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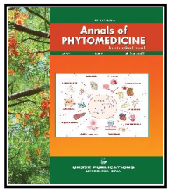

Review Article : Open Access

Therapeutic promise of Lupeol: A comprehensive review of its pharmacological potential

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Abstract

Lupeol, a pentacyclic triterpenoid found in a variety of fruits, vegetables, and medicinal plants, has received a lot of attention due to its diverse pharmacological properties and possible therapeutic applications. A thorough literature search was carried out to acquire important information on lupeol's pharmacological actions and mechanisms of lupeol. Key databases, such as Google scholar, Science Direct, Springer Link, PubMed and Scopus, were used to ensure an extensive review of available literature. The studies included were selected based on criteria requiring peer-reviewed articles, clinical studies, and experimental research published mainly, focusing on the pharmacological properties, bioactivity, and mechanisms of action of lupeol. Lupeol's diverse beneficial effects, which include anti-inflammatory, antioxidant, antimicrobial, anticancer, and hepatoprotective properties, are attributed to its ability to modulate key molecular pathways involved in inflammation, oxidative stress, cellular proliferation, and programmed cell death. Lupeol inhibits the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 by downregulating the NF-κB signaling pathway, leading to reduced inflammation and tissue damage. Its antioxidant properties, which include scavenging reactive oxygen species and increasing the activity of endogenous antioxidant enzymes, help it defend against diseases associated with oxidative stress, such as neurological and cardiovascular problems. Furthermore, lupeol's anticancer capabilities have been extensively studied, with results demonstrating its capacity to inhibit tumor growth, induce apoptosis, and prevent metastasis in a variety of cancer models. This review offers an in-depth analysis of current research on lupeol, highlighting its chemical structure, pharmacological properties, and the molecular mechanisms underlying its functions. By examining lupeol's multifaceted medicinal potential, this study explores its promise in developing innovative treatments for various chronic diseases. Additionally, the review identifies key areas for future investigation, outlining research opportunities to deepen the understanding of lupeol's clinical viability, optimize its therapeutic efficacy, and assess its safety across a broader spectrum of applications.

1. Introduction

Lupeol is a naturally existing pentacyclic triterpenoid found in a variety of plants, fruits, and vegetables, including mangoes (*Mangifera indica*), olives (*Olea europaea*), and strawberries (*Fragaria ananassa*), as well as medicinal plants like *Aloe vera* and *Andrographis paniculata* (Saleem, 2009; Gallo and Sarachine, 2009). Lupeol is structurally defined by its lupane structure, critical in determining its distinct biochemical properties and wide range of biological activities (Mahato and Kundu, 1994). Lupeol's pharmacological relevance has been established, with research demonstrating its powerful anti-inflammatory, antioxidant, antibacterial, anticancer, and hepatoprotective activities. These benefits are mostly due to lupeol's ability to influence various critical biochemical pathways, particularly those associated with inflammation, oxidative stress, and cell proliferation. Lupeol can reduce inflammation and tissue damage by inhibiting pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 *via* the NF-κB signaling pathway (Saleem, 2009). Lupeol, in addition to its anti-inflammatory properties, has high antioxidant activity. It scavenges reactive oxygen species and increases the activity of natural antioxidant enzymes including superoxide dismutase and catalase, protecting cells from oxidative stress. Lupeol's antioxidative potential positions it as a prospective therapeutic agent for the prevention and treatment of oxidative stress-related illnesses, such as neurological and cardiovascular diseases. Lupeol's potential as an anticancer drug has been thoroughly investigated, demonstrating its ability to inhibit tumor progression and spread in a variety of cancer types, including prostate, pancreatic, and skin malignancies (Nidhi Nigam *et al*., 2007). Lupeol's anticancer actions include apoptosis induction, cell growth limitation, and angiogenesis reduction. It has been discovered to affect important proteins in apoptosis, such as Bax and Bcl-2, as well as hinder the PI3K/Akt and Wnt/β-catenin signalling pathways, which are critical for cancer cell survival and propagation (Saleem, 2009). Furthermore, research has focused on lupeol's hepatoprotective properties, notably in cases of liver injury caused by poisons such as carbon tetrachloride

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and alcohol. Its preventive properties include reducing oxidative stress, modulating inflammatory reactions, and encouraging hepatocyte regeneration (Prasad *et al*., 2007). These studies highlight the potential of lupeol as a medicinal agent in the treatment of liver diseases.

Lupeol is emerging as a promising natural molecule for the development of innovative therapeutics for a wide range of disorders, owing to its comprehensive pharmacological properties and accumulating evidence supporting its therapeutic benefits. The objective of this review is to provide a thorough analysis of lupeol's pharmacological potential by exploring its anti-inflammatory, antioxidant, anticancer, and hepatoprotective properties, as well as the molecular pathways through which these effects are mediated. By highlighting the biochemical mechanisms and therapeutic benefits associated with lupeol, this review aims to underscore its value as a potent natural compound with the potential to address various chronic diseases and guide future research efforts toward enhancing its clinical application. Future studies should aim to understand the molecular mechanisms underlying its actions, improve its bioavailability, and conduct clinical trials to validate its efficacy in humans.

2. Sources of lupeol

Lupeol is a naturally occurring pentacyclic triterpenoid found in a variety of plants, including vegetables, fruits, and medicinal herbs, making it a molecule of great interest due to its diverse pharmacological characteristics (Wal *et al*., 2015). Lupeol, found in vegetables such as white cabbage, peppers, cucumbers, and tomatoes, adds to its anti-inflammatory and antioxidant properties. Fruits like olives, figs, mangoes, strawberries, and red grapes contain lupeol, which enhances their health-promoting features such as anticancer, anti-inflammatory, and cardioprotective benefits. Lupeol can also be found in medicinal plants such as American ginseng, shea butter plant, tamarind, *Allanblackia monticola*, *Himatanthus sucuuba*, *Celastrus paniculatus*, *Zanthoxylum riedelianum*, *Leptadenia hastata*, *Crataeva nurvala*, *Bombax ceiba*, and *Sebastiania adenophora* (Table 1). For ages, these plants have been utilized in traditional medicine in North America, Latin America, Japan, China, Africa, and the Caribbean to cure ailments such as inflammation, infections, and wounds (Wal *et al*., 2015). Lupeol's widespread distribution across these diverse sources demonstrates its significant pharmacological potential and important role in natural medicine, particularly in traditional healing practices across cultures.

