Prayogik Rasayan

Medicinal properties of a naturally occurring pentacyclic dihydroxy triterpenoid uvaol

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Abstract

Uvaol is a 6-6-6-6-6 pentacyclic ursane type dihydroxy triterpenoid. It is present in various plants such as *Plumeria rubra*, *Olea europaea*, *Nerium oleander and Malus domestica*. One step conversion of ursolic acid, a 6-6-6-6-6 pentacyclic triterpenic acid having an identical triterpenoid backbone, to uvaol has also been reported. A variety of pharmaceutical properties, including antimicrobial, hepatoprotective, anti-inflammatory, anti-tumour, anti-cancer, cardiovascular effects and healing of cutaneous wounds etc. have been reported. In this review, various plant sources of uvaol and its pharmaceutical properties have been reported.

Keywords: *Plumeria rubra, Olea europaea, Nerium oleander*, *Malus domestica*, uvaol, medicinal properties

1. Introduction

Scientists have focused more and more on plant based chemicals instead of petroleum based crude materials in recent times as plant based chemicals are renewed in every season whereas the petroleum based chemicals are depleting fast. Terpenoids are attractive choice for the development of a sustainable society as these are obtainable from plants and hence renewable, usually nontoxic and biocompatible.[1,2,3,4,5,6,7,8,9] Terpenoids or isoprenoids are the most abundant structurally diversified non-nitrogenous natural products. Triterpenoids are six isoprene units containing *plant secondary metabolites* having general formula $C_{30}H_{48}$. These are bio-synthesized from squalene via enzymatic pathways as prop

osed by Ruzicka and coworkers in 1953 and later on supported by experimental as well as computational studies. Detailed computations were carried out in our laboratory and we observed that all the triterpenoids have nano metric lengths in the range of 1 nm to 3 nm.[10] The triterpenoids with functional diversities containing both

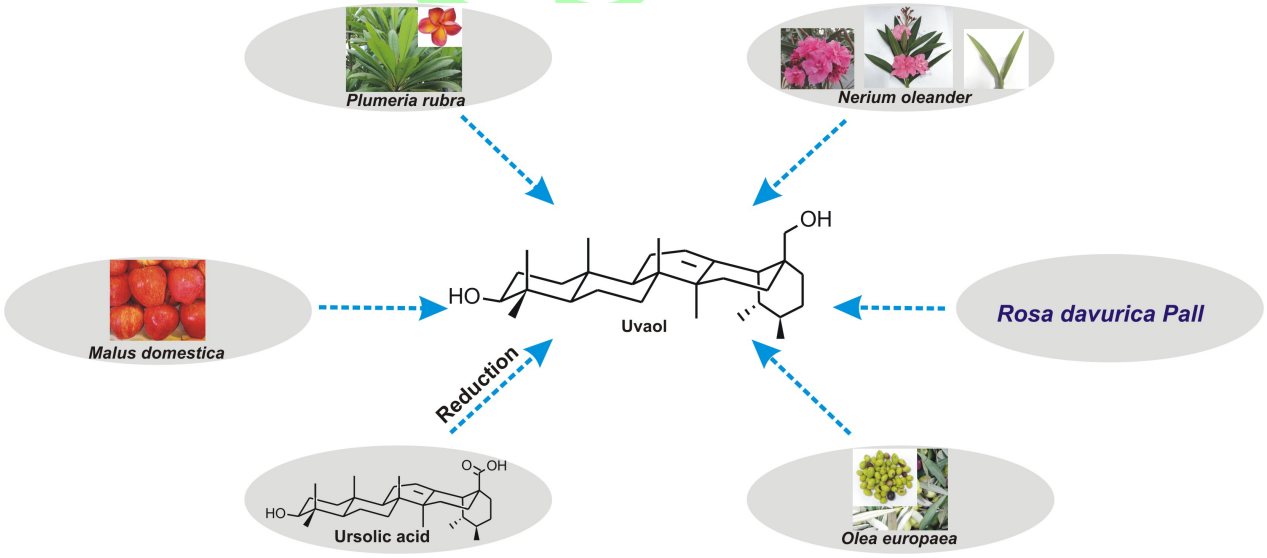

Figure 1: Different sources of uvaol

hydrophobic and polar parts make them an important class of amphiphiles and spontaneous self-assembly of several triterpenoids in different liquids have recently been reported in the literature.[11,12,13,14,15,16,17,18] All the triterpenoids were extracted from various parts of plants such as flowers, barks,

