The Pharmacological Potential of Lupeol and Derivatives: A Corroborative Analysis

By

Rodoshi Mahfuz Sowa

18146086

A thesis submitted to the department of Pharmacy in partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy (Hons.)

Department of Pharmacy

BRAC University

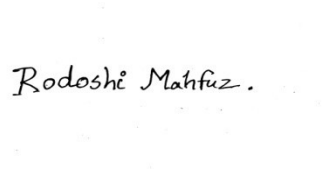
February 2022

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help

Student full name and signature:



Rodoshi Mahfuz Sowa

18146086

Approval

The thesis/project titled “The Pharmacological Potential of Lupeol and Derivatives: A Corroborative Analysis” submitted by Rodoshi Mahfuz Sowa (18146086) has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelors of Pharmacy.

Examining Committee:

Supervisor:
(Member)

_____

Sania Ashrafi

Lecturer, Department of Pharmacy

Brac University

Program Coordinator:
(Member)

_____

Namara Maryam Chowdhury

Lecturer, Department of Pharmacy

Brac University

Departmental Head:
(Dean)

_____

Eva Rahman Kabir, PhD

Dean

School of Pharmacy

Brac University

Ethics Statement

This study does not involve any human or animal trail.

Dedication

Dedicated to my parents and my teachers

Acknowledgement

To begin with and first, I would need to precise my appreciation to All-mighty for his unending endowments, mercy and kindness, what has been given to me in an exertion to supply with the quality and assurance to total this venture job.

It is my veritable joy to offer my sincere appreciation to my scholarly administrator, Sania Ashrafi (Teacher at Brac University's Division of Drug store), for her priceless direction and support amid this inquire about. My project work was made more efficient due to her ongoing supervision and assistance, which allowed me to work more perfectly. I am quite thankful to her for her profitable comments and concepts amid my study, which made a difference me much in completing my venture work in a opportune manner.

My ardent thanks go out to our Chairperson of Department of Pharmacy, Dr. Eva Rahman Kabir, for making a competitive environment that permits us to attain our full potential, for her commitment & leadership towards the department as well as for being a great motivation to all of us.

Finally, I'd need to express my much gratitude to my guardians, who never desist to inspire me and prayer all time.

Table of Contents

List of Acronyms

HIV - Human immunodeficiency virus

HSV- Herpes simplex virus

HBV- HepatitiesB virus

HCV- HepatitiesC virus

EBV- Epstein – Barr virus

ROS - Reactive oxygen species

TRAIL - Tumor necrosis factor apoptosis including ligand

HDL- High density lipoprotein

LDL - Low density lipoprotein

TNF - Tumor necrosis factor

TC - Total cholesterol

TE - Treiterpene extract

MIC- Minimum inhibitory concentration

EGFR- Epidermal growth factor receptor

MCF 7- Michigan cancer foundation

CVD Cardiovascular disease

AUC- Area under curve

CD8- Cluster of Differentiation 8

PBMC- Peripheral blood mononuclear cell

LUP- Lupeol

SQS- Squalene synthase

SE- Squalene epoxidase

FPP- Farnesyl diphosphate

COX2- Cyclooxygenase 2

mTOR- Mammalian target of rapamycin

HL- Hela

NB- Neuroblastoma

AR- Androgen receptor

ADPC- Antibody dependent cellular phagocytosis

TIPARP- Tetrachlorodibenzo-p-dioxin (TCDD) inducible poly(ADP-ribose) polymerase

GBC- Gallbladder carcinoma

MM- Malignant melanoma

PC- Prostate Cancer

APC- Amniocyte Production

CEVEC- Cuyahoga East Vocational Education Consortium

L-DOPA- Levodopa and l-3,4-dihydroxyphenylalanine

DR 3- Death receptor 3

PLGA- Poly lactic-co-glycolic acid

HUVEC- Human umbilical venous endothelial cells

DMBA- Dimethyl benzanthracene

NSAIDs- Non steroidal anti inflammatory drugs

PGE2- Prostaglandin E2

IL-4- Iinterleukin 4

PKC- Protein kinase C

LP- Lupeol palmitate

LL- Lupeol linoleate

MPO- Myeloperoxidase

nAChRs- Nicotinic acetylcholine receptors

SAR- Structure activity relationship

DMAP- Dimethylaminopyridine

CP- Cyclophosphamide

List of Tables

List of Figures

Abstract

Recently researchers are centered on creating drug-like substance as an elective to the accessibledrugs with less adverseeffects.Besides, peopleproceed to be influenced by a fewillnessesbasically due to environmentalstrengths such as drug-fightingorganisms as well ascontaminations. Lupeol is a natural triterpenoid which along with its derivatives exists in a considerable quantity in eatablenatural products and vegetables, and medicinal plants. A plenty of studies about the biological activity of lupeol and its subsidiary derivatives have been conducted and it has been demonstrated that they have broad pharmacological possibilitiesinside them specifically or in a roundabout way. There are also some pharmacokinetic studies, which indicated its bioavailability, absorption, distribution, polarity, excretion rate, AUC and other pharmacokinetic parameters. Along with some structural modifications and derivatives, lupeol has shown significant potency in better pharmacokinetic and pharmacological action in many in-vivo as well as in-vitro studies. The goal of this survey paper is to collaborate all the major biological capacities of this novel compound and its subsidiary derivatives along with the mechanisms of action, clinical as well as preclinical study results, applications in treatment, some limitations and future prospects.

Key words: Phytochemical, lupeol, analogue, confined, carcinoma, triterpenoid, rodents, anti-angiogentic, melanoma, clutter, expansion, lipidemia, cyclophosphamide, divergent, hepatoprotective.

1 Introduction

1.1 Overview

There are ampleproves from different sources, such as composed archives, protected landmarks, and even original unique medicinal plants that the connection betweenhuman and the search for remedies of various ailments from nature dates from the very beginning of life. For example, usage of medicinal plant is mostly used in the purpose of healing (Petrovska, 2012). Several species such as *Curcuma longa* (turmeric), *Cynodon dactylon* (scutch grass) etc are popular products that can heal wound are used by several ethnic groups and cultures. Traditional medicinal plants technically help in cutaneous wound healing in which skin repairs itself (Shedoeva et al., 2019). The combination therapeutic process and complex mechanism of medicinal therapy of natural plants are often unrevealed. In search of rescue from different diseases, people mostly rely on natural therapy just because of less side effects and long term evidence of ancient practices. At that time there was less adequate information regarding the reasons behind illnesses or which plant and how it could be utilized as a remedy for this. By ancient civilizations, their active action has been acknowledged by contemporary science, and it has been included in present day pharmacotherapy as a range of drugs of plant origin (Petrovska, 2012). Many of our present medicines are derived or indirectly or directly from different parts of higher plants. A number of novel plant-derived therapeutic substances have been entered not only into crude herbal medicine market, but too into western medicate markets as anticancer (for case: taxoids and camptothecins), antimalarial compounds. For example, triterpenoid type phytochemicals are utilized for further causes in many provinces in Asia for anti-inflammatory, analgesic, antipyretic, hepatoprotective, cardiotonic, antidiabetic effects.

Treiterprnoid constituent have played some significant role in treating a few diseases too. For example, phytoconstituents such as lupeol displaywithin the crust, leaves, natural products, latex and mess of *Ficus religiosa L*. (Bodhi tree) are dependable for its medicative activities. That’s why, this plant extricates is in a few ayurvedic formulations as well as within the ministration of diabetes, seizures, provocative state of body, gout, microbials, stomatitis, ulcer, mucositis, leucorrhea and against a feworganisms. (Priyanka et al., 2017) Triterpene extricate (TE) from external crust of birch consisting primarily of betulin (analogue of lupeol) which is capable to create an oleogel, was effectively tried within the therapy of actinic

keratosis. The preliminary pharmacokinetics of betulin as well as consequences of a subchronic poisonous quality consider of TE in rodents and mutts. The TE was demonstratedsecure and non-toxic to be utilized for the keratosis treatment.(Jäger et al., 2008)Researchers are centered on sedatecreating substances as an elective to the accessibleimmune suppressant drugs with lower side impacts, such as lupeol. In a think about their essentialimpacts on the resistantframework was examined. Lupeol appeared a dose-dependent diminish in lymphocyte proliferation which appeared suppressive activity against CD8+ which is cytotoxic and partnercells CD4+ T in mice. Expansion of betulinic acid within the concentration of test compounds resulted in incitement of lymphocyte multiplication. (Shahlaei et al., 2013) It was concurred with another report on expanding humoral and cellular resistance by betulinic acid which fortified the multiplication of splenocytes, thymocytes of mice and human PBMC in a time with dose-related way. (Yi et al., 2010) Treatment with lupeol has been detailed to move the pH of urine from alkaline to normal in an experiment. (Roychoudhury et al., 2022)Primarily, medicinal plants are broadly used in non-industrialized social orders, as they are promptlyaccessible and cheaper than present daymedications. Its identification supports the industry by giving a unused source for that bioactive substance (Memon et al., 2010)

