Abstract

Oleanolic acid and ursolic acid are ubiquitous triterpenoids in plant kingdom, medicinal herbs, and are integral part of the human diet. During the last decade over 700 research articles have been published on their research, reflecting tremendous interest and progress in our understanding of these triterpenoids. This included the isolation and purification of these triterpenoids from various plants and herbs, the chemical modifications to make more effective and water soluble derivatives, the pharmacological research on their beneficial effects, the toxicity studies, and the clinical use of these triterpenoids in various diseases including anticancer chemotherapies. A briefly commentary is attempted here for their research perspectives.

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1. “Dose differentiates a poison from a remedy”

Paracelsus pointed out in the 16th century that “All substances are poisons; there is none which is not poison. The right dose differentiates a poison from a remedy”. Like many herbal ingredients, the selection of the appropriate dose of these triterpenoids is critical. Although these triterpenoids are relatively safe, toxicities do occur in certain circumstances. For example, low-doses of oleanolic acid are hepatoprotective, while the high-dose could produce cholestasis and hepatotoxicity. Low-dose of oleanolic acid could produce adaptive responses, similar to “hormesis”. Thus, it should be kept in mind in the future studies that the dose determines the mode of action and the dose makes a poison.

2. Chemical modifications of oleanolic acid

A major advancement during the past 10 years is the synthesis of derivatives from the natural triterpenoids such as oleanolic acid. For example, the oleanolic acid derivative 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) has been generated, which is more potent than the parent compound in anti-inflammatory actions and more effective in inhibiting iNOS and COX2 as a basis of its anti-inflammatory effects (Suh et al., 1998). Other synthetic derivatives, such as carbenoxone and uvaol dihemiphthalate sodium salt analogues, also demonstrate more potent anti-ulcer effects with less toxicity (Farina et al., 1998). Thus, chemical modification of raw natural compounds could produce more effective derivatives with less toxicity.

Water solubility of oleanolic acid and ursolic acid is limited, thus limiting their bioavailability in the body. Efforts have been made to improve their water solubility with chemically modified derivatives. Other means used to increase the solubility of these triterpenoids include non-covalent complex with hydrophilic cyclodextrins, as well as the use of nanosuspensions (Chen et al., 2005). Both pharmacokinetic and pharmacodynamic considerations are equally important in increasing the bioavailability and biological effects of these triterpenoids.

3. Mixtures and chemical interactions

One major feature of the traditional medicine is the use of herb mixtures. Modern pure compound research is nec-
necessary to advance our knowledge of their structure–activity relationships and the mechanism of their biological actions. However, the mixtures of these active ingredients are more effective than a single compound in producing desired biological effects, and are the common practice in health care and clinical treatments. For example, oleanic acid has been used in the formula of anti-inflammatory preparations, in the formula of treating liver fibrosis preparations, as well as in the combined chemotherapeutics for certain tumors. Interactions of these mixtures could occur chemically and biologically to produce more desired effects. Research on chemical mixtures has been difficult but important in the future for fully understanding these naturally occurring compounds in the treatment of various diseases.

4. Hepatoprotection perspectives

Oleanic acid and ursolic acid are well known for their hepatoprotective effects for both acute chemically induced liver injury and chronic liver fibrosis and cirrhosis (Liu, 1995). They are still used alone or in combination with other hepatoprotective ingredients as oral medications. The beneficial effects of these triterpenoids on the liver could be due to their anti-oxidant and anti-inflammatory actions, and their effects on drug-metabolizing enzymes. These triterpenoids are effective inducers of metallothionein, a small cysteine-rich protein acting like glutathione in the body’s defense against toxic insults. Induction of metallothionein could be an important mechanism for the generalized beneficial effects of these triterpenoids, but not the sole mechanism in protection against chemically induced liver injury (Liu et al., 1998). The preliminary gene array study (Liu et al., 1999) revealed that multiple pathways are involved in the beneficial effects of these triterpenoids, which is currently under investigation.

The modulatory effects of oleanolic acid on type-1 collagen and matrix metalloproteinases expression (Mig et al., 2001) are novel findings, which could play a role in its beneficial effects for chronic liver fibrosis.

5. Chemotherapy perspectives

Oleaninc acid and ursolic acid have been shown to act at various stages of tumor development to inhibit tumor initiation and promotion, as well as to induce tumor cell differentiation and apoptosis. In the two-stage mouse skin carcinogenesis model, the protection of oleanolic acid against 12-O-tetradecanoyl phorbol-13-acetate promoted carcinogenesis is associated with inhibition of aberrant gene expression (Oguro et al., 1998). Oleanic acid derivatives are also effective for acute myeloid leukemia by inducing apoptosis of tumor cells (Konoplev et al., 2004). These triterpenoids and their derivatives are also effective in inhibiting angiogenesis, invasion of tumor cells and metastasis, and emergence as a new class of chemotherapeutics (Ovesna et al., 2004). The mechanisms of the anti-tumor effects by triterpenoids warrant further investigation.

6. Signal transduction pathways

The advance of molecular biology techniques has greatly helped our understanding of these triterpenoids. More and more sophisticated studies have been directed at the molecular levels to understand the mechanism of their biological effects. For example, the involvement of MAP kinase pathways (JNK) has been demonstrated in oleanolic acid derivative induced apoptosis in lung cancer cells and in leukemia cells (Zou et al., 2004). The induction of the phase-2 enzymes such as heme oxygenase 1 and NAD(P)H-quinone oxidoreductase by these triterpenoids is shown to be mediated through the Nrf2-Keap1 signaling pathways (Dinkova-Kostova et al., 2005). These triterpenoids also play roles in modulating transforming factor beta and Smad signaling pathways (Murakami et al., 2004), but their effects are dependent on experimental conditions. These pathway investigations could provide insights into the molecular basis for the beneficial effects produced by these triterpenoids.

7. Other pharmacological effects

A variety of novel pharmacological effects produced by these triterpenoids have been reported, including their beneficial effects on cardiovascular systems (Somova et al., 2003), interaction with cytochrome P450s (Kim et al., 2004), protection against kainate-induced excitotoxicity in rat hippocampal neurons and immunomodulatory effects, as well as its effects on intracellular redox balance and osteoclast formation. The monoclonal antibody against oleanolic acid has also been generated. These newly reported pharmacological effects are too many to be mentioned in detail here, but it definitely reflects the growing interest in research on these naturally occurring triterpenoids in the future.

To the end of this brief commentary, the preface of J. Ethnopharmacology is quoted below as a perspective for these triterpenoids: “Many valuable drugs of today came into use through the study of folk remedies. Chemists continue to use plant-derived drugs as prototypes in their attempts to develop more effective and less toxic medicines. The scientific search for pharmacologically unique principles from existing remedies continues and complements the achievements of modern medicine”.

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References