Table 1: List of plants that contain lupeol (Wal *et al*., 2015)

Scientific name	Common name	Scientific name	Common name
Aloe vera	Aloe	*Hemidesmus indicus*	Indian saraparilla
Apocynum cannabinum	Bitterroot	*Juniperus communis*	Common juniper
Cajanus cajan	Congo-pea	*Lawsonia alba*	Henna
Calendula officinalis	Bull's eyes	*Lycopersicon esculentum*	Tomato
Camellia sinensis	Black tea	*Morus alba*	White mulberry
Capsicum annum	African pepper	*Olea Europa*	Olive
Cassia fistula	Indian laburnum	*Panax ginseng*	Asiatic ginseng
Coccinia grandis	Ivy gourd	*Phoenix dactylifera*	Date palm
Cucumis sativus	Cucumber	*Pisum sativum*	Common pea
Daucus carota	Carrot	*Psidium guajava*	Common guava
Ficus carica	Common fig	*Trilisa odoratissima*	Vanilla plant
Gentiana lutea	Bitterroot	*Vitis vinifera*	Common grape wine
Glycine max	Soya bean	*Vitellaria paradoxa*	Bambouk butter shea
Glycyrrhiza glabra	Common licorice	*Helianthus annus*	Annual sunflower

3. Chemical composition and spectroscopic analysis of lupeol

Lupeol's chemical formula is $C_{30}H_{50}O$, with a melting point of 215-216°C. According to this formula, lupeol has a molecular weight of 426.7174 g/mol and contains one hydrogen bond donor and one hydrogen bond acceptor. Lupeol's IR spectroscopy shows the presence of hydroxyl functional groups and olefinic moieties, exhibiting absorption bands at 3235 cm^{-1} and 1640 cm^{-1}, respectively (Sudharsan *et al*., 2005). Lupeol's ^{1}H-NMR spectra reveal seven methyl singlets and olefinic functional groups, indicating it is a major pentacyclic triterpenoid (Sudharsan *et al*., 2005). Lupeol alcohol's low-resolution (LR) IR spectra show strong broadband at 3384 cm^{-1} and medium-intensity bands at 1192 cm^{-1}, revealing O-H bond stretching vibrations in the hydroxyl group at 672 cm^{-1}. Out-of-plane C-H bending vibrations were observed at 826 cm^{-1}. The C=C bond stretching vibration is visible as a faint band at 1654 cm^{-1}. The bands at 2916 cm^{-1} and 1460 cm^{-1} show methyl group stretching and bending vibrations, respectively (Emaikwu *et al*., 2020). The formula suggests six degrees of unsaturation, which corresponds to the reported olefinic activity (Saleem, 2009). The structure of lupeol is depicted in Figure 1.

4. Biosynthetic pathway of lupeol in plants

Lupeol production in plants is a complicated process regulated by triterpene synthases (Phillips *et al*., 2006). Lupeol is first produced in the cytosol as mevalonate (MVA), which is subsequently

transformed into isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP). Farnesyl pyrophosphate (FPP) is formed from these intermediates by the activity of farnesyl pyrophosphate synthase. Then, squalene synthase (SQS) converts FPP into squalene. Squalene is then converted to 2,3-oxidosqualene by squalene epoxidase (SQE). Lupeol synthase (LUS) cyclizes 2,3-oxidosqualene to form the lupenyl cation, which is then transformed into lupeol by deprotonating the 29-methyl group (Phillips *et al*., 2006).

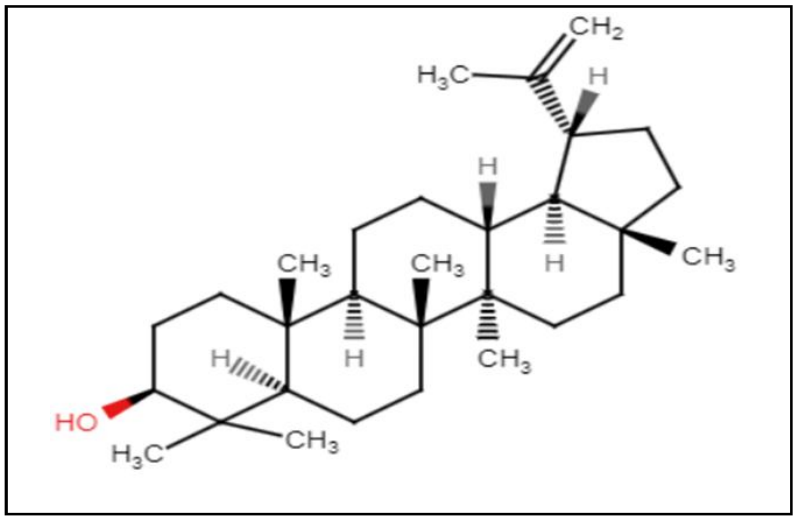

Figure 1: Structure of lupeol.