Table 1: Some Common Examples of Nature Derived Medicines

Drugs	Medicinal use	Source	Reference
Cocaine	Local anesthetic	Coca plant seeds	(Memon et al., 2010)
Atropine	Anti-cholinergic	deadly nightshade of *Atropa belladonna*	
Digoxin	Cardiotonic	Digitalis	
Ephedrine	Antihistamine	*Ephedra sinica*	
Quinine	Antimalarial	Quinine tree	
Thymol	Topical antifungal	*Thymus vulgaris*	
Morphine	Analgesic	Poppy tree	

1.2 Importance of secondary metabolites

Metabolism of a plant is the collected mechanism of all the interrelated biochemical reactions of that plant body. A series of different process of this mechanism (photosynthesis, respiration, and nitrogen fixation) take place at different part or the plant, such as, bark, rook, leaf, stem etc. (*Plant Life: Metabolites: Primary vs Secondary*, n.d.) Plant metabolites have abundant organic functions for plants, including fuel, mechanical signaling, structure, stimulatory, inhibitory, cofactor impact on enzymes, catalytic function, immune defense, and interactions with other organisms. Moreover,plant metabolites are the source of endlesstherapeutic compounds. (Bhuiyan et al., 2020). Primary plant metabolites are the compounds that are straightforwardlyincludedwithin the metabolic pathways of a plant essential for its development, improvement, and propagation. These metabolites are related with the physiological formshappeningwithin the plant. Proteins, vitamis, lipids, carbohydrates, enzymes, ethanol, lactic acidetc are examples of primary metabolites. On the other hand, secondary plan metabolites are those compounds that are not specificallyincludedwithin thedevelopment, improvement, or generation of the plant but are fundamentalwithin theenvironmental and other exercises. For example, terpenoids, steroids, essential oils, alkaloids, phenolics, antibiotics, pigments etc. (*Important Microbiology Terms, Glossary, and Definitions*, n.d.)Lupeol is a pentacyclic triterpene present as a secondary metabolites in plants, but not in fungi and animals. The contrast between essential and auxiliary metabolite is veryenigmatic, since, numerous of the intermediates in essential digestion system is covering with the intermediates of auxiliary metabolites. (Norsuzila Ya'acob et al., 1989) There is an obligatory growing tendency of segregating specific secondary metabolites which are discovered in impressive amounts in precise normal plants.

Table 2: Commonly Used Secondary Metabolites with Biological Activity

Name of the compound	Class of compound	Biological activity	Reference
Nicotine	Alkaloid of tobacco	Insecticidal	(Osbourn & Lanzotti, 2009)
Lutedin	Carotenoid	Anti-inflammatory	
Vinblastin	Antineoplastic	Anticancer	
Quinine	Alkaloid of cinchona	Antimalarial	

1.3 Objective of the Study

Bangladesh is copious and exceptionally wealthy in a diversity of species of medicinal plants because of its topographical location and climate condition. (*The historical use of medicinal plants in traditional and scientific medicine - PubMed*, n.d.) Various common natural substances have been reported to exhibit impressive organic and pharmacological excercises currently all over the world. Utilizing either common or engineered substances exclusively or in combination treatment, it has been risen as a promising and practical target based therapeutic approach to decrease variety of illness. (Chaturvedi et al., 2008) For example, there are throughout 410 tentatively demonstrated medicinal plants having anti-diabetic efficiency, but only 110 have target based therapy. (*A Target Based Therapeutic Approach Towards Diabetes Mellitus Usi...: Ingenta Connect*, n.d.) Single plant extract can have several medicinal properties, such as Garlic extracts. Plants produce chemical compounds which give them an evolutionary advantage for health defense, those are called phytochemicals. Countless phytochemicals have potential pharmacological activities against different disease symptoms. (*A Target Based Therapeutic Approach Towards Diabetes Mellitus Usi...: Ingenta Connect*, n.d.) They have also other advantages like defending against herbivores. (Richards et al., 2016) For example, phytosterol, which is mainly natural triterpenoids, along with its derivatives, has a broad range of pharmacological potentials (*Pentacyclic triterpenoic acids: new chemoprotective compounds. Minireview - PubMed*, n.d.) Lupeol is pentacycline triterpenoid and pharmacologically active compound found in several natural plants worldwide(Howes, 2017) More than 20,000 triterpenoids have been confined from nature till now (Rao et al., 2017). Many of them are exciting as derivatives of lupeol and exhibiting same pharmacological effect. This review will provide detailed account of studies biological aspects of lupeol, a pentacyclic triterpene, with study results and opportunities of this class of compound in drug innovation purpose.

2 Lupeol

Lupeol is a phytochemical compound which pharmacologically dynamic pentacyclic triterpenoid having a few potential medicinal properties. The wide spectrum of biological activities of this dietary triterpene, lupeol along with its derivatives, has acquired wide surveillance of experienced medical professionals, pharmaceutical venders and researchers throughout the world. (M. Saleem, 2009) It is also known as Fagarsterol.

3 Natural sources of lupeol

Lupeol widely exists in vegetables, eatable fruits, cereals and medicinal plants consumed by humans. It is discovered in, green pepper, white cabbage, olive, strawberry, tomato, cucumber, mangoes and red grapes which were found to carrying valuable impacts as a therapeutic and disease preventative agent for many clutters, according to Duke (1992). In some medicinal plants such as *American ginseng*, *Tamarindus indica*, Shea butter plant, *Allanblackiamonticola,* lupeol is reported to be stored naturally in significant amounts. Lupeol is discovered as available as a vital constituent in *Camellia japonica* leaf extract. (Majumder et al., 2020) Ginseng oil contains a high quantity of lupeol, reported as 15.2.mg per each 100 g of oil. (Saleem, 2009, 109-115). Lupeol also happen within the skin of seeds of lupin and within the latex of fig trees and of elastic plants. Thus, lupeol arises across abundance of taxonomically diverse genera.The natural occurrence of Lupeol has been summarized in **Table 3**.

Table 3: Natural Plant Sources of Lupeol

Natural Sources	Scientific Name	References
American ginseng	*Panax quinquefolius*	(M. Saleem, 2009)
Shea butter plant	*Vitellaria paradoxa*	(Caciagli, 2008)
Pea tree	*Tamarindus indica*	(M. Saleem, 2009)
Vegetable tallow tree	*Allanblackiamonticola*	(M. Saleem, 2009)
White cabbage	*Brassica oleracea var. capitata*	(Caciagli, 2008)
Green pepper	*Capsicum annuum*	(Guiné & Barroca, 2012)
Strawberry	*Fragaria ananassa*	Shukla (2009)
Olive	*Olea europaea*	(Parsaeimehr et al., 2017)
Cucumber	*Magnolia macrophylla (large-leaved)*	(Asahina et al., 2007)

Tomato	*Solanum lycopersicum*	(Yasumoto et al., 2017)
Mangoes	*Mangifera indica*	(Lerma-Torres et al., 2019)
Red grapes	*Vitis vinifera*	Anticancer Properties of Fruits and Vegetables: A Scientific Review. World Scientific, 2014 M12 9 - 386 pages.

American ginseng

Strawberry

Capsicum annuum

Mangoes

White cabbage

Red grapes

Olive

4 Chemical Structure and Analysis

Chemical Formula	**$C_{30}H_{50}O$**
Melting Point	215–216 °C
Molecular Weight	426.7174 g/mol
Exact Mass	426.386166214
Synonyms	• 545-47-1 • Fagarasterol • Clerodol • Monogynol B • Lupenol
Spectroscopic Analysis	The IR spectrum of lupeol shows the existance of a hydroxyl functional group (3235 cm-1) aa well as an olefinic moiety (1640 cm-1). Study shows that, using High-Performance Liquid hromatographic (HPLC) techniquealong with ultraviolet spectrometry (UV) and mass spectrometry (MS) it is reported that lupeol exhibits m/z value at 409 which indicates a parent ion peak. [M+H-18][+]]
Solubility	Very soluble in ethanol, aceton, chloroform. Plainly soluble in benzene, ether,petroleum ether, warm alcohol. And insoluble in dilute acid and alkalis practically.
Density	0.9457 g/cu cm.

