularia procumbens* (L.) Nees [*Justicia procumbens* L.] Whole plant	80% Ethanol	[23]
Aphloiaceae	*Aphloia theiformis* (Vahl) Benn. Leaves	Methanol	[24]
Aphloiaceae	*Aphloia theiformis* (Vahl) Benn. Leaves	70% Ethanol	[25]
Betulaceae	*Betula schmidtii* Regel Twigs	80% Methanol	[12]
Bignoniaceae	*Markhamia obtusifolia* (Baker) Sprague Leaves	Acetone	[26]
Bignoniaceae	*Markhamia platycalyx* (Baker) Sprague [*Markhamia lutea* (Benth.) K.Schum.] Leaves	95% Ethanol	[27]
Bignoniaceae	*Markhamia tomentosa* (Benth) K. Schum ex Engl. Leaves	Ethanol	[16]
Boraginaceae	*Anchusa italica* Retz. [*Anchusa azurea* Mill.] Aerial parts	75% Ethanol	[15]
Boraginaceae	*Arnebia euchroma* (Royle) I.M.Johnst. Roots	Methanol	[28]
Caprifoliaceae	*Cephalaria tuteliana* Kuş & Göktürk Not specified	Methanol	[17]
Caryophyllaceae	*Psammosilene tunicoides* W.C. Wu & C. Y. Wu. Roots	80% Ethanol	[29]
Compositae	*Kleinia pendula* (Forssk.) DC. Fresh aerial parts	Methanol	[3]

Plant Family	Species and Organ Investigated	Extraction Solvent	Ref.
Ericaceae	*Rhododendron websterianum* Rehder & E.H. Wilson Fruits	95% Ethanol	[18]
Lamiaceae	*Hyptis capitata* Jacq. Leaves and stems	Methanol	[30]
Lamiaceae	*Isodon rubescens* (Hemsl.) H.Hara Whole plant	-	[31]
Lamiaceae	*Lavandula luisieri* (Rozeira) Riv.-Mart. [*Lavandula stoechas* subsp. *luisieri* (Rozeira) Rozeira] Flowering plant	Ethanol	[32]
Lamiaceae	*Leptohyptis macrostachys* (L'H'erit.), Harley and J.F.B. Pastore (previously *Hyptis macrostachys* Benth.) Aerial parts	95% Ethanol	[33]
Lamiaceae	*Ocimum gratissimum* L. Aerial parts	Methanol	[34]
Lamiaceae	*Perilla frutescens* L. Britton Cell culture from leaves	Methanol	[35]
Lamiaceae	*Perilla frutescens* (L.) Britton var. acuta Kudo Fresh leaves	Methanol	[36]
Lamiaceae	*Perilla frutescens* (L.) Britton Leaves	Ethanol	[37] [38]
Lamiaceae	*Platostoma rotundifolium* (Briq.) A. J. Paton Aerial parts	Ethyl acetate	[39]
Lamiaceae	*Salvia judaica* Boiss. Aerial parts	Ethanol	[40]
Lamiaceae	*Salvia miltiorrhiza* Bunge Roots and aerial parts	Ethanol	[41]
Leguminosae	*Campylotropis hirtella* (Franch.) Schindl. Roots	-	[42]

Plant Family	Species and Organ Investigated	Extraction Solvent	Ref.
Malvaceae	*Triumfetta cordifolia* A.Rich. Stems	Methylene: methanol (1:1)	[43]
Myrtaceae	*Acca sellowiana* (O.Berg) Burret Callus culture from fruit pulp	Methanol	[44]
Myrtaceae	*Callistemon citrinus* (Curtis) Skeels Leaves	Dichloromethane: Methanol (50:50, v/v) Water: Ethanol (50:50, v/v)	[45]
Oleaceae	*Ligustrum robustum* (Roxb.) Blume Not specified	70% Methanol	[19]
Oleaceae	Olea europaea L. Cell-suspension cultures (callus induced from leaf stalk)	Methanol	[20]
Oleaceae	*Olea europaea* L. (varieties Manzanilo, Picual, Koroneiki, and Coratina) Fruits	Methanol	[46]
Oleaceae	*Osmanthus fragrans* Lour Fruits	Methanol	[7]
Polygonaceae	*Rumex japonicus* Houtt. Stems	80% Ethanol	[21]
Rosaceae	*Agrimonia pilosa* Ledeb. Aerial parts	80% Ethanol	[47]
Rosaceae	*Alchemilla faeroensis* (J. Lange) Buser Aerial parts	Ethanol	[48]
Rosaceae	*Cotoneaster simonsii* hort. ex Baker Aerial parts (leaves and twigs)	Chloroform	[49]
Rosaceae	*Crataegus pinnatifida* Bunge Leaves	80% Ethanol	[50]
Rosaceae	*Cydonia oblonga* Mill. Seeds	Methanol	[51]

