Literature review on Pharmaceutical activities of Oleanolic acid

YEUNG Ming Fai

Keywords: Oleanolic acid; pharmaceutical activities; review, hepatoprotective; anti-stomach ulcer; hypoglycemic; anti-hyperlipidemic, anti-hypertensive; cardiotonic; anti-dysrhythmic; anti-aggregation of blood platelet; anti-cancer; protection of renal toxicity; anti-inflammatory; anti-mycobial; anti-fertility; toxicity; pharmacokinetics

Abstract

Pharmaceutical activities of Oleanolic acid (OA) were reviewed and summarized until September 2007. Oleanolic acid has hepatoprotective, anti-stomach ulcer, hypoglycemic, anti-hyperlipidemic, anti-hypertensive, cardiotonic, anti-dysrhythmic, anti-aggregation of blood platelet, anti-cancer, protection of renal toxicity, anti-inflammatory, anti-mycobial and anti-fertility activities with low toxicity.

Introduction

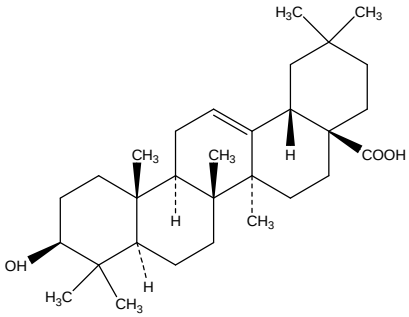

Fig 1 Structural formula of 3 β - hydroxyolean – 12 – en – 28 – oic acid (Oleanolic acid)

Oleanolic acid (OA) is a naturally occurring triterpenoic acid phytochemical presents in leaves, roots and bark of various plants. Its structure (Fig 1)was definitively established by Ruzicka in 1946[1]. Pharmaceutical activities of OA were reviewed and summarized until September 2007.

Pharmaceutical activities of OA

OA shows the following activities.

Hepatoprotection

OA is a fat-soluble compound. Therefore, it is easily to be entered and accumulated in fat-storing and fat-metabolizing organs such as liver. From its structure, it has double-bonds, hydroxyl group and carboxyl group which can be used to react with toxic chemicals so as to protect the liver from hepartotoxicity [8]. OA has multi-functional mechanisms for the protection of liver from toxicity. OA 100 mg/kg (sc) x 3 days in rats can reduce Cd-induced hepatotoxicity. OA reduced the increase of ALT, LPO and iditol dehydrogenase level. It also increased MT level in liver by 30 times but on significant changes of MT level in other organs [3]. OA also protects acetaminophen, bromobenzene, phalloidin, thioacetamide, furosemide, colchicine, CCl_4, D-galactosamine, endotoxin and acetaminophenolrene-induced hepatotoxicity by reduced the increase of ALT and AST level [10-11].

OA increases GSH-Px activity for reduction of GSH and inhibition of $P_{450}2E_1$ expression can inhibition CCl_4 hepatotoxicity. *In-vivo* studies show OA reduces activity of P_{450} enzymes [12]. OA 75 and 150 mg/kg/day (po) for 5 days has immunomodulatory properties. It prolifered synthesis of Prostaglandin E_2 (PGE_2), Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and 3'-5'-cyclic adenosine monophosphate (cAMP) levels but inhibit the secretion of 3'-5'-cyclic guanosine monophosphate (cGMP) and dopamine [13]. OA 20 mg/times for 3 times/days (po) to human protect anti-TB drugs from hepatotoxicity by

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reduction of increase in ALT levels [14]. OA had both hepatoprotective and weak hepatotoxic activities. An optimum dose is needed for the balance between hepatoprotective and hepatotoxic activities of OA [15].

OA 60-90 mg/day plus Vitamin B and Vitamin C had 94.4 % effective in treatment of viral hepatitis and 64.8 % recovered from viral hepatitis in 196 patients [16]. OA 150-360 mg/day (po) plus vitamin B and Vitamin C has 69.81 % effective in treatment of chronic hepatitis in 222 patients [16]. OA is now used for treatment of hepatitis in China [17]. For acute hepatitis, 30 mg/time and 3 times/day for 1 month. For chronic hepatitis, 50 mg/time and 3-4 times/day for 3 months [17].

OA also prevented fibrosis and stimulated liver regeneration [18].

