Life Sciences 88 (2011) 285–293

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Minireview

Beneficial health effects of lupeol triterpene: A review of preclinical studies

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ARTICLE INFO

Article history:
Received 16 September 2010
Accepted 15 November 2010
Available online 28 November 2010

Keywords:
Diseases
Lupeol
Triterpene
Pharmacological
Clinical trial

ABSTRACT

Since ancient times, natural products have been used as remedies to treat human diseases. Lupeol, a phytosterol and triterpene, is widely found in edible fruits, and vegetables. Extensive research over the last three decades has revealed several important pharmacological activities of lupeol. Various in vitro and preclinical animal studies suggest that lupeol has a potential to act as an anti-inflammatory, anti-microbial, anti-protozoal, anti-proliferative, anti-invasive, anti-angiogenic and cholesterol lowering agent. Employing various in vitro and in vivo models, lupeol has also been tested for its therapeutic efficiency against conditions including wound healing, diabetes, cardiovascular disease, kidney disease, and arthritis. Lupeol has been found to be pharmacologically effective in treating various diseases under preclinical settings (in animal models) irrespective of varying routes of administration viz; topical, oral, intra-peritoneal and intravenous. It is noteworthy that lupeol has been reported to selectively target diseased and unhealthy human cells, while sparing normal and healthy cells. Published studies provide evidence that lupeol modulates the expression or activity of several molecules such as cytokines IL-2, IL4, IL5, ILβ, proteases, α-glucosidase, cFLIP, Bcl-2 and NFκB. This minireview discusses in detail the preclinical studies conducted with lupeol and provides an insight into its mechanisms of action.

Contents

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doi:10.1016/j.lfs.2010.11.020

Introduction

Triterpenes

Triterpenes (members of phytosterol family) are natural components of human diet (Moreau et al., 2002). Triterpenes are largely derived from vegetable oils, cereals, and fruits. Although human consumption of triterpenes is estimated to be approximately 250 mg per day in the Western world, it is noteworthy that in Mediterranean countries where most of the diets are olive oil based, the average intake of triterpenes consumed by a person could reach 400 mg/kg/day (Moreau et al., 2002). During the last decade, there has been an unprecedented escalation of interest in triterpenes. Although much of the research is focused on the cholesterol-lowering properties of triterpenes, there are enormous amounts of published data suggesting the utility of triterpenes for the treatment of a wide variety of disease conditions (Ovesná et al., 2004; Liby et al., 2007; Jang et al., 2009). These studies have culminated into several clinical studies, patents and a boom in the marketing of triterpene-based products (ranging from supplemental to cosmetics) frequently found in the shelves of pharmaceutical stores (Ovesná et al., 2004; Alander and Andersson, 2005; Liby et al., 2007; Jang et al., 2009). A recent clinical study comprising 2500 subjects taking different types of triterpenes with (>25 g/day) reported no adverse effects in humans (Moreau et al., 2002, and references therein). Lupeol is a triterpene that has gained the attention of medical professionals, researchers and pharmaceutical marketers for its wide ranging pharmacological activities.

Source of lupeol

Lupeol has been reported to be present in diverse species of the plant kingdom. Lupeol is found in edible vegetables and fruits such as white cabbage, pepper, cucumber, tomato, carrot, pea, bitter root, soy bean, ivy gourd, black tea, figs, strawberries red grapes, mulberries, date palm and guava. Lupeol is also found in abundance in medicinal plants such as, Shea butter plant, licorice, *Tamarindus indica*, *Celastrus paniculatus*, *Zanthoxylum riedelianum*, *Allanblackia monticola*, *Himatanthus sucuuba*, *Leptadenia hastata*, *Crataeva nurvala*, *Bombax ceiba*, *Sebastiania adenophora*, *Aegle marmelos* and *Emblica officinalis* (Erazo et al., 2008; Saleem, 2009 and references therein). The quantification studies have shown that lupeol is present in Olive fruit (3 μg/g), Mango fruit (1.80 μg/g pulp), Aloe leaf (280 μg/g dry leaf), Elm plant (800 μg/g bark), Japanese Pear (175 μg/g twig bark) and Ginseng oil (15.2 mg/100 g of oil).

Physical properties and biosynthesis of lupeol

The chemical formula of lupeol is $C_{30}H_{50}O$ and its structure is presented in Fig. 1a. The infra-red spectrum of lupeol shows the presence of a hydroxyl function and an olefinic moiety at a spectrum of 3235 and 1640 cm^{-1} and HPLC–MS studies of lupeol confirmed a parent ion peak at m/z 409 (M + H-18)(+) (Saleem, 2009). The melting point of lupeol is 215–216 °C and the structural analysis shows that it possesses the exact mass of 426.386166 (Saleem, 2009).