Plant Family	Species and Organ Investigated	Extraction Solvent	Ref.
Rosaceae	*Eriobotrya deflexa* f. *buisanesis* [*Eriobotrya deflexa* (Hemsl.) Nakai.] Leaves	Methanol	[52]
Rosaceae	*Eriobotrya fragrans* Champ. ex Benth Leaves	95% Ethanol	[53]
Rosaceae	*Eriobotrya japonica* (Thunb) Lindl. Leaves	80% Methanol	[54]
Rosaceae	*Eriobotrya japonica* (Thunb.) Lindl. Leaves	95% Ethanol	[55] [56]
Rosacae	*Eriobotrya japonica* (Thunb.) Lindl Cell suspension culture (callus induced from leaves)	Ethanol	[57]
Rosaceae	*Eriobotrya japonica* (Thunb.) Lindl. Callus cultures induced from an axenic leaf	Ethanol	[58]
Rosaceae	*Eriobotrya japonica* (Thunb) Lindl. Cell suspension culture (obtained from immature embryos)	95% Ethanol	[59]
Rosaceae	*Eriobotrya japonica* (Thunb.) Lindl. Cell suspension culture (callus induced from leaves)	95% Ethanol	[4]
Rosaceae	*Fragaria* × *ananassa* Duch. var ‘Falandi’ Fresh fruit	95% Ethanol	[60]
Rosaceae	*Fragaria* × *ananassa* Duch. var ‘Hokouwase’ Green unripe fresh fruit	Methanol	[61]
Rosaceae	*Geum japonicum* auct. [*Geum macrophyllum* Willd.] Whole plant	Methanol	[62]
Rosaceae	*Geum rivale* L. Flowering aerial parts	Chloroform: Methanol (9:1)	[63]

Plant Family	Species and Organ Investigated	Extraction Solvent	Ref.
Rosaceae	*Geum urbanum* L. Roots and aerial parts	Methanol	[64]
Rosaceae	*Malus domestica* Borkh varieties “Mela Rosa Marchigiana” and “Golden Delicious” Pulp callus culture	Methanol	[65]
Rosaceae	*Margyricarpus setosus* Ruiz & Pav. [*Margyricarpus pinnatus* (Lam.) Kuntze] Aerial parts	Methanol	[66]
Rosaceae	*Potentilla anserina* L. Roots	-	[67]
Rosaceae	*Potentilla anserina* L. Roots	70% Ethanol	[68]
Rosaceae	*Potentilla chinensis* Ser. Whole plant	95% Ethanol	[69]
Rosaceae	*Potentilla fulgens* [*Potentilla lineata* Trevir.] Roots	Methanol	[70]
Rosaceae	*Poterium ancistroides* Desf. [*Sanguisorba ancistroides* (Desf.) Ces.] Aerial parts	Ethyl acetate	[71]
Rosaceae	*Poterium ancistroides* Desf. [*Sanguisorba ancistroides* (Desf.) Ces.] Herb	Methanol	[72]
Rosaceae	*Rosa nutkana* C.Presl Fruits	Methanol	[73]
Rosaceae	*Rosa roxburghii*	-	[74]
Rosaceae	*Rosa rugosa* Thunb. Roots	Methanol	[75]