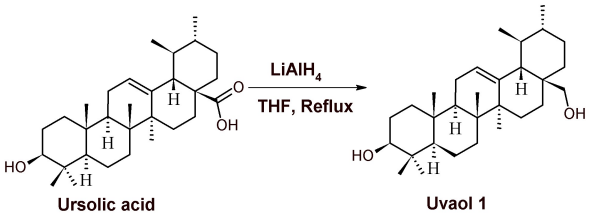

Figure 2: synthesis of uvaol from naturally occurring ursolic acid

leaves, roots, fruits and heavy-woods etc. Uvaol is a 6-6-6-6-6 pentacyclic ursane type dihydroxy triterpenoid. It is present in various plants such as *Plumeria rubra*, *Olea europaea*, *Nerium oleander and Malus domestica* (Figure 1). In this review, isolation from different plant sources of uvaol, its structural characterization and its medicinal properties have been discussed.

2. Synthesis of Uvaol

While carrying out investigations on the reduction of triterpenic acids to the corresponding alcohols, Wu and coworkers reported in 1950 that triterpenic acids can be reduced to the corresponding alcohols by following the reduction method reported by Brown and coworkers using lithium aluminium hydride in dry tetrahydrofuran.[19,20] Along with other triterpenic acids, the reduction of pentacyclic triterpenoid ursolic acid to its corresponding alcohol uvaol was also reported by them (Figure 2). Later on, this dihydroxy triterpenoid was fully characterized and it was also extracted from various plants as discussed below.

3. Various plant sources of uvaol

The pentacyclic ursane type dihydroxy triterpenoid, uvaol was first isolated by Valverde and coworkers in 1973 from *Lavandula pedunculta*.[21] The isolation of uvaol was also reported by Depascual and coworkers from the plant *Nepeta argonesis* in 1978.[22] In 2008 Hassan and co-workers reported the isolation of uvaol from the plant *Plumeria rubra*. [23] Jager and co-workers in 2009 reported the isolation of uvaol from the plant *Malus domestica.*[24] Siddiqui and co-workers reported the isolation of uvaol from the plant *Nerium oleander*[25] in 2009. In 2015 Fiad and co-workers reported the isolation of uvaol from the plant *Olea europaea*. [26]

4. Chemical structure

Uvaol is a pentacyclic ursane type dihydroxy triterpenoid. In 1974 Dodrell and coworkers established the structure of uvaol by ^{1}H and ^{13}C NMR, IR spectrum and mass spectroscopic analysis.[27] It has a 6-6-6-6-6 pentacyclic hydrophobic backbone and two hydroxyl groups are present at the two extreme ends of the molecule (Figure1). To our knowledge, the structure of uvaol is yet to be supported single crystal X-ray crystallography.