Ref: (Martelanc et al., 2007)(Corrêa et al., 2009)

So, lupeol is a secondary alcohol and pentacyclic triterpenoid, in which the hydrogen atom at the 3 beta position is substituted by a-OH group. Bioactivity study results of several isolated and synthesized lupeol derivatives showed that, some derivatives exhibit stronger activities with moderation to C-3 or C-19 (SAR).(K. Liu et al., 2021)

The structure is shown in **Figure 1.**

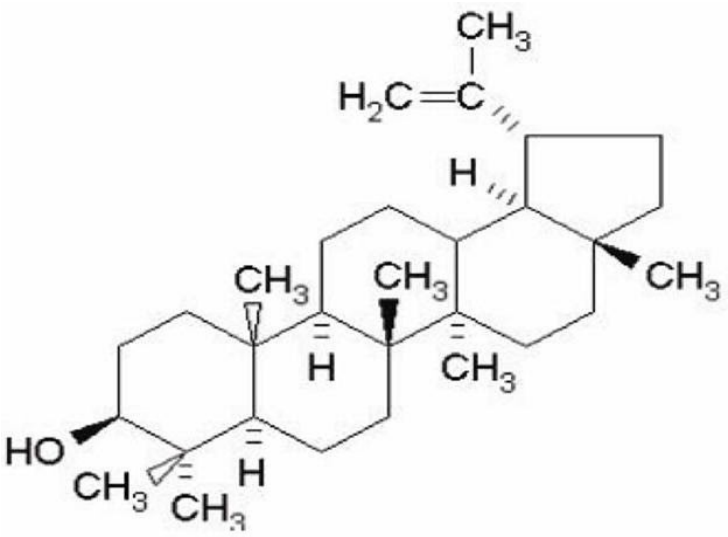


Figure 1: Structural Formula of Lupeol

5 Isolation and Synthesis of Lupeol

The initial fusion of lupeol was reported as total synthesis of lupeol. An additional effictive and enantioselective total synthesis of lupeol was reported in 2009. This enantioselective synthesis of lupeol was developed by processing two sincerely crafted cation-π cyclization stages, so that the pentacyclic structure with total stereo control can be produced. (Surendra &Corey, 2009) Typically, dry plant material is extracted with CHCl3, MeOH or even H2O. (Abdollahi & Rad, 2012)

5.1 Isolation pathway of lupeol from *Walsura Trifoliata*

Lupeol was isolated from *Walsura trifoliata* (Walsura piscidia Roxb subspecies) for the first time. It's a new source of Lupeol. Lupeol was isolated from leaves through chloroform extraction. First of all, the new takes of leaves of *Walsura trifoliata* were accumulated and were shade wilted together for 48 hours and then dusted coarsely. Around one kg of powdered clears out was taken into RBF (radial basis function). By using soxhlet apparatus for 12 hrs, lupeol is extracted with chloroform. Finally, the extract was dried and was purified

with the help of column chromatography technique. Mass spectra were recorded on the technology called Agilent Chemstation Software.(Rao et al., 2017)

5.2 Biosynthesis of lupeol in microbial platforms

Lupeol is delivered by a few life forms from squalene epoxide and lupeol synthase enzyme catalyzes this reaction. Studies show that squalene plays the role as a precursor here. (Majumder et al., 2020) Production of lupeol can be moved forward in yeast by enlisting qualities from diverse living organisms. Biogenesis of triterpenes in microbial menifesto is much more challenging than other synthesis. Engineering of the triterpene synthesis pathway in *Saccharomyces cerevisiae*and *Escherichia coli*cells can be done by enlisting the three genes of lupeol pathway of codon-optimization from divergent organisms. The lupeol synthesis pathway under two divergent yeast backgrounds called EPY300 and WAT11 have processed the best lupeol-producing ability so far andthe noteworthy sum of lupeol was obtained. It presents the premises for medicinal application of lupeol within the future. (Qiao et al., 2019)

5.3 BiosyntheticPathway

The lupeol pathway chemical variants are inferred from different living organisms. For the improvement of biosynthesis of lupeol in microorganisms or pathogens, the following steps are done into a biosynthesis reaction. Firstly, three genes of lupeol pathway, SQS, SE and LUP were confined from divergentliving cells, (SQS from *T. elongatus,* SE from *R. norvegicus,* LUP from: *A. thaliana, O. europaea, G. glabra, L. japonicus)* were codon-optimized based on *E. coli* or *S. cerevisiae* inclinationas well astheirin-vivo execution was evaluated. Secondly, the synthesis pathway of lupeol was reconstituted by selecting the superior pathway candidate qualities. The utility of this pathway had beenassessedbeneath two diverseyeast strains which are WAT11 and EPY300. In case of strain of EPY300, the flux up of carbon to FPP **(**farnesyl diphosphate) which is the pregenitor for lupeol biosynthesis as shown in the above figure.It was hereditarilyupgraded by overexpressing precursor genes. (Nguyen et al., 2012)

Thirdly, the lupeol pathway starts from FPP (farnesyl diphosphate). The biosynthesis of lupeol strats with the precipitation of 2 atoms of FPP into squalene by squalene synthase (SQS). Squalene is at that point oxidized into 2, 3-oxidosqualene by a monooxygenase enzyme with is membrane-bound and called squalene epoxidase (SE). There could be

adepartment point for either lupeol biosynthesis or sterol (ergosterol). LUP is lupeol synthase, by the help of which oxido-squalene can be cyclized to form lupeol. In this biosynthesis pathway a genuine congestion of building lupeol biosynthesis in E. coli which was firstly discovered. (Qiao et al., 2019)

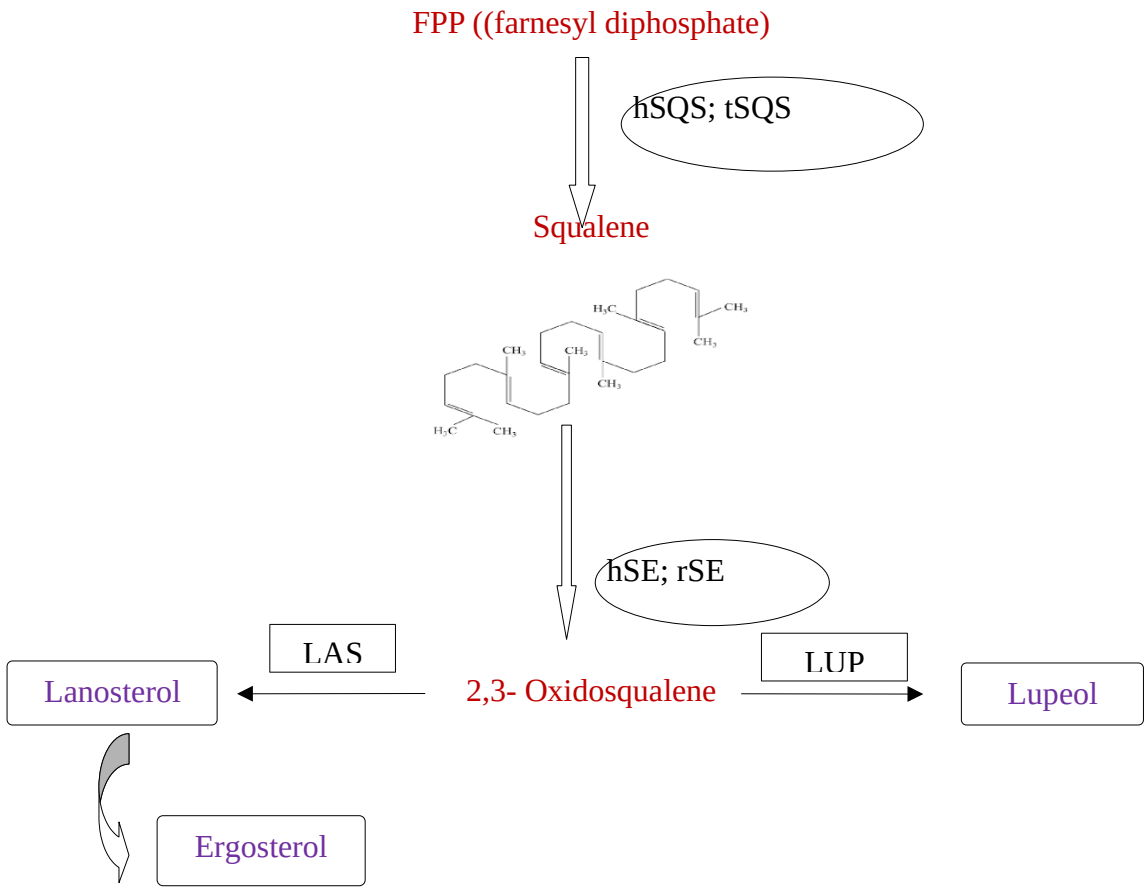


Figure 2: Biosynthetic Pathway of Lupeol

6 Pharmacological aspects of lupeol

Numerous research demonstrated that lupeol executes many advantageous pharmacological actions counting antioxidant, anti-inflammatory, anti-hyperglycemic, anti-dyslipidemic, anti-mutagenic, anti-arthritic, anti-diabetic, cardioprotective, anti-asthma, neuroprotective, hepatoprotective, nephroprotective, anti-neuroinflammation and anticancer efficiency (Tsai et al., 2016). That is why lupeol is called bioactive triterpene.