Plant Family	Species and Organ Investigated	Extraction Solvent	Ref.
Rosaceae	*Rubus chingii* Hu Roots and rhizomes	Ethanol	[76]
Rosaceae	*Rubus crataegifolius* Bunge Leaves	Methanol	[77]
Rosaceae	*Sanguisorba officinalis* L. Root	Cold water Hot water Methanol	[78]
Rosaceae	*Sarcopoterium spinosum* (L.) Spach. Aerial parts	-	[79]
Rubiaceae	*Knoxia valerianoides* Thorel ex Pit. [*Knoxia roxburghii* subsp. brunonis (Wall. ex G.Don) R.Bhattacharjee & Deb] Roots	Ethanol	[80]
Sapotaceae	*Tridesmostemon omphalocarpoides* Engl. Wood and stem bark	Dichloromethane: Methanol (1:1)	[81]
Saxifragaceae	*Tiarella polyphylla* D. Don Whole plant	Methanol	[14]
Staphyleaceae	*Euscaphis konishii* Hayata [*Euscaphis japonica* (Thunb.) Kanitz] Twigs	95% Ethanol	[82]
Urticaceae	*Cecropialyratiloba* Miq. [*Cecropia pachystachya* Trécul.)] Roots	Methanol	[13]
Urticaceae	*Cecropia pachystachya* Trécul Roots, root bark, stem and stem bark	Ethanol	[22]
Urticaceae	*Debregeasia salicifolia* D. Don. [*Debregeasia saeneb* (Forssk.) Hepper & J.R.I.Wood] Stems	Methanol	[5]

Plant Family	Species and Organ Investigated	Extraction Solvent	Ref.
Urticaceae	*Myrianthus arboreus* P.Beauv Stem bark	Methylated ethyl acetate	[83]
Urticaceae	*Myrianthus arboreus* P.Beauv Root wood	Methylated spirit	[84]
Urticaceae	*Myrianthus arboreus* P.Beauv Stems	Chloroform	[85]
Urticaceae	*Myrianthus serratus* (Trecul) Benth. Trunk wood	Ethyl acetate	[86]
Urticaceae	*Pourouma guianensis* Aubl. Leaves	Methanol	[87]
Urticaceae	*Sarcochlamys pulcherrima* (Roxb.) Gaudich. Aerial parts	Methanol	[88]
Vochysiaceae	*Vochysia divergens* Pohl. Stem bark	Ethanol	[89] [90]

3. Pharmacological Activity of TA

Tormentic acid was found to possess various biological activities, including anti-inflammatory [60], antidiabetic, hypoglycemic [4][71], hepato-, neuro-, cardio-protective [15][69][91], anticancer, cytotoxic, antiproliferative [30][79][92], anti-osteoarthritic [93], antinociceptive [89], antibacterial [23], antiviral [62], and insect antifeedant [32] activities. The molecule was investigated in both in vitro and in vivo assays. **Table 2** summarizes available data on TA activities and mechanisms of its action.

Table 2. Pharmacological activity of tormentic acid.

Biological Activity	Model	Ref.
Anti-inflammatory (anti-osteoarthritic): –decreasing the interleukin (IL)-1β-stimulated expression of MMP-3 and MMP-13; –inhibition of the IL-1β-induced expression of iNOS and COX-2, and the production of PGE2 and NO; inhibition of IL-1β-induced NF-κB activation	In vitro Human Articular Chondrocyte Culture	[94]

Biological Activity	Model	Ref.
Anti-inflammatory: –inhibition of nitric oxide (NO) and prostaglandin E 2 (PGE 2) production by inhibiting iNOS and COX-2 expression; –inhibition of LPS-stimulated production of TNF-α and IL-1β; –activation of LXRα (liver X receptor α) and inhibition of LPS-induced NF-κB activation	In vitro BV2 microglial cells	[95]
Antioxidative and anti-inflammatory: –decreasing reactive oxygen species (ROS) generation; –inhibition of the expression of inducible nitric oxide synthase (iNOS) and NADPH oxidase (NOX); –decreasing the production of tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and IL-1β; –preventing phosphorylation of nuclear factor-κB (NF-κB) subunit p65 and degradation of NF-κB inhibitor α (IκBα)	In vitro Rat vascular smooth muscle cells (RVSMCs);	[96]
Anti-inflammatory: –decreasing paw edema; –increasing the activities of catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) in liver tissue; –attenuating the level of thiobarbituric acid reactive substances (TBARS) in the edematous paw; –decreasing the nitric oxide (NO) levels at the serum level and diminishing the serum tumor necrosis factor (TNF-α); –decreasing the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2)	Ex vivo and in vivo RAW264.7 macrophages and λ-carrageenin-induced hind paw edema model in mice	[57]
Anti-inflammatory: –reducing the production of NO, prostaglandin E2 (PGE2), and tumor necrosis factor-α (TNF-α) induced by LPS; –suppressing the LPS-induced expression of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and TNF-α at the mRNA and protein levels; –decreasing DNA binding of nuclear factor kappa B(NF-kB) and nuclear translocation of the p65 and p50 subunits of NF-kB; –suppressing degradation and phosphorylation of inhibitor of kappa B-Alpha	In vitro LPS stimulated RAW264.7 cells	[97]