Anti-stomach ulcer activity

OA 50-200 mg/kg (po) has anti-ulcer activity by alcohol-induced and asparin-induced gastric lisions in mice in dose-dependant manner [19]. OA 600 mg/kg/day (po) for 14 days reduced the stomach ulcer area by acetic acid-induced chronic gastric lesions in rats [20].

Hypoglycemic activity

OA 50-100 mg/kg/day (sc) for 7 days before or after the treatment of alloxan decreased the blood glucose level in alloxan-induced diabetic mice; the elevation of blood glucose caused by adrenaline 0.2 mg/kg (ip) or glucose 2 g/kg (ip) was also attenuated by OA treatment [21]. When rats were intoxicated with alloxan 170 mg/kg (ip), followed by OA treatment (100 mg/kg 4 times/day for 1 week), the elevation of blood glucose was also ameliorated, and hepatic glycogen and insulin were higher than the pathological controls [22].

Anti-hyperlipidemic activity

OA 200 mg/kg (po) reduced TG, Cholesterol and β-lipoprotein levels in blood serum of normal and hyperlipidemic mouse [23]. Treatment of experimental hyperlipidemic rats with OA 50 mg/kg (po) for 9 days decreases the elevated blood cholesterol and β-lipoprotein levels by more than 40 % [24]. OA did not affect the blood lipoprotein levels in normal rabbits, but decreased the elevated blood cholesterol levels and prevents lipid precipitation in blood vessels and major organs of experimental hyperlipidemic rabbits. The serum concentrations of high density lipoproteins were decreased following OA treatment [25].

Anti-hypertensive, cardiotonic and antidysrhythmic

OA did not reduce blood pressure of normal mouse but has cardiotonic activity directly. OA 60 mg/kg/day (ip) for 6 weeks prevent severe development of hypertension by direct cardiac effect (heart rate decrease by 34 %), antihyperlipidemic (increase high density cholesterol content by 66 %, decrease low density cholesterol content by 54 % and decrease triglycerices by 47 %), antioxidant (GSH-Px increase by 12 %; SOD increase by 12 %), hypoglycemic (blood glucose decrease by 20 %) on rats [26].

OA had vasorelaxant effects on depolarized or endothelium-denuded aortic segments of isolated thoracic rat aorta. The relaxation was significantly attenuated by pre-treatment with the NO synthase inhibitor N^{ω}-nitro-L-arginine-methylester (3×10^{-4} M). The endothelial production of NO maybe the mechanism [27].

OA acted as beta-adrenergic antagonists, blocking effect of adrenaline and isoprenaline for the dose-response vasodepressor effect for the treatment cardiotonic and antidysrhythmic disease [28].

Anti-aggregation of blood platelet

OA 75-300 mg/kg (po) produced an inhibitory effect on blood platelet aggregation induced by ADP, collagen and increased electrophoretic mobility in 30 weaks old mice. Hence, it can be used to treat atheromatous diseases in slow blood flow rate old patients [29-30].

Anti-cancer activity

OA had inhibition effect on human colon carcinoma cell line HCT15 due to change in cell morphology, cytotoxicity and cell cycle *in-vitro* [31]. It decreased the proliferative ability of highly potentially metastatic lung cancer cell line PGCL3 *in-vitro*, and the IC_{50} was 40.71 μmol/L. After treatment with OA (45 μmol/L) for 96 hours, the invasive ability of PGCL3

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cells was significantly decreased compared with that of control groups by invasion test of reconstitututed basement membrane. The adhesive and migration ability, the secretion of cathepsin B and colony-formation number in semi-solid agar were significantly decreased after PGCL3 cells were treated with 45 μmol/L OA for 96 hours by laminin adhesion test, chemotactic migration test and enzymological method of cathepsin B respectively, and the inhibition was in a dose-dependant manner. The percentage of apoptosis of cells was abviously increased after treatment of OA (45 μmol/L) for 48 hours, compared with the control group by acridine orange-ethidium bromide fluorescent stain. The mechanism of inhibition of OA on human lung cancer cells may be due to inhibition of the adhesion, migration and the cathepsin B secretion of the cells [32].

OA stimulated secretion of NO and TNF-α release and was able to upregulate iNOS and TNF-α expression (by reverse transcription-polymerase chain reaction) through NF-κB transactivation (by transient transfection assay and electrophoretic mobility shift assay), which maybe the mechanism for its anti-tumor effect [33].