Lupeol has been proved possessing a broad extend of pharmacological activities such as:

- ✓ AnticancerProperties
- ✓ Antioxidant Properties
- ✓ Anti-Inflammatory Properties
- ✓ Antimicrobial Properties
- ✓ Antiprotozoal Properties
- ✓ Anti-Proliferative Properties
- ✓ Antidiabetic Effect
- ✓ Anti-Invasive Properties
- ✓ Anti-Angiogenic Properties

6.1 Anticancer Effect of Lupeol

Lupeol has been expressed to weild anticancer reactions in numerous cancer cells in various in-vivo studies. It was also investigated for its therapeutic effectiveness towards several types of cancers. Its anticancer reaction is moderated by three diverse mechanisms: (1) Antiproliferative effect, (2) Antiangiogenic effect and (3) Alteration of antigens on the surface of tumor cells that leads to the induction of the immune system. These mechanisms also support its antitumor activity. It has been reported that lupeol downregulates COX2 and mTOR/AKT/PI3K pathways to instigate apoptosis. (Min & Park, 2009, 320-330) These pathways are intracellular signaling pathways which are important in regulating the cell cycle. Lupeol seperated from *Elephanto pusscaber L*. has anticancer potentials on MCF-7 cell line. (Pitchai et al., 2014) Betulin, analogue of lupeol confined from the rhizome of *Sarracenia flava*, illustrated antineoplastic movement against epidermis cancer cells of the nasopharynx oh human body. (Miles et al. 1974, 1976) During betulinic acid was sheilded in-vitro against an extensive of cancer cell lines in human body, strong hindreance was appeared against a few human melanoma cell lines. (Tsai et al., 2016)A bioanalytical assay-guided research associated with the ethanol extricate from *Dendropanax querceti* leaves uncovered lupeol as dependable for the cytotoxic effect againsthuman epidermoid carcinoma A431, human hepatocellular carcinoma Hep-G2 and mouse hepatoma cells H-4IIE. (Moriarity et al.,

1998) A test through screeningof compounds confined from *Ventilago leiocarpa* disclosed no cytotoxic action for lupeol by significantly inhibiting S180 malignancy growth and enhancing the immune function of tumor- bearing mice, which have higher IC50 values. (Cheng et al., 2021) A phytochemical analysis of *Bombax ceiba* and segregating lupeol from this appeared a frail cytotoxicity in melanoma SK-MEL-2 cell of human, carcinoma cell of lung named A549 cell and murine melanoma cancer cell lines named B16-F10 of human body too. (You et al., 2003) Lupeol seperated from the timber of *Vepris punctata* was screened to see if it has any cytotoxic potential. It served cytotoxic action on human ovarian cancer cell line named A2780, Hep-G2, A-431 and H-4IIE tumour cell lines and exhibited good IC50 values. (Chaturvedula et al., 2004) Lupeol gave rise cytotoxicity in promyelocytic leukemia HL-60 of human, human neuroblastoma NB-1 cell lines and human leukemia monocyte lymphoma U937. (Hishiya & Takayama, 2008) Remarkably, lupeol has been appeared to stifle EGFR (epithelial growth factor receptor) function in oral squamous cell carcinoma as well as carcinoma in gallbladder. (Min et al., 2019)Lupeol was proved as a strong prohibitor of androgen receptor (AR) in vivo and in vitro. Lupeol altogether restrained androgen simple initiated transcriptional action of AR and lumped the official of AR to AR-responsive qualities counting PSA, SGH, IL-6 and TIPARP, and restrained the enrollment of RNA Pol II to target qualities. Lupeol supressed the carsinogenicity of both CRPC and ADPC cells in animals. (Siddique et al., 2011) In a study, GBC-SD cells (gallbladder carcinoma) were served by lupeol. Lupeol was managed intravenously to assess the anti-cancer magnitude in vivo. The result appeared that lupeol prohibited the multiplication, intrusion and initiated apoptosis of GBC-SD cells in a dose-conditioningway in vitro. And in vivo study appeared that lupeol administration reduced tumor extension. The mechanism of action is related with the suppression of some protein signaling, such as EGFR/MMP-9 signaling. It was significantly considered as an anti-invasive effect of lupeol. (Y. Liu et al., 2016)A study was done to assess the anti-carcinogenic potency of lupeol on human adenocarcinoma cell lines A549 and anti-apoptotic genes expression. A549 cell line was used as an in-vitro model in the investigation of big cell lung cancer and provided an intution into the programmed cell death and anti-metastatic potential of lupeol. The comes aboutuncovered that lupeol diminished the cell practicality in a dose-dependent way and expansion of lupeol diminished cell movementverifying anti-metastatic potential of lupeol. Moreover, lupeol treated cells down-regulated expression of anti-apoptotic qualitiesaffirming the apoptotic potential of lupeol. (Babu ST, 2019) Another study focused on the exploration of the impact of lupeol against

two human malignant cell lines MM (Malignant melanoma), RPMI-7951 and A375. The in vitro results reflected the concentration reliant and selective cytotoxicity of lupeol against both MM cell lines, with estimation of good IC50 values. It reduced cell confluence and apoptosis-specific atomic highlights with the potential of anti-melanoma effect. (Bociort et al., 2021)

6.2 Lupeol in Several Cancer Treatment

6.2.1 Prostate Cancer Treatment

Lupeol and related compounds showed promising result in diseases like prostate cancer. It disposed 18.5 M and IC 50 values of 21 against the human prostate cancer cell lines CWR22Rv1 and LNCaP correspondingly. CWR22Rv1 cells were implanted into nude mice for in vivo test and lupeol showed anticancer actions by a notablereduction of tumor volume after the nursing of mice with 1mg of lupeol. (M. Saleem, Kweon, et al., 2005)To the contrary, dicers studies regarding human prostate cancer also exhibited apowerlesshindrance of PC-3 cell multiplicationby lupeol. For example, afterthe treatment of PC-3 cell using betulinic acid, where mechanism of action of it’s by cell death was confirmed. A ‘DNA scratch sensor’ which was cleaved while apoptosis was running, appraised as a biogenic marker of this handle. (Prasad, Nigam, et al., 2008a) In addition, inoculation of lupeol medication driven to the capture of recumbent broadening in rodent treated with testosterone by ROS (reactive oxygen species) intervened cell deaththrough the mitochondrial pathway. This result was noticed in body fluidal node malignancy of the prostate (LNCaP) cells too when lupeol was given. (Prasad, Kalra, et al., 2008) Lupeol allows different mechanisms on the same cell while working in accordance with the dose employment. For example, investigations appeared that lupeol not only gave rise significant restraints of cells (PC-3, DU 145) which areandrogen insensitivebut also androgen inconsiderate (LNCaP, CWR22Rv1) human prostate cancer. (Wal et al., 2011) Lupeol has capability to diminish the CaP cells’ regulator proteins expression at transcriptional & translational levels. For example, inhibition of activators of androgen receptors, CdK-1 etc. CaP cells are CEVEC's (Pharmaceuticals) Amniocyte Production cells which are an commemorate cell line based on primary human amniocytes and were produced by transfection of those primary cells. (Wal et al., 2011) Lupeol also diminished the NF-B expression and lupeol powerwas highlighted by TNF against the inflammatory actions which is common in human recumbent cancer (M. Saleem et al., 2009)

6.2.2 Pancreatic Cancer Treatment

Lupeol can be utilized to treat another deadly infection like pancreatic cancer because it has appeareddevelopment inhibitory action on AsPC-1 human pancreatic adenocarcinoma cells. Lupeol therapy of AsPC-1 cells initiated apoptosis. (M. Saleem, Kaur, et al., 2005) A laterconsider has illustrated that the in vitro as well as in vivo tweakingimpact of lupeol specially on TRAIL-persuade apoptosis in cancer cell lines AsPC-1 and PANC-1 of pancreas, which is chemo resistant, by expanding the uttering level of dynamic caspase-8 as well as down-regulating the uttering of cFLIP. (M. Saleem, Kaur, et al., 2005) TRAIL induced apoptosis means Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), which is verified effective to various cancers. (Wang et al., 2019) .