Biological Activity	Model	Ref.
Anti-inflammatory/antinociceptive (20–30 mg/kg)	In vivo Writhing Assay; Hot-Plate Test; Carrageenan-Induced Edema in Sprague–Dawley Rats	[75]
Anti-inflammatory: –inhibition of the production of interleukin-6 and interleukin-8; –inhibition of TLR4 (Toll-like receptor 4) expression; –inhibition of activation of nuclear factor kappa B (NF-κB); –inhibition of activation of mitogen-activated protein kinases (MAPKs)	In vitro LPS-stimulated human gingival fibroblasts (HGFs)	[98]
Anti-inflammatory: –inhibition of LPS-induced NO production	In vitro	[52]
Anti-inflammatory: –inhibitory effect on IFN-γ secretion –inhibition of COX-1 and COX-2 –apoptosis-inducing effect	In vitro LPS-stimulated Raw 264.7 macrophage	[34]
–Anti-inflammatory; –Potent inhibitory effect on Epstein-Barr virus early antigen (EBV-EA) activation; –Antitumor-promoting activity (strong)	In vivo: –TPA-induced ear edema inflammation in mice; –two-stage carcinogenesis test of mouse tumor; In vitro EBV-EA activation experiment	[37]
–Cytotoxic activity against the HeLa cell line; –Antidiabetic activity –Inhibition of PTP1B (Protein tyrosine phosphate)	In vitro	[47]
Cytotoxic to sensitive and multidrug resistant leukemia cell lines; Active toward a multidrug resistant (MDR) leukemia cell line overexpressing glycoprotein-P (P-gp)	In vitro (anti-MDR activity in Lucena-1, a leukemia cell line that overexpresses P-gp and presents cross resistance to several unrelated cytotoxic drugs)	[13]

Biological Activity	Model	Ref.
Cytotoxic	In vitro HCT-8, A549, P-388, L-1210 tumor cell lines	[30]
–Cytotoxicity in human oral tumor cell lines: human salivary gland tumor and human oral squamous cell carcinoma –Inhibition of the activation of Epstein–Barr virus early antigen (EBV-EA)	In vivo EBV genome-carrying lymphoblastoid cells In vitro human oral squamous cell carcinoma (HSC-2), human salivary gland tumor (HSG)	[58]
Antidiabetic and antihyperlipidemic: –Antihyperlipidemic: decreasing gene expressions of fatty acids, increasing the content of phosphorylated AMPK-α in liver and adipose tissue, inhibition of DGAT 1 expression, and decreasing the level of triglycerides in blood –Antidiabetic: down-regulation of phosphenolpyruvate carboxykinase (PEPCK), improving insulin sensitization (at 1.0 g/kg), and decreasing the expression of the hepatic and adipose 11-β-hydroxysteroid dehydroxygenase (11β-HSD1) gene	In vivo high-fat fed C57BL/6J mice	[4]
Hypoglycemic: decreasing the blood glucose level (at 10 mg/kg)	In vivo normoglycemic Wistar rats	[71]
Hypoglycemic effect (at 30 mg/kg): –decreasing glucose levels in normal rats; –increasing fasting plasma insulin levels Acute toxicity not observed (at 600 mg/kg, intraperitoneally)	In vivo normoglycemic, hyperglycemic, and streptozotocin-induced diabetic Wistar rats	[72]
Hypoglycemic effect: –direct stimulation of insulin secretion by pancreatic islets of Langerhans	In vitro pancreatic islets of Langerhans isolated from fed Wistar rats	[99]
Antidiabetic: –inhibition of alfa-glucosidase	In vitro	[70]