5. Medicinal Activity

5.1 Anti tumour activity

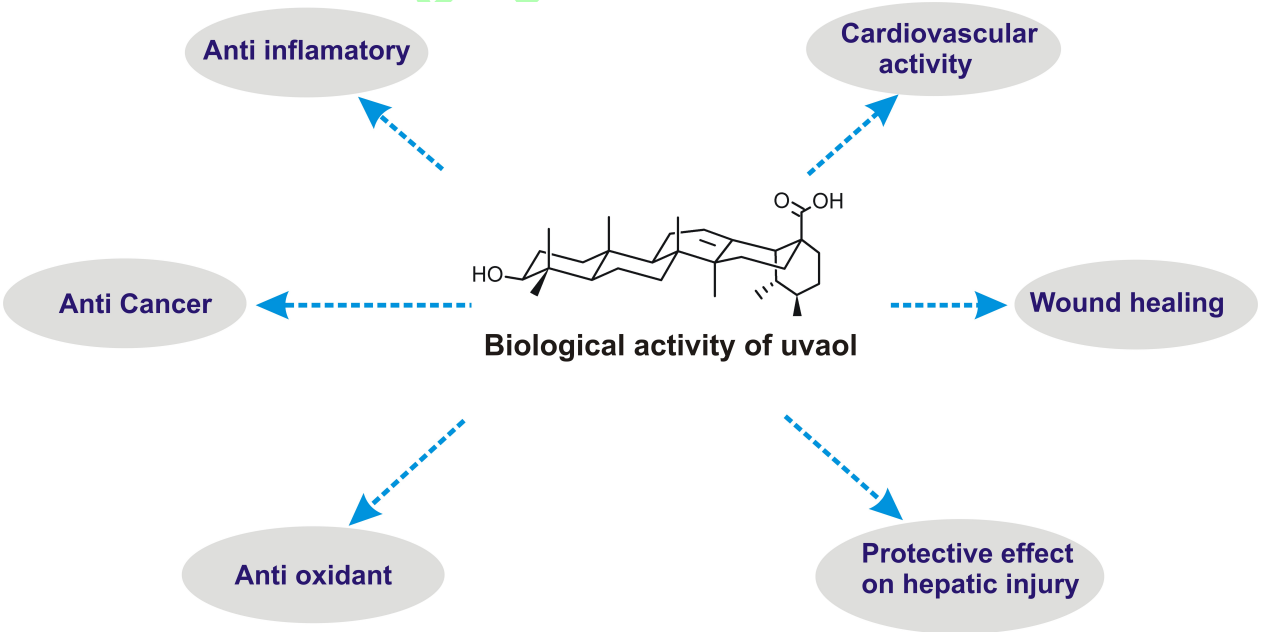

Figure 3: Medicinal activity of uvaol

Cole and co-workers reported the anti tumour activity of the bioactive triterpenoid uvaol in 1976.[28] The pentacyclic triterpenoid, uvaol was shown to have tumor inhibitory effect against the P 388 lymphocytic leukemia test system (3PS).

5.2 Inhibitory effect uvaol on HIV-I protease

Inhibitory effect uvaol on HIV-I protease was reported by Kim and co-workers in 1999. They reported that uvaol shows inhibitory action on HIV-1 protease with IC50 values of 5.5 μM.[29]

5.3 Cardiovascular effects

The cardiovascular properties of triterpenoids have been reported recently by Somova and coworkers in 2004. The pentacyclic triterpenoid uvaol showed a significant, dose-response vasodepressor effect. This is one of the most economic and conventional treatments of hypertension.[30]

5.4 Anti Cancer

The anti-cancer activity of bioactive uvaol in the HepG2 cell line was reported by Sarek and coworkers in 2006.[31] It has a clear and selective anticancer activity in HepG2 cells supported by a significant anti-migratory capacity and a significant increase in the expression of HSP-60. A suppressive effect in reactive oxygen species (ROS) levels in HepG2 cells was also observed. Uvaol shows anti-proliferative and pro-apoptotic effect on hepatocellular carcinoma (Figure 3 and 4). [32]

5.5 Healing of cutaneous wounds

Healing of cutaneous wounds of uvaol in the *in vitro* and *in vivo* was reported by Barreto and coworkers in 2020.[33] They showed the positive effects of uvaol on migration of fibroblasts and endothelial cells in the scratch assay and potentially promoting cutaneous healing (Figure 5).