6.2.3 Melanoma Skin Cancer treatment

Lupeol actuated melanin biosynthesis, which is an marker of melanoma cell differentiation and it repressed cell expansion too. The examination of this result was done by utilizing B16 2F2 cells, a substituted cell line obtained from mouse melanoma cells named B16 having high demarcation capacity. (Hayami, 1970) The results with betulinic acid and betulonal also played imperative parts in apoptotic impacts and against the pretested tumor cell lines selectively (Hata et al., 2003) Current studies appeared that the treatment of B16 2F2 cells utilizing lupeol also produced cell differentiation when it is short-time treatment, but if the treatment is of 48h, induced up-regulation chemicals that activated the color cell differentiation, which may concern in melanoma cancer. (Ogiwara & Hata, 2009)It had been watched that lupeol as well as betulin displayed frail reluctance of mushroom tyrosinase which is a pointer stimulant in the catalysis of L-DOPA oxidation to regeneration of melanin. It enhances the ability of lupeol to actuate the production of melanin. (Sauriasari et al., 2017) The morphological commutes such as a sub-G1 cell cycle crest and fragmentation of DNA illustrated that lupeol was inducing programmed cell death. For example, there was the definite inhibition of melanoma by betulinic acid. (Pisha et al., 1995)

6.2.4 Cardiac Cancer Treatment

Lupeol ameliorated the cyclophosphamide incited cardiac lysosomal damage considered in rodent model. When cyclophosphamide is used as an alkylating agent for cancer chemotherapy, it is more likely to cause cardian lysosomal damage and cell death. Lupeol decreased lysosomal hydrolases and other alterations caused by cyclophosphamide and showed protective effect against cardiotoxicity. (Periyasamy Thandavan Sudharsan et al., 2006)

6.2.5 Hepatic Cancer Treatment

Afla-toxin B 1 could be a subsidiary parasitic metabolite determinated for its hepatotoxic and hepatic carcinogenic impacts. (Oyeka et al., 2019) Lupeol illustratedsome usefulness in decreasingthe function of it (Preetha et al., 2006)In another in vivo experiment, lupeol pretreated rodents had the serum level and liver enzymes level reestablished to nearlynormal. Again, medicaments with lupeol considerably normalized the degenerative changeswithin the hepatocytes with grainy cytoplasm.(Prasad et al., 2007) Lupeol treatment alsoinitiated cell development hindrance and programmed cell death in hepatocellular carcinoma cells (such as SMMC7721) by down regulating the death receptor 3 (DR3) expression. (L. Zhang et al., 2009)

6.3 Anti-Angiogenic Properties

The antiangiogenic strengh of lupeol loaded with PLGA (poly lactic-co-glycolic acid) was assessed utilizing in vitro as well as in vivo models. PLGA was used for controlled release drug delivery facilitation for ocular disease. Because angiogenesis is specifically related with visual maladies such as macular retrograssion or diabetic retinopathy. Two essential endothelial cell exercises, expansion and movement, givedata on the instruments by which angiogenesis is being advanced or quelled. A criticaldiminish of around 40% in cell multiplication after treatment was watched, which triggers the angiogenic impact of the drug. (Käßmeyer et al., 2009) Lupeol happened a discernible in vitro restraint of tube arrangement by endothelial cells of human umbilical vein (40-60%) (You et al. 2003). The methanol extract of the stem barks of *Bombax ceiba* was found to induce a significant antiangiogenic activity on in vitro tube formation of human umbilical venous endothelial cells (HUVEC) (Soares et al., 2017).

- Another process is familiar as “programmed cell death”, which is utilized to expelincapable or hopelessharmed cells. Lupeol actuates apoptosis in this process. When the signals of apoptosis are activated, cells experience organized corruption with proteolytic chemicals, which are at that point divided from their pre-phase to their dynamicphase to begin of apoptosis. (Riedl & Shi, 2004)
- Another major anticancer mechanism of action tends to be antiproliferative activity. When a substance has the ability to anticipate or retard the spread of cells, particularly dnagerous cells, into encompassing tissues, is called antiproliferative. The anti-proliferative activity of the isolated lupeol was investigated against several cell lines and conditions of animals.

6.4 Antiproliferative action

Lupeol was experimented on bladder carcinogenesis. The result revealed that lupeol treatment demonstrated inhibition of tumor growth in the bladder by histopathological confirmations and significantly decreased the expansion of tumor necrosis factors. So preventive lupeol administration acts as effectual Cox-2 inhibitors which activates the tumor suppressor protein. and treats bladder carcinogenesis by antiproliferative as well as anti-inflammation properties. (Prabhu et al., 2016) Ordinary human melanocytes multiplication was not influenced by lupeol, but it did hinder the expansion of human essential WM35 & metastatic 451Lu melanoma cell lines in an in vivo test. (Wal et al., 2011) Lupeol also reduced the expansion of human breast cancer cells named MDA-MB-231 in a dose related manner. (Wal et al., 2011) Betulin influenced MCF-7 suppression at a least concentration of 23 nM in a study (Blom et al., 1998) The effect of lupeol on cell proliferation and cell death was assessed utilizing the human PCa cells, PC-3 (Prostate Cancer cells). A potential drop of apoptosis was recorded due to increase of lupeol exposure to PC-3 cells. Thus, the study suggested that lupeol possesses novel antiproliferative and apoptotic strength conductance against prostate cancer. (Prasad, Nigam, et al., 2008b) Lupeol moreover actuated a particular cell cycle capture at G1/S phase, which activatedchanges in a few G1 cell cycle administrative proteins such as, CdK-, cyclin D1 and -D2. In addition, lupeol actuated an increment in WAF1/p21, a protein that controlssection into the S-phase (M. Saleem et al., 2008).

6.5 Mechanism of Action as Anti-cancer Effect

As the implement of the anticancer actions of lupeol, tumorigenesis suppression, the initiation of apoptosis, regulation of cell cycle, the improvement of the cytotoxic work of common executioner cells and chemo sensitization have been reported.

- To begin with compassion of lupeol's cytotoxic movement was credited to its capability to restrain topoisomerase II (topo II) chemical, which is an essential enzyme in eukaryotic cells to relax supercoiled DNA. Lupeol has its amplitude for hindering the transformation of super-twisted plasmid DNA into relaxed DNA by topo II enzyme. (Vithana et al., 2019)
- It was moreoverillustrated that binding of topo II to DNA was obstracted with lupeol, avoiding the double complex arrangement between them. It's a distinctivecomponent of activity compared with other anticancer drugs, such as etoposide (Wada et al., 2001)
- Lupeol showed competence to lessen the lyase function of DNA polymerase with a good IC50 value. This lyase function inhibitors are anticipated to excite cancer cells to DNA-ijured operators and to heighten their cytotoxicity. (terpenes U 0200 *14- 184*, 2005)
- Lupeol diminished the enzyme named farnesyltransferase, creating it a potential anticancer agent in tumors. (*Regulation of the levels of health promoting compounds: lupeol, mangiferin and phenolic acids in the pulp and peel of mango fruit: a review*, n.d.)
- Farnesyl-tranferase enzyme adds a farnesyl group to proteins at the carboxyl terminus of it. The farnesyltransferase inhibitors are a lesson of test compounds that target protein farnesyl-transferase with the downstream impact of avoiding the right functioning which is unusually dynamic in cancer. That is how lupeol also works as farnesyltransferase inhibitor. (Tamanoi et al., 2001)
- Lupeol induces the expansion of ER (estrogen-receptor), which may clarify its development inhibitory activity in breast cancer cells (Lupien et al., 2010)
- Chemical alteration of the C-3 hydroxyl work of distinctive triterpenoids like lupeol, especially acylation or change of this gather into a ketone and another into an oxime work, by and largedriven to a compound with a better level of

cytotoxic movement. Besides, noteworthyexpansion in anticancer movement of lupeol subsidiaries were gotten for ketone 5, which was from 5- to 7-fold more dynamic against all sorts of tried cell lines than the parent compound lupeol. (Bednarczyk-Cwynar et al., 2016)

- In another mechanism of action,lupeol has been demonstrated to act through an inhibitory pathway called angiogenic imhibition. Angiogenesis is the method of arrangement of modern blood vanules from pre-existing vanules and is considered to play a vitalpart in tumor development and metastasis. The inhibition of angiogenesis is one of the major pathways to prevent tumor growth. Lupeol inhibitsthe development of unused blood vessels from previously existing vessels and is known to play a criticalpart in tumor widening andmetastasis. (Käßmeyer et al., 2009)