Biological Activity	Model	Ref.
Antidiabetic and antihyperlipidemic activity: –lowering blood glucose, triglycerides, free fatty acids, leptin levels; –decreasing the area of adipocytes and ballooning degeneration of hepatocytes; –reducing visceral fat mass, reducing hepatic triacylglycerol contents; –enhancing skeletal muscular Akt phosphorylation and increasing insulin sensitivity; –decreasing blood triglycerides by down-regulation of the hepatic sterol regulatory element binding protein-1c (SREBP-1c) and apolipoprotein C-III (apo C-III) and increasing the expression of peroxisome proliferator activated receptor (PPAR)-α	In vivo C57BL/6J mice with induced type 2 diabetes and hyperlipidemia	[100]
Influencing the processes present in vasculoproliferative diseases (diseases related to vascular smooth muscle cell (VSMC) abnormal proliferation): –increasing apoptosis of serum-deprived A7r5 cells and inhibiting A7r5 cell proliferation; –rapid induction of significant modifications in the vascular smooth muscle cell (VSMC) phenotype; –inhibition of VSMC proliferation and VSMC cell death	In vitro Clonal rat embryonic VSMCs (A7r5) and human umbilical vein endothelial cells (HUVEC)	[90]
Anti-melanogenesis effect (melanin synthesis inhibitory activity with less cytotoxicity) Antibacterial activity against *Propionibacterium acnes* Promotion of skin collagen synthesis	In vitro Mouse melanoma cell line B16; *Propionibacterium acnes* (NBRC 107605)	[101]
Hepatoprotective (preventing fulminant hepatic failure): –blocking the NF-κB signaling pathway for anti-inflammatory response (alleviating the pro-inflammatory cytokines, e.g., TNF-α and NO/iNOS by inhibiting nuclear factor-κB activity); –inhibition of hepatic lipid peroxidation; –decreasing serum aminotransferase and total bilirubin activities; –attenuating hepatocellular apoptosis	In vivo lipopolysaccharide/d-galactosamine-induced acute hepatic failure in male C57BL/6 mice	[69]

Biological Activity	Model	Ref.
Hepatoprotective: –inhibition of the production of pro-inflammatory factors such as: tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), and IL-6; –inhibition of inducible NO synthetase (iNOS) and cyclooxygenase-2 (COX-2); –inhibition of nuclear factor –κB (NF-κB) activation; –inhibition of the activation of mitogen-activated protein kinases (MAPKs); –retention of enzymes (essential for the antioxidative properties of liver): superoxidase dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT)	In vivo Acetaminophen-induced hepatotoxicity in male ICR mice	[102]
Protective effect against liver fibrosis: –inhibition of the activation of hepatic stellate cells; –reducing aspartate aminotransferase, alanine aminotransferase, and total bilirubin activity; –inhibition of expression of collagen type I and III; alleviation of collagen-based extracellular matrix deposition; –promoting cell apoptosis via blocking of the PI3K/Akt/mTOR and NF-κB signaling pathways	In vitro Hepatic stellate cells (HSCs) stimulated with platelet-derived growth factor-BB	[103]
Cardioprotective (protective effects on hypoxia/reoxygenation (H/R)-induced cardiomyocyte injury)	In vitro Neonatal rat cardiomyocytes subjected to hypoxia/reoxygenation (H/R) insult	[15]
Anti-hypoxic (protecting vascular endothelial cells against hypoxia-induced damage via the PI3K/AKT and ERK 1/2 signaling pathway)	In vitro (EA.hy926 cells)	[104]
Antiproliferative: –causing apoptosis and G0/G1 phase arrest in cancer cell lines; –induction of cell cycle arrest via changing the cyclin D1 and cyclin-dependent kinase 4 mRNA expression levels; –down-regulation of the NF-kappa-B cell survival pathway and the expression level of phosphorylated ERK (extracellular signal-regulated kinase)	In vitro Cancer cell lines: human hepatoma cells HepG-2 and Bel-7402, lung cancer cell A549, breast cancer cell MCF-7 Normal LO2 cell line	[105]
Antiproliferative	In vitro	[79]