5. Biologically derivatives of lupeol

The chemical structure of lupeol derivatives contains many functional groups that amplify their therapeutic utility even more. Esters of these derivatives can be prepared using various acid anhydrides or acids esterification of lupeol under mild conditions in the presence of a condensation agent; for example, DMAP that is stronger than pyridine as Lewis and Brønsted base (Li *et al*., 2013; Yu *et al*., 2006). Some lupeol derivatives have been isolated from different natural sources and are documented in the literature. This structural variation often leads to the production of lupeol derivatives with higher bioavailability and potency. The isolated and synthesized derivatives are active in many disease models. For instance, a few lupeol derivatives have been shown to possess cytotoxic and anticancer properties in preclinical investigations. Such compounds include the 3-O-acyl derivatives of lupeol (Bednarczyk-Cwynar *et al*., 2016), lupeol-3β-sulfate, calendula oil-3β-mono sulfate, heliantriol B2, and 3β-aminolupane (Castro *et al*., 2019), lupenone hydrazine, 3, 4-dimethoxy cinnamic acid, and 3, 4, 5-trimethoxycinnamic acid (Li and Xiao, 2018), and a pyrimidine-2(5H)-thione derivative (Saini *et al*., 2019). Certain lupeol derivatives also exhibit immunomodulatory activity by acting on adenyl cyclase 5 (Shahlaei *et al*., 2013). Lupeol linoleate exerted several biological activities such as those inhibiting hypercholesterolemia (Sudhahar *et al*., 2007), hepatotoxicity (Sunitha *et al*., 2001), metabolic disorders caused by hypercholesterolemia (Sudhahar *et al*., 2006) and hyperoxaluria (Sudhahar *et al*., 2008b). Furthermore, lupeol acetate and 3-(p-chlorocinnamoyl) lupeol have well-established activities as acetylcholinesterase inhibitors, antiestrogenic, and anti-inflammatory activities (Ben Nejma *et al*., 2017; Mahapatra *et al*., 2015).

6. Pharmacokinetics and bioavailability

Lupeol, a pentacyclic triterpene, exhibits various pharmacological activities, including anti-inflammatory, anticancer, and antioxidant effects. However, its therapeutic potential is limited by challenges in pharmacokinetics and bioavailability, which play crucial roles in determining its efficacy and clinical relevance. Due to its low water solubility, lupeol faces difficulties in dissolving within gastrointestinal fluids, which impedes oral absorption and restricts uptake through the intestinal epithelium (Gallo and Sarachine, 2009). Although, lupeol's lipophilicity facilitates passive diffusion across cell membranes, its overall absorption and bioavailability remain low (Gallo and Sarachine, 2009). To overcome these limitations, researchers have investigated advanced drug delivery systems and chemical modifications to enhance lupeol's solubility and absorption. Lipid-based formulations, such as nanoemulsions and solid lipid nanoparticles (SLNs), have shown promising results in improving lupeol's solubility and bioavailability (Siddique *et al.,* 2020). Other advanced drug delivery systems, including liposomes, polymeric nanoparticles, and micelles, could also be explored to enhance the stability and targeted delivery of lupeol. Additionally, chemical modifications to the lupeol molecule such as the addition of hydrophilic groups or conjugation with biocompatible polymers might further improve its solubility and pharmacokinetic profile, ultimately supporting its potential in clinical applications.Lupeol's high lipophilicity permits it to accumulate in lipid-rich organs such as the liver, adipose tissue, and perhaps the central nervous system (CNS), providing both therapeutic benefits and potential safety concerns with long-term use (Wozniak *et al*., 2015). Lupeol's high binding to plasma proteins, especially albumin, can limit its therapeutic effectiveness but also serve as a reservoir for slow release (Ríos *et al*., 2012). Lupeol's lipophilicity suggests that it may be able to pass the blood-brain barrier (BBB), although, actual CNS penetration is likely restricted. According to studies, new formulations like as nanoparticles may allow for more effective CNS administration.

Lupeol is extensively metabolized in the liver, with Phase I (oxidation by cytochrome P450 enzymes) and Phase II (conjugation with glucuronic acid, sulfate, or glutathione) converting it into more hydrophilic metabolites for easy excretion (Wozniak *et al*., 2015).

These metabolites' biological activity varies; some may retain therapeutic capabilities, while others may be less active or inactive, potentially decreasing lupeol's overall therapeutic efficacy (Siddique *et al*., 2020). Lupeol and its metabolites are mostly eliminated through the biliary system, while some are also excreted through the kidney. Enterohepatic recirculation, in which conjugated metabolites are reabsorbed after being discharged into the bile, can prolong lupeol's half-life, however, the importance of this mechanism in humans is unknown (Wozniak *et al*., 2015).

Lupeol's oral bioavailability is significantly low, often as low as 1%, due to its poor solubility and significant first-pass metabolism, limiting its potential for clinical use when consumed orally (Gallo and Sarachine, 2009). To improve this, many formulation approaches have been investigated. Nanoparticle systems have improved lupeol solubility, stability, and bioavailability, resulting in higher plasma levels and better therapeutic effects (Siddique *et al*., 2020). Lipid-based delivery methods, such as liposomes and solid lipid nanoparticles, have also improved lupeol bioavailability by boosting absorption and decreasing first-pass metabolism (Sharma and Kumar, 2018). Co-administration with bioavailability enhancers such as piperine, which inhibits metabolic enzymes and increases intestinal absorption, has also been studied as an approach for increasing lupeol bioavailability (Siddique *et al*., 2020). Furthermore, other administration methods, such as intravenous or intramuscular injections and transdermal patches, have been investigated to avoid the gastrointestinal system and first-pass metabolism, potentially resulting in increased bioavailability (Sharma and Kumar, 2018).

To maximize lupeol's therapeutic potential, it is critical to continue research into improving its pharmacokinetic profile using novel formulation technologies, particularly those involving nanotechnology. Furthermore, while preclinical research provides significant information about lupeol's pharmacokinetics, clinical trials are required to validate these findings in humans. These studies should investigate lupeol's absorption, distribution, metabolism, and excretion in various populations to effectively recommend its therapeutic use.