7 Antioxidant Effect of Lupeol

There are numerous in vitro experiments that have confirmed that lupeol can act as an antioxidant. As a result, lupeol has been used for many years as a remedy for skin diseases. For example, the application of triterpenes in makeup is centered in most cases on lupeol-rich plant extricates. White birch bark is a wealthy source of triterpenes used in cosmetics.Aloe vera is another example of a lupeol-rich plant and commonly utilizing in cosmetics preparations because of its antioxidative, moisturizing, anti-inflammatory, anti-bacterial, anti-viral properties. The sticky sap from harmedtakes off of aloe is an fixing with antioxidative properties. (M. Saleem et al., 2008) The significant thing is lupeol enriched plant extracts work as indirect antioxidants.They may or may not be redox-active but are included in a complex process as the inducers of cytoprotective proteins. These proteins take partwithin thesynthesis and recovery of coordinatecancer prevention agents which works by deactivating the responsive oxygen species. (Abyshev et al., 2007) A pentacyclic triterpene, lupeol showed activity against the poisonous signs of persistent cadmium introduction. Lupeol was supplemented at a dosage concurrent with cadmium administration which showed an improvement in the antioxidant condition. The oral administration of triterpenes changed the tissue redox system by improving the antioxidant profile of the liver. It was a hepatoprotective effect of Lupeol. (Nagaraj et al., 2000) A study was performed to assess the wound mending movement of lupeol in streptozotocin-induced hyperglycemic rats. Lupeol-treated rats gather appeared expanded rate of wound closure and compression. Diminished

provocative cell invasion, expanded expansion of fibroblasts, vascularization was revealed by Histopathological observation. The mRNA expression level was prominantly increased in response to lupeol. These discoveries indicated that lupeol can posess wound mending potential in hyperglycemic conditions of body. (Beserra et al., 2020) The triterpene celestrol, an analogue of lupeol, has been appeared to have a powerful inhibitory impact against lipid peroxidation in liver mitochondria. Celastrol is a dienone-phenolic triterpene. It appeared inhibitory impact on lipid peroxidation in rodent liver mitochondrial membranes initiated by ADP and Fe2+. The anti-peroxidative effect of celastrol was very strong and more effective than alpha-tocopherol. (Sassa et al., 1990) Lupeol and its esters have cardioprotective effects on cyclophosphamide (CP) - induced oxidative stress. Cyclophosphamide is an alkylating agent used in cancer chemotherapy that causes fatal cardiotoxicity. The cardioprotective effects of lupeol and lupeol linoleate were highlightly observed as antioxidant properties of triterpenes, altering the effect induced by CP. (P. T. Sudharsan et al., 2005)Alcoholic extracts such as ethanolic and methanolic extracts of *Ficus religiosa L.* bark were reported to have phytosterols such as lupeol. This plant possesses powerfull antioxidant activity and it is included in a few ayurvedic formulations for the treatment of diabetes, epilepsy, diery conditions, microbials, gout, stomatitis, leucorrhea, ulcers and against may other microbes. (Priyanka et al., 2017) In a study, a phytoconstituent from *Solanum xanthocarpum*, lupeol, helped to decrease the concentrations of antioxidant enzymes, whichmay be aconceivable causeof different shapes of tissue damage. Treatment with lupeol also increased antioxidant levels, with a diminish within the level of thiobarbituric acid-reactive oxygen species in that theory. (Taylor et al., 2011) Lupeol also re-established antioxidant enzymetic actions in rodent liver which was affected by 7, 12-dimethylbenzanthracene (DMBA) initiated oxidative stress. (Wal et al., 2011) Inquire about was done to decide the impact of modern lupeol subordinates on keratinocyte and fibroblast migration and expansion, as well as to examine different mechanisms of their antioxidant action. Triterpene extracts from Birch bark showed an ex-vivo molecular mechanism of keratinocyte migration. Lupeol esters influenced the motility of skin cells and their expansion. They have ability to reduce reactive oxygen species (ROS) and act by implication ensuring the skin protein structure from being oxidized by free radicals. (M. A. Malinowska et al., 2021b)

7.1 Mechanism of action of antioxidant effect

Mechanisms of actions	Phytochemical	Reference
Reducing reactive oxygen species (ROS) For example- decreasing the level of thiobarbituric acid	Lupeol extracted from bark of several Eurasian and North American birch trees. Dry *Betula papyrifera* extract (80% lupeol) Aloe vera *Solanum xanthocarpum*	(M. A. Malinowska et al., 2021a)
Keratinocyte as well as fibroblast migration and proliferation		
Hydroxyl group act as direct antioxidants		
Promoting local blood circulation and increasing oxygen supply		
Inducing cytoprotective proteins and act as indirect antioxidant	*Cortex betula*(75.2% terpinoid)	(Abyshev et al., 2007)
Changing the tissue redox system of a specific organ.	Lupeol	(Nagaraj et al., 2000)
Inhibiting lipid peroxidation (anti-peroxidative effect)	Celastrol (dienone-phenolic triterpene) Analogue of lupeol	(Sassa et al., 1990)
Inhibiting oxidative stress	*Crataevanurvala* stem bark	(P. T. Sudharsan et al., 2005)

8 Anti-inflammatory effect of Lupeol

A few anti-inflammatory drugs work by avoiding the arrangement of a fewtypicalinflammatory mediators produced by body defense cells. There are several plants employed to treat provocative side effects that have been appeared to contain lupeol as one of

their active standard. Lupeol were investigated for their anti-inflammatory, antinociceptive and antipyretic properties compared to NSAIDs drugs in rodent models. They have hydro-aromatic ring frameworks more or less comparable to that of steroids but destitute of side impacts and the distinct advantage of its opportunity from gastric ulcerogenic effects. (Geetha & Varalakshmi, 2001a) Moreover, arthritis-induced rats were used as animal models which had thicken paws due to arthritis. For evaluating the degree of inflammation, the arthritic rats were treated with lupeol and in the result they showed decreased in the thickness of their paws due to anti-inflammatory effects of lupeol. (Geetha & Varalakshmi, 2001a) An in-vitro study of lupeol showed that lupeol had anti-inflammatory potency, which was likely to depend on its capacity to anticipate the generation of a few pro-inflammatory mediatorssuch as, prostaglandin E2 (PGE2) production, cytokine production etc. (Fernández et al., 2010) Lupeol reduces the IL-4 (interleukin 4) production by Th2 cells (T-helper type 2). Oral administration of lupeol delivered dosage related restraint of IL-2, IFN-gamma and TNF-alpha within the pleural exudate with the foremost noteworthy impact at 100 mg/kg. (Jang et al., 2008) Lupeol viewed some prohibition of mezerein (protein kinase C activator) or (PKC) and ear edema induced by croton oil. The anti-inflammatory action of lupeol may depend on the reduction of protein kinase C activator, without any involvement of neurogenic inflammatory mechanisms. (*Anti-inflammatory and anti-arthritic activities of lupeol and related... | Download Table*, n.d.)

Lupeol and its hemisuc-cinyle ester expanded reconstitution of epidermal tissue in topical aggravation whereas palmitoylation of the OH-3 and acetylation gather diminished it. When its OH-3 gather was esterified, an improvement of the lupeol antiarthritic viability was noticed. (Srivastava et al., 2014) Another study was done for testing its inhibitory impacts on murine models of irritation and peritoneal macrophage capacities in-vitro. Lupeol was managed topically to suppress the mouse ear edema, which was initiated by tetradecanoyl-phorbol acetic acid derivation. Quantitation of the neutrophil illustrated that its topical action was related with decrease in cell invasion into aroused tissues. So, lupeol had anti-inflammatory action which depended on its capacity to avoid the generation of a few pro-inflammatory mediators. (Fernández et al., 2010) The major phytochemical constituent of petroleum ether extricates of two plant species *Strobilanthus heyneanus* and *Sort Strobilanthus* were confined. They were distinguished as lupeol and 19 α-H lupeol individually and broadly screened for anti-inflammatory and againstjointexercises. Verbal organization of lupeol created a measurements subordinate restraint of carrageenan initiated

paw oedema of rodent demonstrate. (Rangari & Agarwal, 2003) Two plant-derived pentacyclic triterpenoid lupeol (L) Lupeol-3-palmitate (LP) and lupeol-3-linoleate (LL) were examined in vitro as potential inhibitors of serine protease movement. lupeol palmitate and lupeol linoleate repressed trypsin action in a waysteady with blendedrestraint but lupeol esters appeared no inhibitory impact on the catalytic action of porcine pancreatic elastase. So this considerappeared that lupeol triterpenes are particular protease inhibitors. (Hodges et al., 2003) Confinement of chloroform leaf extricate division (CEF) containing anti-inflammatory marker compound of the *Crateva adansonii* leaf extricate lupeol was done to ponderits in vitro and in silico anti-inflammatory impact. Lupeol shown the binding affinities against all five targets of inflammation COX-2, MPO, TNFα, IL1β & IL6. (Thirumalaisamy et al., 2020) *Quercus obtusata* leaves are a copious source of lupeol (173.59 µg/g of test), of which anti-cyclooxygenase action has been utilized for deciding bioactivity of lupeol in a consideration. The result appearedcriticalpresence of lupeol as it were in fluidextricates from *Q. obtusata* species. The presence of lupeol in *Q. obtusata* leaves makes this oak species a future non-conventional source for lupeol with organicaction and anti-inflammatory potential. (Sánchez-Burgos et al., 2015)