Biological Activity	Model	Ref.
Anti-cancer (anti-hepatocellular carcinoma activity): –decreasing cell viability, colony formation, and cell migration; –induction of apoptosis; –changing the levels of caspase-3 and poly ADP-ribose polymerase expression	In vitro Hepatocellular carcinoma cells (HepG2, Bel-7405, Sk-hep-1)	[59]
Anti-cancer: –induction of cell cycle arrest; –enhancement of ROS production; –targeting the mTOR/PI3K/AKT signaling pathway in cisplatin-resistant human cervical cancer cells	In vitro Cisplatin-resistant human cervical cancer cells (HeLa cells)	[92]
Anti-osteoarthritic (inhibition of IL-1β-induced chondrocyte apoptosis by activation of the PI3K/Akt signaling pathway): –inhibition of IL-1β induced cytotoxicity and apoptosis in chondrocytes; –increasing B-cell lymphoma (Bcl)-2 expression; –decreasing capsase-3 activity and Bax expression; –increasing the expression of p-PI3K and p-Akt in IL-1β-induced chondrocytes	In vitro IL-1β-treated human osteoarthritic chondrocytes	[93]
Antinociceptive (anti-allodynic)	In vivo two models of chronic pain (neuropathic pain and inflammatory pain) in mice	[89]
Antibacterial	In vitro	[23]
Antibacterial and antibiofilm effect: –inhibition of growth of *P. aeruginosa*; –depolarization of bacterial *P. aeruginosa* membrane; –inhibition of biofilm formation due to suppressed secretion of pyoverdine and suppressed secretion of protease and swarming motility of *P. aeruginosa*	In vivo Mouse model of catheter infection for evaluation of antibiofilm activity and BALB/c mouse model for determination of in vivo toxicity In vitro *P. aeruginosa* cultures; murine macrophage cell line (RAW 264.7) for cytotoxicity assay	[88]
Antibacterial against *S. aureus* Antifungal against *C. albicans*	In vitro	[64]
Antibacterial against *S. aureus*	In vitro	[73]

Biological Activity	Model	Ref.
Bacteriostatic against *S. aureus*: –inhibition of extracellular protease production resulting in inhibition of *S. aureus* growth	In vitro	[45]
Antivirus: inhibition of virus HIV-1 protease	In vitro	[62]
Insect antifeedant	In vivo *Spodoptera littoralis* L6 larvae	[32]
Neuroprotective: –protecting against neurotoxicity (preventing neuronal loss); –blocking MPP^+-induced apoptosis; –inhibiting intracellular accumulation of reactive oxygen species (ROS); –protecting from neuronal death through reversing the inhibition of the PI3-K/Akt/GSK3b pathway	In vitro Parkinson's disease cellular model: MPP^+-induced neurotoxicity in human neuroblastoma SH-SY5Y cells	[106]
Neuroprotective: –decreasing amyloid plaque deposition; –reducing microglial activation and decreasing the secretion of pro-inflammatory factors; –suppressing the production of pro-inflammatory markers and the nuclear translocation of nuclear factor-κB (NF-κB); –reducing inhibited neurotoxicity and improving neuron survival	In vivo Amyloid β precursor protein (APP)/presenilin 1 (PS1) transgenic mice In vitro BV2 microglia cells	[91]

4. Derivatives of Tormentic Acid

Although tormentic acid (TA) is found in a variety of plants in its "basic form", it also occurs in the form of various derivatives. Some common structures are shown in **Figure 1**. TA and its derivatives are found in commonly known cultivated and consumed fruits or vegetables, e.g., strawberries [107], rose fruits [73], apples [65], and quince [51].