7. Pharmacological properties of lupeol

7.1 Anti-inflammatory activity

Exaggerated inflammation is caused by the disarray of immune responses, resulting in the overproduction of pro-inflammatory cytokines and chemokines that maintain acute or chronic disease states (Zhong and Shi, 2019). IL-1β, TNF-α, and iNOS level elevation in LPS-induced inflammation in mice were reduced with lupeol along with the inhibition of microglia and astrocyte activation through inhibition of c-JNK and P38 MAPK phosphorylation (Badshah *et al*., 2016). LPS-induced IL-1 expression in immune cells was down-regulated by lupeol along with mRNAs of iNOS, NLRP3, and TNF and up-regulated mRNA of glial-derived neurotrophic factor, nerve growth factor as well as enhancing the shh-Gli signaling pathway (Oliveira-Junior *et al*., 2019). Intraperitoneal applications of lupeol reduced mRNA levels of pro-inflammatory cytokines IL-6, IL-1β and TNF-α, and increased IL-10 in rats with cerebral artery ischemia (Zhang *et al*., 2020). Lupeol reduced immune cell invasion in diabetic rats in inflamed tissue (Beserra *et al*., 2019). Lupeol further decreased the expression of NF-κB and inflammasome mRNA as well as decreased D-ular-inflammatory cytokine secretion in NLRP3, ATP, and LPS-treated macrophages (Buakaew *et al*., 2021). This was supported by another study which indicated that IL-6 and Il-1β cytokines levels and inflammatory cell invasions in the mice and zebrafish models of LPS/D-GalN-induced acute liver injury were significantly less in luperol-treated fish compared to untreated ones (Huang *et al*., 2021). Levy *et al*., (2020) discovered that injecting rats with 100 mg/kg of lupeol orally presented anti-inflammatory properties on cotton pellet-induced granuloma and carrageenan-induced rat paw oedema in part by suppressing MPO activity impact, PGE2, and various cytokines pro-inflammatory. In contrast to IL-10 stimulation, increased IL-12 was noted upon treatment of M(INF-γ/LPS) with lupeol at both 25 and 50 μM concentrations (Saha *et al*., 2020). When macrophages were pretreated with lupeol at 25 outcomes targeting IL-10 and inhibiting IL-12 before reducing IL-1b with a dosage of 25 and 50 μM (Saha *et al*., 2020). So far, no toxic side effects have been observed, indicating the potential therapeutic role of lupeol in the various inflammatory models: Carrageenan-induced rat paw oedema (Nguemfo *et al*., 2009), TPA-induced mouse ear oedema and A23187 induced mouse peritoneal macrophages (Fernández *et al*., 2001).

7.2 Antidiabetic and antihyperlipidemic activity

Diabetes mellitus (DM) is a metabolic condition marked by elevated blood glucose levels caused by inadequate insulin release from pancreatic B cells and insulin resistance (Hannan *et al*., 2020). Diabetes pathogenesis is closely related to oxidative stress, inflammation, and hyperlipidemia (Hannan *et al*., 2021). Several animal investigations have shown that lupeol has an antidiabetic effect. Lupeol has been shown to reduce oxidative stress in both alloxan-induced type 1 diabetes rats (Hashmi *et al*., 2020) and high-fat diet-induced type 2 diabetic rats (Padmapriya *et al*., 2019). Diabetes is also associated with the down-regulation of insulin signaling components, such as the insulin receptor (IR) and the glucose transporter type 4 (GLUT4), resulting in blood glucose level abnormalities. Lupeol was found to effectively regulate glucose homeostasis in hyperglycemia and hyperinsulinemia by reducing IR and GLUT4 levels (Pushpanjali *et al*., 2019).

Hyperlipidemia is also a well-known risk factor for the development and progression of diabetes. Lipid levels increased in diabetic rats fed a high-fat, sucrose-containing diet. A high-fat diet supplies the components for endogenous lipid production in the liver, which leads to elevated lipid levels. Lupeol therapy significantly reduced diabetic rats' lipid profiles (Kottireddy *et al*., 2019). Lupeol's antidiabetic potential has been proven by recent findings, which include the reversal of abnormalities in oxidative stress, lipid profile, and glycogen concentration, as well as the different expressions of IR and GLUT4 in the gracilis muscle of type 2 diabetes. Insulin resistance is a major cause of type 2 diabetes (DeFronzo and Tripathy, 2009). The IRS-2 protein expression was significantly lowered in diabetic rats. According to several pieces of evidence, lupeol may influence the liver by modulating the expression and phosphorylation of IRS-2, allowing the cell to provide therapeutic advantages against T2DM (Deepika *et al*., 2019).

7.3 Inflammatory bowel disease

IBD is the most common chronic bowel ailment that affects the lower gastrointestinal tract, and it is distinguished by ulcerative colitis and Crohn's disease. The inflammation associated with IBD is caused by an imbalance between classically activated (M1) and alternatively activated (M2) macrophages. Lupeol is a pentacyclic triterpene that acts as a potent natural anti-inflammatory agent and may be used to

treat intestinal disorders without adverse effects. Some recent investigations have revealed that lupeol can decrease pro-inflammatory cytokine release while also influencing macrophage polarization. As a result, it has the potential to significantly improve the management of IBD symptoms (Zhu *et al*., 2016). Lupeol may suppress LPS-induced IκBα phosphorylation and degradation, as well as NF-κB DNA binding activity. Lupeol administered orally has been proven to considerably reduce the severity of both acute and chronic murine colitis models. The medication suppresses the NF-κB pathway in IECs and macrophages, improving experimental colitis and making it a promising therapeutic option for IBD (Lee *et al*., 2016).

Recently, several lupeol derivatives were synthesized and tested for anti-inflammatory properties. These include derivatives such as indoles, pyrazines, oximes, and esters. Lupeol has been shown to decrease LPS-induced NO generation in RAW 264.7 and J774A.1 cells, making it an effective NO inhibitor (Bhandari *et al*., 2014). Because of its limited water solubility, scientists developed alternative forms for its application using nanotechnology to boost solubility. Some strategies include emulsification/solvent evaporation and size distribution (Ramírez *et al*., 2015). Lupeol is also used as a nutraceutical that does not harm the wild population (Deyrup *et al*., 2014).

Lupeol and lupeol linoleate are two pentacyclic triterpenes that have been studied for their anti-inflammatory, antinociceptive, antipyretic, and ulcer-protective effects (Geetha *et al*., 2001). *Alhagi maurorum* is a good source of lupeol as it is available throughout the year and is cheap (Lagharia *et al*., 2011). Another source includes *Adenophora triphylla* var. japonica is found to contain lupeol, lupenone, and taraxerol, which enhance mucin production and affect the expression of genes in airway epithelial cells, consistent with its traditional use to treat inflammation of the lungs (Yoon *et al*., 2015).