OA had been shown to act at various stages of tumor development, including inhibition of tumorigenesis, inhibition of tumor promotion, and induction of tumor cell differentiation. It effectively inhibited angiogenesis, invasion of tumor cells and metastasis. However, the mechanisms by which the mechanisms were still poorly understood [34].

Protection of renal toxicity

OA 75 and 150 mg/kg/day (po) for 5 days had renal protective effect on mice. It prolifered synthesis of Prostaglandin E_2 (PGE_2) and Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) level in mice kidney. The 3'-5'-cyclic adenosine monophosphate (cAMP) levels also prolifered but inhibited the secretion of 3'-5'-cyclic guanosine monophosphate (cGMP) and dopamine [13].

Renal glomeruli congestion, swelling and fibrosis, proximal tubular lining cells swelling in $CdCl_2$ –treated rats were significantly ameliorated by OA treatments, which were revealed by light microscopy. Ultrastructure examination showed the pathologic changes in constituents of glomeruli and subcellular constituents like mitochondria in proximal tubular cells were less severe in OA treated rats than those in $CdCl_2$ treated rats. Therefore, OA improved renal histopathological changes induced by cadmium in a subchronic model in rats [35].

Anti-inflammatory

OA had inhibitory effects on carrageenan-induced rat paw edema and formaldehyde-induced arthritis [36]. The mechanisms of anti-inflammatory effects of OA had been attributed to the following aspects: Inhibition of histamine released from mast cells induced by compound 48/80 and concanavalin A [37-39]; the synthesis and release of PGE2 and leukotriene B were suppressed by OA [37-39]; inhibition of elastase, the IC_{50} for elastase inhibiton by OA was 6.4 μM. Elastase is thought to play a role in tissue inflammatory response in rheumatic disease [40]. Inhibition of complement activity [41], possibly through the inhibition on C3-convertase of the classical complement pathway [42].

Anti-mycobial

OA had *in-vitro* inhibitory effect on *Bacillus subtillis* (M_1), *Escherichia carotovora* (M_2), *Xanthomonas campestris* Pv. Citri (M_3), *Staphlococcus aureaus* (M_4), *Clostridium sp* (M_5), *Pseadomonas aeruginosa* (M_6), *Bacillas megaterium* (M_7), *Sarcina maxima* (M_8), *Escherichia coli* (M_9) and *Proteus vulgaris* (M_{10}) and were tabulated (Table 1) [43-44].

Anti-fertility

OA was shown to have anti-fertility effects in male rats [45]. It also had been shown to be an inhibitor of testosterone 5α-reductase, and to have anti-male hormone activities [46].

Toxicity

OA is relatively non-toxic. LD_{50} of OA on mice was 340 mg/kg (sc) . One g/kg (po) and 500 mg/kg (sc) on mouse. OA 1.0 g/kg (sc) to mice or to rats, no mortality was observed during 5-day period [47-48]. During multiple administration of OA 180 mg/kg (po) for 10 days and 100 mg/kg/day (po) for 50 days, no abnormalities were observed in brain, heart, lung, liver, kidney, thyroid, testes, stomach, spleen or intestine in mouse [49]. A 70-case clinical

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Compounds	M_1	M_2	M_3	M_4	M_5	M_6	M_7	M_8	M_9	M_{10}
Oleanolic acid	+	+	+	+	+	+	+	+	+	+

+ = inhibition

- = no effect

Table 1. Inhibitory effect on *Bacillus subtillis* (M_1), *Escherichia carotovora* (M_2), *Xanthomonas campestris* Pv. Citri (M_3), *Staphlococcus aureaus* (M_4), *Clostridium sp* (M_5), *Pseadomonas aeruginosa* (M_6), *Bacillas megaterium* (M_7), *Sarcina maxima* (M_8), *Escherichia coli* (M_9) and *Proteus vulgaris* (M_{10}) for OA.

trial using oleanolic acid (60-90 mg/day, for 30 days) for acute jaundice hepatitis demonstrated that it was therapeutically effective in the absence of apparent side effects [50]. Long-term use of OA (> 3 months) in 188 cases of chronic hepatitis indicated that OA is safe [51].