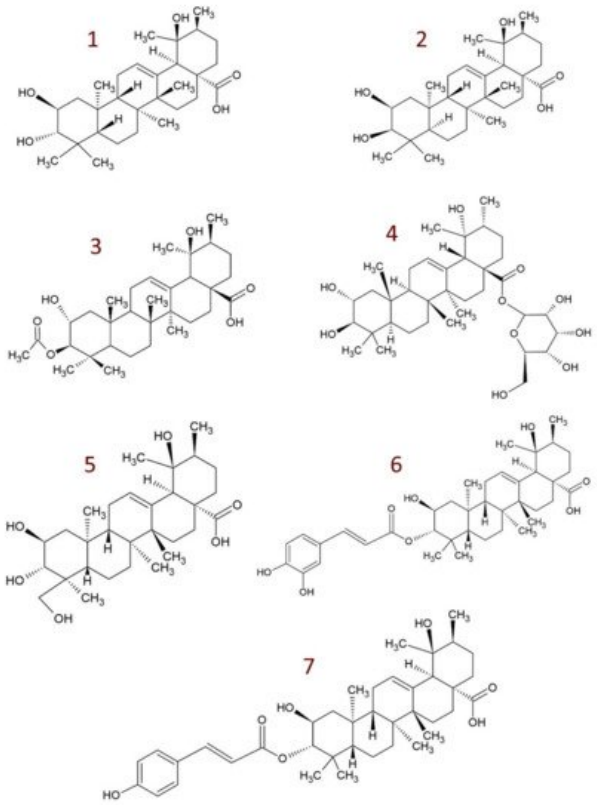

Figure 1. Structure of tormentic acid (**1**) and its common natural derivatives; **2**—euscaphic acid; **3**—3β-acetyl tormentic acid; **4**—rosamultin; **5**—23-hydroxytormentic acid; **6**—3-*O*-*trans*-caffeoyltormentic acid; **7**—3-*O*-*cis*-*p*-coumaroyltormentic acid.

The reported TA derivatives include:

- euscaphic acid (EA)—a stereoisomer of tormentic acid [9][77][75][83][108][109][110];
- 2-epi-tormentic acid (2β,3β,19α-trihydroxy-urs-12-en-28-oic acid) [9][111];
- acetylated compounds, e.g., 3β-acetyl tormentic acid; 2α-acetyl tormentic acid [13][112][113][114]
- hydroxylated derivatives, e.g., 23-hydroxytormentic acid [77]; 24-hydroxytormentic acid [43][115]; 11α-hydroxytormentic acid [25][107][109]; hydroxytormentic acid [25];
- coumaroyl esters, e.g., 3-*O*-*cis*-*p*-coumaroyltormentic acid; 3-*O*-*trans*-*p*-coumaroyltormentic acid [6][19][116];
- caffeoyl esters, e.g., 3-*O*-*trans*-caffeoyltormentic acid [6][52];
- glucosides, e.g., tormentic acid 3β-*O*-β-d-quinovopyranoside; tormentic acid 3β-*O*-β-d-fucopyranoside; tormentic acid 3β-*O*-β-d-rhamnopyranoside; rosamultin (tormentic acid 28-*O*-glucoside) [77][75][107][117][118]; tormentic acid β-d-glucopyranosyl ester [66][119];
- others, e.g., 6-methoxy-β-glucopyranosyl ester [109]; dihydrotormentic acid and methoxytormentic acid [107]; 3b-*p*-hydroxybenzoyloxytormentic acid [120]; (3*R*,19*R*)-methyl-3,19-dihydroxy-2-oxo-urs-12-en-28-carboxylate; (2*R*,19*R*)–methyl-2,19-dihydroxy-3-oxo-urs-12-en-28-carboxylate; (19*R*)-methyl-2,19-dihydroxyursa-3-oxo-1,12-dien-28-carboxylate; (2*S*,3*R*,19*R*)–methyl-2,3,19-trihydroxyurs-12-en-28-carboxylate; (2*R*,3*R*,19*R*)-2,3-bis(acetyloxy)-19-hydroxyurs-12-en-28-carboxylic acid; (2*R*,3*R*,19*R*)-2-acetyloxy-3,19-dihydroxyurs-12-en-28-carboxylic acid; (2*R*,3*R*,19*R*)-3-acetyloxy-2,19-dihydroxyurs-12-en-28-carboxylic acid; (3*R*,19*R*)–methyl-3-acetyloxy-19-hydroxy-2-oxo-urs-12-en-28-carboxylate; (2*R*,19*R*)-methyl-2-acetyloxy-19-hydroxy-3-oxo-urs-12-en-28-carboxylate; (2*R*,3*R*,19*R*)–methyl-2,3-bis(chloroacetyloxy)-19-hydroxy-urs-12-en-28-carboxylate; (2*R*,3*R*,19*R*)–methyl-2-chloroacetyloxy-3,19-dihydroxyurs-12-en-28-carboxylate; (2*R*,3*R*,19*R*)–methyl-3-chloroacetyloxy-2,19-dihydroxyurs-12-en-28-carboxylate [9].

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