7.4 Cardioprotective and antidyslipidemic effects of lupeol

Lupeol has been shown to be cardioprotective in cyclophosphamide-treated animals. Treatment with 200 mg/kg for 10 days significantly lowered ATPase activity as well as urea, uric acid, and creatinine levels in the treated animals' blood and urine (Sudharsan *et al*., 2005, Sudharsan *et al*., 2005). The administration of 50 mg/kg for 10 days was observed to protect animals from cyclophosphamide-induced cardiotoxicity (Sudhahar *et al*., 2007).

Lupeol has been proven by multiple researchers to reduce hypercholesterolemia, a condition known to severely affect cardiovascular function. Lupeol (50 mg/kg) was able to normalize lysosomal hydrolases and return lipoprotein and lipid levels to normal for the first time in a rat model of hypercholesterolemia caused by air intake in agricultural animals. In addition, lupeol demonstrated antidyslipidemic benefits in a hamster dyslipidemia model. Triglyceride and cholesterol levels in hamsters were determined after an intraperitoneal injection of 100 mg/kg streptozotocin. It has been reported that lupeol at a dose of 50 mg/kg can be utilized to counteract these effects in hamsters with dyslipidemia (Siddique and Saleem, 2011).

7.5 Anticancer activity

Even though antineoplastic drugs are becoming better and better, cancer is still a major global health problem. The development of resistance to conventional drugs encourages further research efforts to find alternative anticancer drugs. Recent and emerging studies of phytochemicals, of which lupeol is one such compound, have given hope in the field because of their anticancer properties (Rahman *et al*., 2021a). There is an increased interest in lupeol because it has been touted to be a prospective anticarcinogen against various cancers that include bones, liver, lung, colon, rectum, and bladder (Liu *et al*., 2021). The mechanisms through which it could affect anticancer effects include induction of apoptosis, prevention of cancer cell migration, invasion, reduction of cell proliferation, and increased sensitivity of cancer cells to chemotherapy and radiotherapy (Liu *et al*., 2021). Lupeol causes apoptosis in cancer cells and also inhibits metastasis (Shen *et al*., 2019). Lupeol inhibited osteosarcoma cell viability and invasion and mediated apoptosis by upregulation of miR-212-3p targeting and thereby inhibiting HMGA2 in MNNG/HOS and MG-63 osteosarcoma cell lines, thereby suppressing the development of osteosarcoma (Zhong *et al*., 2020).

Lupeol has also been reported to be beneficial in the treatment of liver cancer. Lupeol inhibits cell growth and induces death in hepatocarcinoma cell lines (SMMC7721 and HepG2) at 50 μM by downregulating Bcl-2 and upregulating BAX, caspase-3, caspase-8, and caspase-9 (Shen *et al*., 2019). It also affected the MAPK pathway, specifically the activation of ERK1/2, P38, and JNK (Shen *et al*., 2019). Lupeol inhibited metastasis in human liver cancer cell lines, including HepG2 and SK-HEP-1, by decreasing N-cadherin, α-SMA, vimentin, and MMP-9 levels while increasing E-cadherin expression (Liu *et al*., 2020).

Lupeol has shown anticancer efficacy against breast cancer (MCF-7 cell line) by reducing cell viability and increasing apoptosis (Pitchai *et al*., 2014). Lupeol prevented N-butyl-N-(4-hydroxybutyl) nitrosamine-induced bladder carcinogenesis in male albino wistar mice by limiting tumour growth and proliferation (Prabhu *et al*., 2016a, 2016b). Siddique *et al.* (2011) reported further anticancer potential in prostate cancer, as did Liu *et al.* (2016) in gallbladder cancer.

According to studies on colorectal cancer, lupeol reduces cell viability while increasing apoptosis. Lupeol inhibited carcinogenesis in DMBA-induced golden Syrian hamsters by acting as an antioxidant and regulating detoxification (Palanimuthu *et al*., 2012). Furthermore, it demonstrated the modification of apoptotic markers in DMBA-induced oral cancer in the aforementioned hamsters (Manoharan *et al*., 2012). Lupeol inhibited the EGFR signalling pathway in oral squamous cell carcinoma by reducing tumour cell proliferation and death. Lupeol triggered S-phase arrest and mitochondria-mediated apoptosis, reducing the proliferation of cervical cancer cells and HeLa (Prasad *et al*., 2018).

Lupeol has been shown in NSCLC cell lines (H1299, A549, H460, H292) and WI38 lung fibroblasts to reduce EGFR/STAT3 activity and induce death. Lupeol reduced angiogenesis in mouse melanoma models (Bhattacharyya *et al*., 2019). Lupeol injections, both local and systemic, limit the growth of B16 2F2 melanoma cells in melanoma-bearing animals by arresting the cell cycle.

7.6 Antiprotozoal activity

Lupeol is effective against a variety of pathogenic protozoa, including malarial, leishmanial, and trypanosomal protozoa. The growth of the malaria parasite *Plasmodium falciparum* was suppressed. Lupeol

prevented *Plasmodium falciparum* merozoites from entering red blood cells. The IC_{50} value was 1.5 µg/ml (Suksamrarn *et al*., 2003; Ziegler *et al*., 2004; Ziegler *et al*., 2006). Lupeol is thus believed to have anticancer and antiplasmodial properties. Structural activity relationship studies between lupeol and *Plasmodium falciparum* show that lupeol insertion into the erythrocyte membrane is most likely related to an alteration of the shape of the host cell's membrane, with no mechanism for direct toxic effects on the parasite's organelles or metabolic pathways (Rodrigues and de Souza, 2008).

7.7 Hepatoprotective effects of lupeol

Lupeol has been shown to have promising hepatoprotective effects. Lupeol has recently been shown to be effective in protecting against aflatoxin B1, a strong hepatotoxic agent, in an *in vivo* administration manner. Interestingly, lupeol had a far stronger hepatoprotective impact than silymarin, a well-known natural substance with recognized hepatoprotective effects (Al Rehaily *et al*., 2001). In experimental animals, lupeol and lupeol-enriched mango extract were also found to prevent carcinogenic events produced by 7,12-dimethylbenzo(a)anthracene (DMBA) (Prasad *et al*., 2007). Several trials have been undertaken to establish lupeol's potential for improving liver function and preventing liver disease. In one study, treating rats with hypercholesterolemia with lupeol (50 mg/kg) for 15 days improved liver function and increased cholesterol clearance.