5.6 Anti-inflammatory action

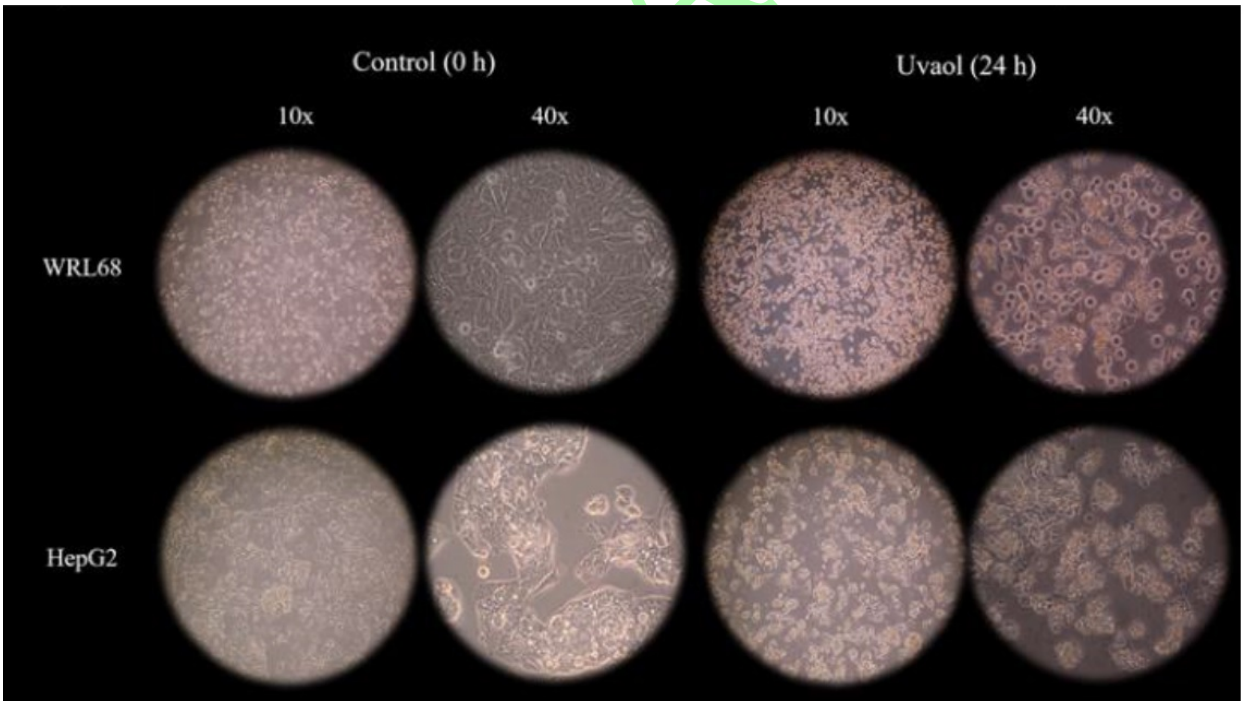

Figure 5: Morphological changes in response to uvaol treatment incubated at IC_{50} after 24h in the WRL68 (IC_{50}: 54.3 μg/mL) and HepG2 (IC_{50}: 25.2 μg/mL) cell line.[32]

The anti-inflammatory activity of bioactive uvaol was reported by Du and coworkers in 2020.[34] It showed immune response by affecting complement and antibody production. The hydroxyl group at C28 may be involved in the anti-inflammatory action of the triterpenoid uvaol. For colonic inflammation uvaol acts as a prospective anti-inflammatory agent which is correlated with the suppression of colonic macrophage activation. Thus naturally occurring triterpenoid uvaol may act as a potential drug for anti-inflamation of colon.

6. Conclusion and Future Prospects

In this review, the different plant sources of bioactive triterpenoid uvaol and several biological properties such as anti cancer, protective effect on induced hepatic injuries, cardiovascular effects and anti-inflammatory action