Lupeol biosynthesis in plants is orchestrated by the triterpene synthases and is considered as one of the most complex reactions occurring in nature (Phillips et al., 2006). The biosynthesis of lupeol is briefly presented in Fig. 1b. Lupeol biosynthesis occurs in the cytosol and occurs through the stepwise formation of the mevalonate (MVA), the isopentenyl pyrophosphate (IPP), and dimethylallyl pyrophosphate (DMAPP) and farnesyl pyrophosphate (FPP) from acetyl CoA. This reaction is catalyzed by farnesyl pyrophosphate synthase (FPS). Next, Squalene synthase (SQS) converts FPP into squalene. Squalene epoxidase (SQE) oxidizes squalene to 2, 3-oxidosqualene, which is then cyclized by lupeol synthases (LUS), to form the lupenyl cation. Finally, lupenyl cation is converted into lupeol by deprotonation of the 29-methyl group (Phillips et al., 2006).

An overview of therapeutic and preventive potential of lupeol

Lupeol is reported to exhibit a spectrum of pharmacological activities against various disease conditions (Fig. 2). These include conditions such as inflammation, arthritis, diabetes, cardiovascular ailments, renal disorder, hepatic toxicity, microbial infections and cancer (Al-Rehaily et al., 2001; Fernández et al., 2001a,b; Chaturvedi et al., 2008; Sudhahar et al., 2008a,b). The available literature suggests that lupeol is a non-toxic agent and does not cause any systemic toxicity in animals at doses ranging from 30 to 2000 mg/kg (Geetha et al., 1998; Al-Rehaily et al., 2001; Saleem et al., 2004, 2005, 2008; Bani et al., 2006; Preetha et al., 2006; Prasad et al., 2008; Sudhahar et al., 2008a,b; Murtaza et al., 2009). The doses of lupeol which have been tested in animal models (representing various human diseases) are summarized in Table 1. Lupeol has been shown to target molecules which are known to play a key role in the development of various human ailments. A summary of molecular targets of lupeol is presented in Fig. 3. The summary of preclinical studies conducted to test the pharmacological action of lupeol for various ailments is discussed as following:

Lupeol as an anti-arthritic agent

The potential of lupeol as an anti-arthritic agent has been tested in various in vitro and in vivo models of arthritis (Geetha et al., 1998; Geetha and Varalakshmi, 1999a,b, 2001; Bani et al., 2006; Azebaze et al., 2009; Blain et al., 2009). Arthritis is a systemic disease and causes alteration in lysosomal integrity and metabolism of connective tissue (Geetha and Varalakshmi, 1999a). Alteration of lysosomal integrity results in significantly increased destruction of connective tissue and cartilage by lysosomal enzymes (Geetha and Varalakshmi, 1999a). A study conducted by Geetha and Varalakshmi (1999a) established the role of lupeol in treating the arthritic condition in a rat model. In this study, arthritis was induced by the intradermal injection of 0.1 ml of Complete Freund's Adjuvant (CFA; 10 mg heat killed *Mycobacterium tuberculosis* in 1 ml paraffin oil) in the right hind paw. Arthritic rats treated with lupeol (50 mg/kg for 7 days) showed significantly reduced levels of lysosomal enzymes and increased collagen levels (Geetha and Varalakshmi, 1999a). Chronic inflammation, bone degradation and swelling at joints are the markers of human arthritis (Blain et al., 2009). Arthritic animals exhibit similar features as are observed in human disease (Geetha et al., 1998; Geetha and Varalakshmi, 1999a; Azebaze et al., 2009). As evident from several published reports, lupeol treatment decreases inflammation and paw swelling in animals suffering from arthritis (Geetha et al., 1998; Azebaze et al., 2009; Geetha and Varalakshmi, 1999a,b, 2001) lupeol treatment also improved the overall condition of arthritic animals by affording protection from pain and improving their mobility (Geetha et al., 1998; Azebaze et al., 2009; Geetha and Varalakshmi, 1999a,b, 2001). Arthritic animals exhibit decreased collagen levels and increased excretion of urinary hydroxyproline, hexosamine, hexuronic acid and glycosaminoglycans (Geetha and Varalakshmi, 2001). Lupeol treatment is reported to restore altered levels of hydroxyproline, hexosamine, hexuronic acid and glycosaminoglycans to the normal (Geetha and Varalakshmi, 1999a, 2001). Notably, when compared to well known anti-inflammatory agents indomethacin and aspirin (Geetha and Varalakshmi, 2001; Bani et al., 2006), lupeol does not exhibit any antinociceptive and ulcerogenic actions in arthritic animals, suggesting that the mechanism of action of lupeol is different from the non-steroidal anti-inflammatory drugs (Geetha and Varalakshmi, 2001; Bani et al., 2006; Preetha et al., 2006).

Lupeol as an anti-microbial agent

Lupeol has been found to exhibit antimicrobial activity against a wide range of commonly encountered microbes (Hernández-Pérez et al., 1994; Ajaiyeoba et al., 2003; Tanaka et al., 2004; Erazo et al., 2008; Shai et al., 2008; Abd-Alla et al., 2009; Ahmed et al., 2010). Lupeol is reported to inhibit the growth of a several types of bacteria, fungi and viral species (Hernández-Pérez et al., 1994; Ajaiyeoba et al., 2003; Tanaka et al., 2004;