Surprisingly, lupeol significantly increased the amounts of vitamin C and E in these mice. Furthermore, it functioned remarkably well in restoring normal liver function by blocking or activating enzymes involved in lipid metabolism. A second study found that lupeol, at an oral dose of 150 mg/kg/day, could recover metal-induced hepatotoxicity in a rat model, which supported the compound's potential as a hepatoprotective (Siddique *et al*., 2011).

7.8 Nephroprotective activity

The global prevalence of various kidney disorders, including chronic kidney disease, is increasing at a concerning pace (Uddin *et al*., 2021b). The major risk factors for CVDs are hyperlipidemia, hypertension, and obesity, which in turn cause the development of renal disorders (Uddin *et al*., 2021a). Scientific research has shown that lupeol is an efficient drug for reducing kidney problems and risk factors. Lupeol post-treatment restored renal biochemical profiles, relieving diabetic nephropathy in rats fed a high-fat diet and sucrose-induced type 2 diabetes (Dharsan *et al*., 2019). In addition, Sinha *et al.* demonstrated lupeol's potential against renal cell carcinoma by modulating mitochondrial dynamics in a human RCC cell line (Sinha *et al*., 2019).

7.9 Antioxidant activity

Oxidative stress is defined as the imbalance between the different levels of prooxidants and the antioxidant defences within living organisms, linked to the pathogenesis of many diseases (Hannan *et al*., 2020a). Antioxidants from the diet mitigate oxidative stress through the neutralization of ROS or an improvement in the body's antioxidant defence mechanisms (Hannan *et al*., 2020b). Lupeol and its derivatives' antioxidant effects have been reported in the literature for more than two decades. Lupeol, drastically elevated the expression of SOD-2 and HO-1 antioxidant enzymes in STZ-induced hyperglycaemic mice while also improving wound healing (Beserra *et al*., 2019). Lupeol treatment also increased pancreatic antioxidant levels such as GSH and ascorbic acid, as well as the activities of SOD, CAT, GST, and GPx, while increasing lipid peroxidation and NO levels in STZ-induced diabetic mice, lowering oxidative stress and preventing protein oxidation damage (Gupta *et al*., 2012). Lupeol at 10 mg/kg reduced lipid peroxidation in the cortex, cerebellum, and liver of male Sprague-Dawley mice treated with $STZ/AlCl_3$, boosting levels of CAT, SOD only in the cortex, and GSH in the cortex and cerebellum. Lupeol supplementation at a dose of 35 mg/kg increased antioxidant activity (GSH, SOD, and CAT), decreased MDA level, and reduced ischemia-induced kidney injury in STZ-induced hyperglycaemic rats (Tiwari *et al*., 2019). Lupeol isolated from *Ficus pseudopalma* may scavenge NO, hydroxyl, and superoxide radicals (Santiago and Mayor, 2014). In triton-induced hyperlipidaemic mice, chalcone derivatives of lupeol increased antioxidant activity by inhibiting superoxide anions, hydroxyl radicals, and lipid peroxidation (Srivastava *et al*., 2013).

7.10 Neuroprotective activity

Degenerative brain illnesses and ischemic stroke are common types of dementia in the elderly, and oxidative stress and neuroinflammation play important roles in their development (Zhong *et al*., 2018). Natural substances, like as lupeol, have been shown to have neuroprotective properties. This effect was accomplished by blocking the P38-MAPK, JNK, and mitochondrial apoptotic pathways. Lupeol also increased the levels of anti-inflammatory and neurotrophic factors in cell culture models (Badshah *et al*., 2016).

Its antioxidant and anti-inflammatory properties have been shown to enhance memory and cognitive impairments, particularly in Alzheimer's disease models, by activating the Nrf-2/HO-1 pathway and reducing Aβ levels and beta-secretase-1 (BACE-1) expression (Ahmad *et al*., 2020). Lupeol also showed promise against ischemic brain damage in models employing middle cerebral artery closure due to improvements in neurological function, cerebral blood flow, infarct size reduction, and neuronal loss. These effects are connected with the activation of the PI3K/Akt and Nrf2 pathways, as well as the suppression of cell death signalling (Zhang *et al*., 2020).

7.11 Antiarthritic agent

Lupeol has been studied as an antiarthritic drug using various types of *in vitro* and *in vivo* arthritis models. Arthritis is a systemic illness that primarily affects lysosomal membrane integrity and connective tissue metabolism (Geetha and Varalakshmi, 1999a). It significantly impairs lysosomal integrity and accelerates cartilage and connective tissue deterioration *via* lysosomal enzymes (Geetha and Varalakshmi, 1999a). Geetha and Varalakshmi (1999a) found lupeol to be an effective medication for treating arthritis in rats. In this experiment, arthritis was induced by injecting 0.1 ml of complete freund's adjuvant (CFA; 10 mg of heat-killed *Mycobacterium tuberculosis* in 1 ml of paraffin oil) into the right hind paw. Following a 7-day therapy with lupeol at a dose of 50 mg/kg, lysosomal enzyme levels in arthritis-affected rats were significantly reduced, whereas collagen levels increased. Chronic inflammation, bone deterioration, and joint oedema are common hallmarks of human arthritis (Blain *et al*., 2009). Arthritic animals demonstrated symptoms similar to those seen in humans (Geetha *et al*., 1998; Geetha and Varalakshmi, 1999a; Azebaze *et al*., 2009). Studies showed that the lupeol treatment decreases inflammation and paw edema in arthritic animals (Geetha *et al*., 1998; Azebaze *et al*., 2009; Geetha and Varalakshmi, 1999 a, b,