8.1 Mechanism of Actions of Anti-inflammation Effect of Lupeol

Mechanisms of actions	Phytochemical	Reference
Inhibitory impact on prostaglandin synthetase.	Lupeol and lupeol linoleate, respectively 39% & 58%	(Geetha & Varalakshmi, 2001b)
Blocking the opioid antagonist naloxone	Lupeol from *Himatanthus drasticus*	(Lucetti et al., 2010)
Producing some pro-inflammatory mediators (Cytokine, PGE2)	Lupeol	(Fernández et al., 2010)
Inhibiting PKC (protein kinase C activator)	Lupane-type triterpene presented in the plant, animal kingdoms and fungi.	(Wal et al., 2011)
Increasing epidermal tissue reconstitution in	Hemisuc-cinyle ester of lupeol	(Srivastava et al., 2014)

topical inflammation		
Diminishing cell infiltration into topically inflamed tissues.	Lupeol	(Fernández et al., 2010)
Competitive and noncompetitive inhibition of trypsin and chymotrypsin.	Lupeol and 19 α-H lupeol extracted from *Strobilanthus heyneanus* and *Genus Strobilanthus.*	(Rangari & Agarwal, 2003)
Effecting keratinocyte proliferation on topical inflammation	Lupeol and its esters	(Rangari & Agarwal, 2003)
Selective protease inhibitors	Lupeol palmitate and lupeol linoleate	(Hodges et al., 2003)
Increasing the binding affinities against all five targets sights of inflammation (COX-2, MPO, TNFα, IL1β & IL6)	*Crateva adansonii* leaf extract containing lupeol	(Thirumalaisamy et al., 2020)
Anti-cyclooxygenase activity	*Quercus obtusata* leaves extract containing Lupeol [lup-20(29)-en-2-ol]	(Sánchez-Burgos et al., 2015)

9 Antimicrobial Activity of Lupeol

The anti-plasmodial impact of these sorts of compounds appears to be connected withchanges within the membrane configuration of the master cell, instead of a focused onharmfulimpact on the metabolic pathwaysof parasite organelles (Fernandes Rodrigues & Souza, 2008)For the primary time lupeol was tried in opposition to*Mycobacterium tuberculosis*. Where lupeol analogue betulinic acid and betulinaldehyde both displayed eligible inhibition of concentrations of 25 g/mL (MIC). (Suksamrarn et al., 2006) betulinaldehyde and betulinicacid are derived from butelin which could be a lupanetype pentacyclic triterpene

inferred from lupeol. As like as lupeol, betulinicacid may ensure the tree against parasitic and bacterial assault through the bark. (*Amount of betulin, betulinic acid, lupeol and other triterpenes in... | Download Table*, n.d.) Lupeol and lupeol acetic acid derivation triterpenes were separated from n-hexane with methanolic extricate and evaluated against *Macrophomina phaseolina* which is an deft human pathogen. It appearedpowerful antifungal properties in this consider. (Javed et al., 2021) The bioassay-guided inquire about of a plant utilizedwithin the treatment of jungle feverside effects from Cameroon driven to the separation of adivisionaffluent with alkaloid in conjunction with lupeol and its subordinates which shownmooperson potencies against two distinctive strains of *Plasmodium falciparum*. (Fotie et al., 2006) Boraginaceae, a therapeutic plant utilized against infectious maladies, was explored to check its antimicrobial effect. It was demonstrated that the methanol extricate of it is dynamic against numerous pathogenic microbes. On the other hand, the n-hexane extricate of root barks hascircuitous antimicrobial impacts. Lupeol is the most elevated compound in n-hexane extricate. It upgrades the action of anti-microbials against methicillin-resistant *Staphylococcus aureus* (MRSA). (P. N. Okusa et al., 2007)A few terpenoids have been detected to associated with the impression of PBP2a (penicillin authoritative protein 2a). Hence it decreases the resistance of MRSA. Other terpenoids have been appeared to display an circuitous antimicrobial impact, either by diminishing the stability of MRSA cell membrane or re establishing the movement of antibiotics. (Philippe N. Okusa et al., 2014) Organic tests pointing for normal antimalarial operators uncovered that lupeol can moderate in vitro developmentrestraint of *Plasmodium falciparum*, but needsaction in an in vivo test. (Pan et al., 2018) To clarify the antimalarial mode of activity of lupane-type triterpenes, it was illustrated that the erythrocyte membrane configuration can be altered irreparably by lupeol and related-compounds at congregationcomparable to their in vitro anti-plasmodial IC50 values. (Ziegler et al., 2002)

(McAuley et al., 2019)watched lupeol's capacity of repressing the neuraminidase activity, which may be a glycoprotein present exterior the fluinfectionmolecule. Within the case of Flu A and herpes simplex infection, lupeol appearedmore prominent EC50 esteem than its subordinates such as methylidene thioureido methyl betulonate. (Flekhter et al., 2004) Lupeol separated from *Strobilanthes cusia* root uncovered 100% inhibition of HSV-1 infection plaque formation. (Zafrul Azam et al., 2012) Betulinic acid, inferred from lupeol, a normallyhappening pentacyclic triterpenoid, appearedmovement against human immunodeficiency infection (HIV) replication occured in H9 lymphocytes within the human

body in an in vivo study. Their betulinic acid was from the clears out of *Syzigiumc laviforum*(From & Clavzflqrum, 1994)It was detailed that derivatives of lupane triterpenoids such as lupeol, betulin, betulinic acid show antiviral action, especially, with regard to human immunodeficiency infection (HIV), herpes simplex infection (HSV), and Epstein – Barr virus (EBV). (Flekhter et al., 2004) Triterpenoid saponins, lupine type triterpenes, are a different groups of natural products in plants and aredemonstrated as cautious compounds against pathogenic organisms and herbivores. (Sawai & Saito, 2011)

Table 4: Examples of Microbes Affecting by SeveralCompounds

Lupeol	***Penicilliumnotatum*(90%), *Fusariumsolani*,*Aspergillusniger*,*Rhizoctoiaphaseoli*,*Candidaalbicans*,*Penicilliumchrysogenum*,*Cantharellusflavus* and *Microsporumcanis*, *Sporothrixschenckii*, Aspergillus fumigatesHuman Immuno Deficiency virus (HIV), Herpes Simplex virus (HSV), and Epstein – Barr virus (EBV).**	**(Javed et al., 2021)** **(Wal et al., 2011)** **(Flekhter et al., 2004)**
β-Sitosterol (Lupeol derived sterol)	*Aspergillusniger*, *Cladosporiumcladosporioides*, *Fusariumverticillioides* (82%),	(Javed et al., 2021)
Betulinic acid (Derivative of lupeol)	*Aspergillus fumigates*, *Sporothrixschenckii*, *Microsporumcanis*, *Aspergillus fumigates*, *Candida albicans*, *Cryptococcus neoformans*, *Candida guilliermondi*, *Candida spicata* HIV, HSV, EBV	(Wal et al., 2011) (Flekhter et al., 2004)

9.1 Mechanism of actions of antimicrobial effect of lupeol

Mechanisms of actions	Affected microbes	Phytochemical	Reference
Reducing the growth of biomass	*Macrophomin aphaseolina* (plant pathogen)	Lupeol and lupeol acetate (highest antifungal). betulin (77–79%), β-sitosterol, β-amyrin, oleanolic acid, vanillic acid (74–79%), protocatechuic acid**,** from *Monotheca buxifolia.*	(Javed et al., 2021)
Enhancing the actions of antibiotics against MRSA / enhancing the function of four β-lactams	Methicillin-resistant *Staphylococcus aureus*	*Cordia gilletii* (Boraginaceae) root bark	(P. N. Okusa et al., 2007)
Interacting with the expression of PBP2a (penicillin binding protein 2a) and increasing the actions of antibiotics against MRSA	Methicillin-resistant *Staphylococcus aureus*	*Cordia gilletii* (Boraginaceae) root bark Cyclohexane (Ch) extracts of Boraginaceae plants.	(Philippe N. Okusa et al., 2014)
Decreasing the steadiness of MRSA cell membrane	Methicillin-resistant *Staphylococcus aureus*	*Cordia gilletii* (Boraginaceae) root bark	(Philippe N. Okusa et al., 2014)
Growth inhibition of antiplasmodial activity	*Plasmodium falciparum P. berghei*	Stem bark of *Spathodeacam panulata* : ursolic acid, tomentosolic acid	(Sawai & Saito, 2011) (VIncent P.K. Titanji, 2008)