Pharmacokinetics of OA

Pharmacokinetic parameters, maximum plasma concentrations (C_{max}), their time of occurrence (T_{max}) of OA, the area under the plasma concentration-time curve (AUC) from the time zero to the last measured concentration (AUC_{0-t}), terminal half-life ($t_{1/2}$), clearance (CL/F, L/h) and the volume of distribution (V/F, L) for 18 healthy male Chinese volunteers after oral administration of a single 40 mg dose of OA capsules were reviewed and tabulated (Table 2) [52].

Parameters	Mean (±SD)
C_{max} (ng/mL)	12.12 (6.84)
T_{max} (h)	5.2 (2.9)
$T_{1/2}$ (h)	8.73 (6.11)
AUC_{0-t} (ng h/mL)	114.34 (74.87)
$AUC_{0-\infty}$ (ng h/mL)	124.29 (106.77)
CL/F (L/h)	555.3 (347.7)
V/F (L)	3371.1 (1990.1)

Table 2. Pharmacokinetic parameters of OA in 18 healthy male Chinese volunteers after oral administration of a single 40 mg dose of the capsules

The pharmacokinetics of OA evaluated *in-vitro* and *in-vivo* was reviewed and tabulated (Table 3, 4) [53].

Parameter	0.5 mg/kg (mean±SD)	1 mg/kg (mean±SD)	2 mg/kg (mean±SD)
$T_{1/2}$ (min.)	41.9±12.6	52.7±24.3	48.0±13.2
AUC (µg min./mL)	16.0±1.9	32.6±10.4	71.6±12.7
MRT (min.)	18.6±7.2	13.8±6.5	14.8±4.5
CL (mL/min./kg)	31.7±4.0	33.0±9.2	28.6±4.7
V_{ss} (mL/kg)	583±209	451±213	437±192
Ae_{0-24h} (% of dose)	> LOD	> LOD	> LOD

Table 3. Pharmacokinetic parameters of OA after iv injection of various doses to rats (n=6) .

From Caco-2 cell permeation studies, OA was a low permeability compound with no directional effects, suggesting a low *in vivo* absorption mediated by a passive diffusion. OA was metabolically unstable following incubation with rat liver microsomes in the presence of NADPH. After 0.5, 1 and 2 mg/kg (iv) doses, OA showed dose-linear pharmacokinetics as evidenced by unaltered CL (28.6-33.0 mL/min/kg), Vss (437-583 mL/kg), dose-normalized AUC (16.0-17.9 µg min/mL based on 1 mg/kg) and $t_{1/2}$ (41.9-52.7 min.) OA 10, 25 and 50 mg/kg (po), T_{max}, $t_{1/2}$, dose normalized C_{max} (66-74 ng/mL) based on 25 mg/kg) and dose-normalized AUC (5.4-5.9 µg min/mL based on 25 mg/kg) were comparable between 25 and 50 mg/kg dose, but the plasma concentration at 10 mg/kg dose were not measurable as they were below the limit of

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Parameter	10 mg/kg (n=7) (mean±SD)	1 mg/kg (n=6) (mean±SD)	2 mg/kg (n=7) (mean±SD)
AUC (μg min./mL)	Not calculable	5.9±5.5	10.7±10.0
T_{max} (min.)	Not calculable	25.0±18.2	21.0±17.0
C_{max} (ng/mL)	Not calculable	74.0±57.2	132.0±122.0
$T_{1/2}$ (min.)	Not calculable	46.5±48.6	65.3±20.2
Ae_{0-24h} (% of dose)	0.008±0.010	0.054±0.092	0.058±0.107
F (%)	Not calculable	0.7	0.7

Table 4. Pharmacokinetic parameters of OA after oral administration of various doses to rats .

quantitation (2 ng/mL). The absolute oral bioavailability was 0.7 % for oral doses of 25 and 50 mg/kg. The extent of urinary excretion was minimal for both iv and po doses. The very low oral bioavailability of OA could be due to a poor absorption and extensive metabolic clearance [53].

Conclusion

From the review, OA has hepatoprotective, anti-stomach ulcer, hypoglycemic, anti-hyperlipidemic, anti-hypertensive, cardiotonic, anti-dysrhythmic, anti-aggregation of blood platelet, anti-cancer, protection of renal toxicity, anti-inflammatory, anti-mycobial and anti-fertility activities with low toxicity. This provides additional information on previous published materials [54-59].

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