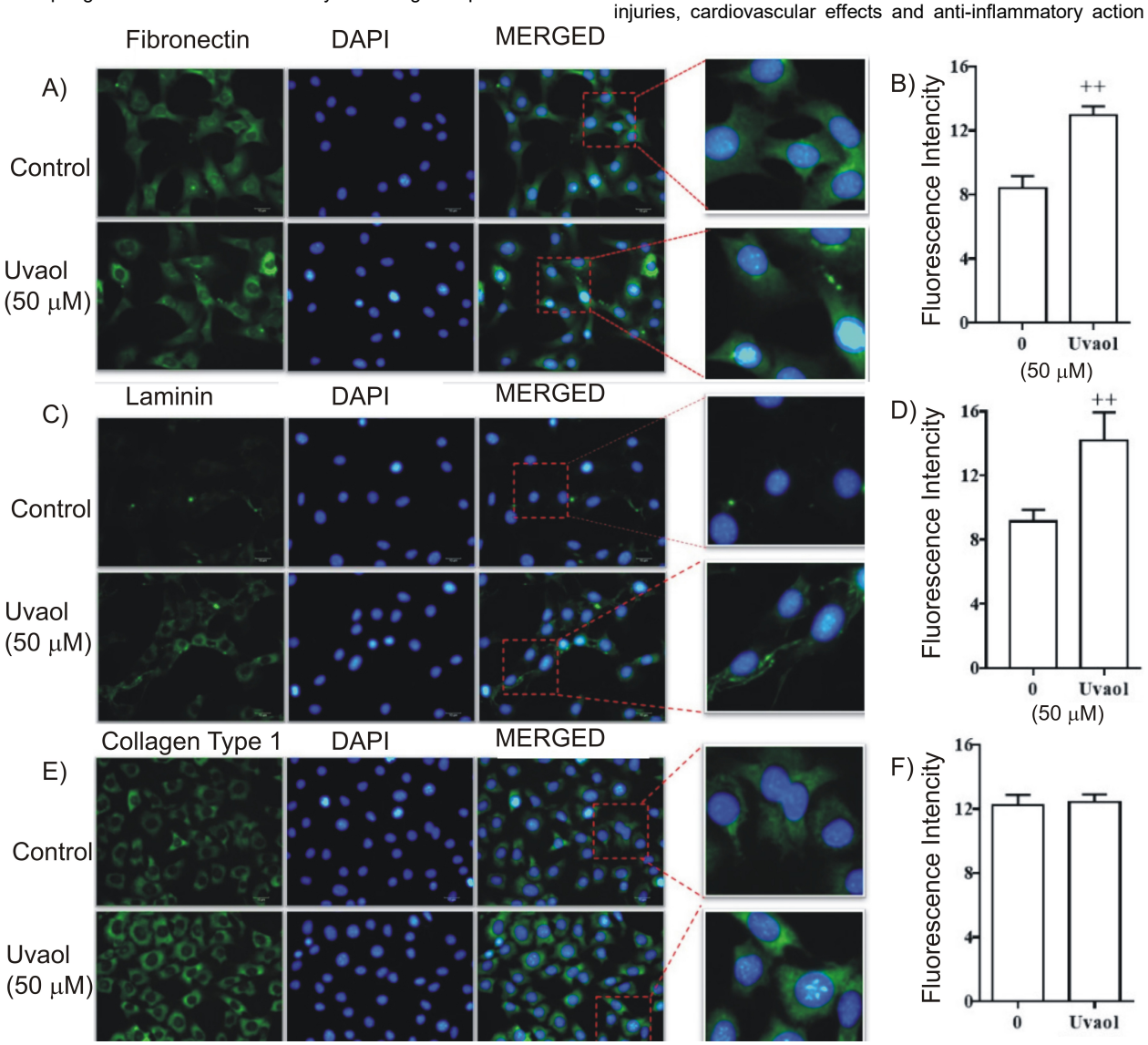

Figure 5: Effect of uvaol on the levels of fibronectin, laminin, and collagen type I in fibroblasts using immunofluorescence analysis. Fibroblasts were cultured with and without 50 μM uvaol. After 24 h, the cells were fixed and the extracellular matrix was immuno-stained using antibodies against fibronectin (**A**), laminin (**C**), and collagen type I (**E**). Nuclei were stained with DAPI. Each panel shows an image of one representative field from three independent experiments. Graph showing the results of the quantification of extracellular matrix synthesis of images from the respective panel (**B**,**D**,**F**). The image is displayed at × 400 original magnification and the red box indicates the region acquired for the quantification of extracellular matrix. Bars represent mean ± SD of three independent experiments. Statistical significance between groups was determined by ANOVA followed by Bonferroni's test. (++) $p < 0.01$ compared with respective medium-treated group.[33]

have been discussed. Presence of two polar hydroxyl groups at the two extreme ends of the molecule and a pentacyclic triterpenoid lipophilic hydrocarbon backbone make it an interesting amphiphile for the study of its self-assembly properties in different liquids. Studies along these lines are in progress and the results will be reported in due course.

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