2001). Lupeol further enhanced the general condition of arthritic animals by giving symptomatic relief from pain and improving their mobility (Geetha *et al*., 1998; Azebaze *et al*., 2009; Geetha and Varalakshmi, 1999 a; Geetha and Varalakshmi, 1999 b, Geetha and Varalakshmi, 2001). Arthritic animals have lower collagen levels and higher urinary excretion of hydroxyproline, hexosamine, hexuronic acid, and glycosaminoglycans (Geetha and Varalakshmi, 2001). Lupeol treatment was shown to normalize the altered levels of hydroxyproline, hexosamine, hexuronic acid, and glycosaminoglycans (Geetha and Varalakshmi, 1999a, Geetha and Varalakshmi, 2001). Interestingly, unlike the common anti-inflammatory drugs indomethacin and aspirin, lupeol does not manifest antinociceptive and ulcerogenic activities in arthritic animals and suggests that this compound may have a different mechanism of action as compared to the other non-steroidal anti-inflammatory drugs (Geetha and Varalakshmi, 2001; Bani *et al*., 2006; Preetha *et al*., 2006).

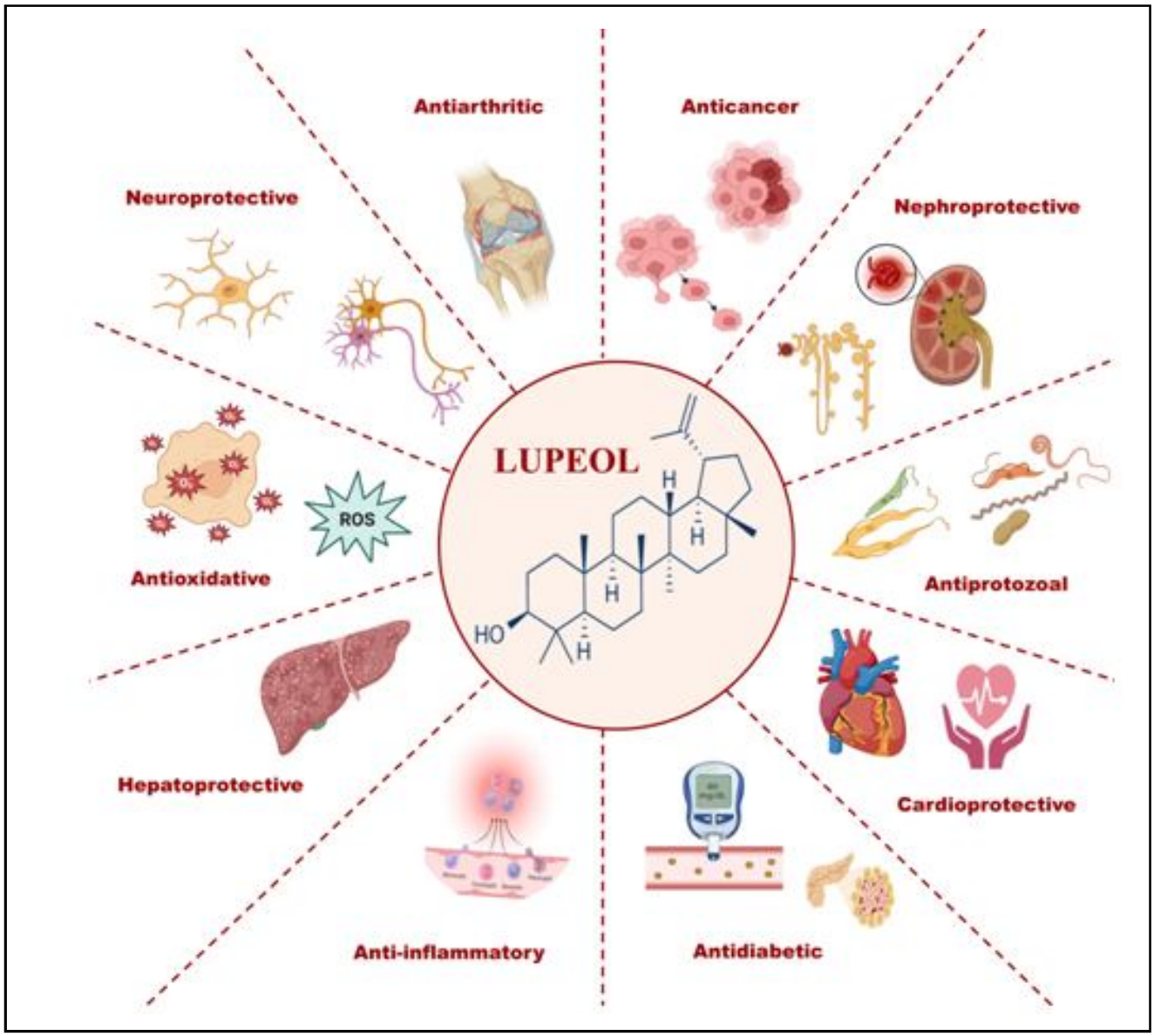

Figure 2: Pharmacological properties of lupeol.

8. Enhancing lupeol's bioefficacy: Solutions to pharmacokinetic and pharmacodynamic issues

Lupeol is a promising derivative of natural compounds; however, it has many pharmacokinetic and pharmacodynamic drawbacks that make its clinical efficacy very low. These are mainly due to the drug's poor water solubility and low bioavailability, which prevent its absorption and further distribution in the body. Lupeol is also metabolically unstable since it degrades rapidly in the liver to produce a short half-life and rapid clearance from the system. This instability significantly decreases the amount of the active compound that eventually reaches the target tissues, especially in cases of neurological disorders where they must cross the blood-brain barrier (BBB). Moreover, low cellular permeability and lack of specificity of lupeol for targeted delivery provide an additional challenge since it could distribute non-specifically in the body, therefore lowering

its efficacy and increasing its potential off-target effects. To overcome these challenges, several strategies for the enhancement of the pharmacokinetics and pharmacodynamics of lupeol have been proposed. Pharmacokinetic and pharmacodynamics enhancement of lupeol has been carried out through various delivery systems based on nanotechnologies, such as nanoparticles, liposomes, and micelles that encapsulate the lupeol molecule, thus improving its solubility and stability, and bioavailability with targeted delivery and controlled release. Other promising approaches include chemical modification and prodrug development to increase its solubility and stability, and the cellular membrane and BBB permeability. Encapsulation using biopolymers such as chitosan or PLGA could shield it from rapid metabolism, broaden the therapeutic window, and improve controlled release. More importantly, it may be absorbed further in combination with permeability enhancers, such as surfactants or cell-penetrating peptides, especially in tissues such as the brain that are inaccessible to drugs. A combination therapy of synergistic compounds or bioavailability enhancers that go along with lupeol also presents some promising ways by which its therapeutic effects can be improved. Through such means, the pharmacological potential of lupeol might be significantly increased, making it, therefore, an even better therapeutic agent.

9. Clinical trials

Lupeol, a pentacyclic triterpene compound, has been shown in preclinical research to have an impressive range of pharmacological effects, including anti-inflammatory (Geetha and Varalakshmi, 2001), antioxidant (Sudhahar *et al*., 2007a), anticancer (Saleem *et al*., 2005), hepatoprotective (Vasconcelos *et al*., 2008), and cardioprotective properties (Sudhahar *et al*., 2007b). These promising results show lupeol's potential for treating various kinds of health issues; nevertheless, more research in human populations is required to determine its clinical effectiveness. To use these preclinical findings in clinical applications, a series of carefully organized clinical trials is proposed.

The first study examines the anti-inflammatory properties of lupeol in people with osteoarthritis. This randomized, double-blind, placebo-controlled Phase II research will determine if lupeol can successfully reduce pain and improve joint function in people aged 45 to 75 years with confirmed knee osteoarthritis. Participants will be given either a lupeol capsule or a placebo over a 24-week period, with outcomes determined by changes in pain, physical function, and quality of life (Clinical Trials.gov, 2015).The second proposed trial, also a Phase II study, seeks to evaluate lupeol's potential in prostate cancer treatment. The trial will see if Lupeol can affect prostate-specific antigen (PSA) levels in individuals who have a biochemical recurrence of prostate cancer after initial treatment. Participants in this double-blind, placebo-controlled research will be given either lupeol or a placebo, with significant goals including PSA level changes, time to PSA progression, and safety over 12 months (ClinicalTrials.gov, 2013). A third trial would examine lupeol's potential liver-protective effects in patients with non-alcoholic fatty liver disease (NAFLD). This randomized, double-blind, placebo-controlled Phase II study will explore whether Lupeol can improve liver function and slow disease progression in adults with biopsy-confirmed NAFLD. Key outcomes include changes in liver enzymes, liver fat content (*via* imaging), and liver histology, with a treatment period of 24 weeks (Clinical Trials. gov, 2018). Finally, a fourth trial will look into lupeol's cardioprotective potential in people with metabolic diseases, notably those with type 2 diabetes and an extra cardiovascular risk factor. Over the course of 24 weeks, this randomized, double-blind, placebo-controlled research will look at how lupeol affects glycaemic management, lipid levels, and cardiovascular risk factors. HbA1c, lipid profile, endothelial function, and other cardiovascular indicators are used to assess lupeol's capacity to reduce cardiovascular risks in this at-risk population (Jäger *et al*., 2009). These proposed trials are based on current preclinical data and seek to further study lupeol's therapeutic potential across a variety of illnesses. These trials use randomized, double-blind, placebo-controlled methods to give solid evidence on lupeol's safety, efficacy, and dosage requirements for human usage. If successful, these studies could make lupeol a feasible therapy option for chronic inflammatory, oncological, liver-related, and metabolic illnesses.

10. Conclusion and future perspective

Lupeol, a triterpenoid molecule found abundantly in fruits, vegetables, and medicinal plants, has promising therapeutic advantages, perhaps making it a "mysterious drug" for future pharmaceutical applications. Its pharmacological profile is comprehensive, with anti-inflammatory, anticancer, antioxidant, hepatoprotective, and antibacterial properties, highlighting its adaptability in controlling various health issues. Importantly, lupeol's anticancer properties, particularly its selective toxicity against cancer cells while causing minimal harm to normal cells, make it a promising choice for cancer treatment. Furthermore, its antioxidant and anti-inflammatory properties make it potentially useful in the treatment of chronic inflammatory illnesses and oxidative stress-induced cellular damage. Despite these benefits, there are several obstacles to using lupeol in clinical trials, such as limited bioavailability and quick metabolism. Newer drug delivery strategies, such as nanotechnology and encapsulation approaches, provide to address these problems by improving the pharmacokinetic profile and efficacy. More research and well-designed clinical studies are required to better understand its therapeutic potential, appropriate dosage, and long-term effects on people. Continued research into the characteristics of lupeol may reveal other mechanisms of action, leading to new therapeutic advances and combination therapies. Thus, lupeol's numerous biological activities make it a highly useful strategy for the search for innovative, safe, and efficient therapies for several disorders, crossing traditional and modern medication.

Lupeol is a promising natural compound with wide spectra of pharmacological activities such as anti-inflammatory and antioxidant, anticancer, and hepatoprotective effects. However, low water solubility, limited bioavailability, and other pharmaceutical drawbacks decrease the oral efficacy of its therapeutic application. Such an inadequate understanding of the pharmacokinetics of lupeol, including metabolism, biodistribution, and elimination, still prevents predictions about in vivo behavior and limits its clinical potential. In addition, despite promising benefits in its preclinical studies both in vitro and animal models, its efficacy and safety in human subjects have yet to be confirmed by robust clinical trials. Methods and dosages vary between studies, making it difficult to carry out a meaningful comparison and standardization across different studies. Future work could address these issues by integrating more advanced drug delivery systems such as liposomes, nanoparticles, and micelles that would improve the solubility and bioavailability of lupeol. Other modifications, such as prodrug formation or introduction of hydrophilic groups, may also improve its pharmacokinetic

properties. Clinical studies would be necessary to validate the efficacy and safety of lupeol in humans, determine optimal dosing needs, and achieve regulatory approval. More research and development may eventually propel lupeol as a promising natural therapeutic agent in handling chronic diseases.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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