Changing the erythrocyte membrane shape	*Plasmodium falciparum*	Lupane-type triterpenes	(Ziegler et al., 2002)
Inhibiting the neuraminidase activity	Influenza virus particle	Lupeol	(McAuley et al., 2019)
Producing a 50% inhibition of the virus growth	HIV virus, HSV virus and Epstein – Barr virus (EBV).	Lupeol, betulin, betulinic acid	(Flekhter et al., 2004)
Inhibiting virus plaque formation	HIV-1	*Strobilanthes cusia* root extract containing lupeol	(Zafrul Azam et al., 2012)
Activity against replication into human lymphocytes	HIV replication	Betulinic acid from *Syzigiumc laviforum* leaves	(From & Clavzflqrum, 1994)

9.2 Limitations of Antimicrobial Efficiency of Lupeol

Lupeol and numerous of its derivatives or compounds did not appearaffectability or were inert against a fewmicrobes species, countinga fewsafe strains. (Chaaib et al., 2003) For illustration, Lupeol acetic acid derivation did not show any action against gram-negative microbes and parasites. (Anas et al., 2017) A few synthesized ester subordinates from lupeol within the C-3 position yielded as it wereweak antimicrobial compounds (COMe, COCHMe2, COPh). (Phan et al., 2021) Lupeol moreoverfailed to showcalculableaction against *Candida albicans*. The antibacterial activities of lupeol as well as betulinicacid are clashingas well. Those diverseactivities are really based on cytotoxic LC50 values of both compounds (Shai et al., 2008) Lupeol was toodormantin opposition to *Cryptococcus neoformans, Cladosporium sphaerospermum and Cladosporium cladosporioides* (*WO2014147581A1.pdf*, n.d.) (Favre-Godal et al., 2015)

Furthermore lupeol has appearedweak antiviral exercises in a fewconsidersin spite of the fact that it has delivered as lead medicate for the era of increasedsuccessful compounds. For instance, within the case of Influenza A and herpes simplex virus, lupeol appearedmore prominent C50 esteem than its derivatives. (Wal et al., 2011)

10 Cardio-Protective Effect of Lupeol

Right now, commonitems are rising for the treatment of hypertension to keep away from the adverseeffects of drugs in order toprotect the sensitivity or heart. From laterthinks about, lupeol is known to be successful against hypertension in creaturetests.

It has been investigated that lupeol has cardioprotective effects. It was demonstrated that naturally hapening substances, such as triterpenes (lupeol, amyrin, oleanolic acid, ursolic acid) showed 53.5%–78.8% LDL protective activity. (Andrikopoulos et al., 2003)

Lupeol and lupeol acetic acid derivation have moreoverappeared hypotensive action, which can make them conceivable preventative negotiators in this cardiac clutter and other ensuing cardiovascular maladies. (R. Saleem et al., 2003)

Cyclophosphamide, a medication employed in the therapy of cancer and auto-immunological disorders, may induce cardiac oxidative injury. This cardiotoxicity is related with modifications of electrolytes both in serum and cardiac tissues. Lupeol or lupeol linoleate supplementation was compelling against this oxidative damage or cardiac tissue. (P T Sudharsan et al., 2010)

It was revealed thatthe mode of activity of triterpene by a rebuilding of a few transmembrane chemicals, add up to triglycerides, cholesterol and phospholipids to typical levels can prevent hypertrophic condition in cardiac histology. (Sudhahar et al., 2007a)

Ten lupeol ester derivatives were synthesized and a nicotinic acidsubsidiary was found that shownway better lipid bringing down profile (LLP). But lupeol showed at a dose two times higher impact than them in conjunction with an antihyperglycemic impact. It uncovered the potential of lupeol as a framework for creating drugs focusing on coronary infection. Lupeol brought down the triglyceride by 26%, cholesterol by 9%, glycerol by 10%, free greasy acids by 23% and expanded the HDL cholesterol by 44% and the HDL/cholesterol proportion was 63% in hamster model (Papi Reddy et al., 2009b)

To check the effect of lupeol and sometimes its linolateester (lupeol linoleate), plant derived triterpenes, on the lipid profile and biochemical changes of heart tissue, male

Albino Wistar rodent were used for in vivo tests. Triterpene treatment decresaed the alterations generated in hyper cholesterolemic rodents and avoided the hypertrophic cardiac histology and reestablished the ordinary ultrastructural design. In this way lupeol mediation minimized the lipid anomalies and unusual biochemical changes in creature models. (Sudhahar et al., 2007b)

The interaction of lupeol with α3β4 nicotinic acetylcholine receptors (nAChRs) was investigated in a research study. Combined application of acetylcholine and lupeol inhibited the function of α3β4 nAChRs in a concentration-dependent, voltage-independent, and reversible manner. α3β4 nAChRs effects on transmission in the sympathetic ganglion of heart. So lupeol brings down hypertension by interceding its impact on α3β4 nAChRs. In the end, lupeol is proposed as a novel helpful approach including the antihypertensive focusing on of α3β4 nAChRs. (Eom et al., 2020)

10.1 Mechanisms of action of cardio-protective effect of lupeol

Mechanisms of actions	Phytochemical	Reference
Minimizing the lipid variations from the normal level and irregular biochemical changes	Lupeol and its linoleate ester	(Sudhahar et al., 2007b)
Lowering hypertension by interceding its effects on α3β4 nAChRs (transmitter of cardiac system)	Lupeol	(Eom et al., 2020)
Protecting blood LDL from oxidation	Dipterocarpaceae family terpenes, Boraginaceae root gum tritarpenes, amyrin and oleanolic acid.Amyrin and oleanolic acid are derivatives of lupeol.	(Andrikopoulos et al., 2003)
Reduction of MABP (Mean Arterial Blood Pressure) by oral route and causing hypotension.	Lupeol and lupeol acetate	

	isolated from *Bombax ceiba* stem bark.	(R. Saleem et al., 2003)
Protecting cardiac tissue from cyclophosphamide induced lipidaemic instability.	Lupeol or lupeol linoleate from *Crataeva nurvala* stem bark	(P T Sudharsan et al., 2010)
Restorating several transmembrane enzymes to normal level and preventing cardiac hypertrophy.	Several triterpenes	(Sudhahar et al., 2007b)
Lowering the lipid profile with antihyperglycemic effect. Lowering triglycerides, cholesterol, fatty acids, Increasing HDL and HDL/Cholesterol ratio.	Lupeol ester derivatives confined from the leaves extract of *Aegle marmelos.*	(Papi Reddy et al., 2009b)

11 Anti-Diabetic Effect of Lupeol

Expandingstudies have proposed that different triterpenoids displayed antidiabetic movement in typical or/and diabetic animal models since, triterpenoids were appeared to decrease the plasma glucose level and improve glucose resistance of testanimals. A few current considers were outlined to assess the antidiabetic potential of lupeol and its semisynthetic analogues to induceaunused and strong antidiabetic operator. For example, the ethanol extricate of *Crataeva nurvala*, its hexane and chloroform solvent divisions and lupeol separated from the extractives were assessed for this reason and animal model for this was rats. . Compared to the essential particle, lupeol, few derivatives of lupeol appeared more strong antidiabetic movement. Such as , it was found that the ester derivatives of lupeol havesuperior antidiabetic potential when compared to lupeol. (Lakshmi et al., 2015) In an experiment, lupeol disconnected from *Solanum xanthocarpum*, lupeol, stifled the movementof diabetes after 21 days. Lupeol diminished the level of glycated hemoglobin, serum glucose and nitric oxide, with a concomitant increase in serum insulin level. (Taylor et al., 2011) Impeded

wound recuperating is one of the weakening complications of diabetes. Lupeol is known to stimulate expressions of cytokines and developmentvariablesincluded in wound mending. To assess the wound recuperatingaction of lupeol in streptozotocin-induced hyperglycemic rats, a study was done. All the discoveriesshown that lupeol has wound healing potential in hyperglycemic conditions and that's why it can be valuable as a treatment for incessant wounds in diabetic patients. (L. Zhang et al., 2009). In another research based on an examination of the in vivo antihyperglycemic action of Lupeol, separated from the ethanol extricate of banana bloom in an alloxan initiated diabetic rodentshow. The diabetic bunch of rats brought about in a criticaldiminishment of diabetic indications polyphagia, polydipsia, polyuria and pee sugar along withanprogressed body weight after treating with lupeol. Other than they expanded the hepatic glucose utilization in diabetic rats by fortifyinginsulindischarge. (Ramu et al., 2016) Different considers affirmed that the glucose-lowering impacts of plant extricates, ie, lupeol and iso-orientin, empowered them to be utilized as antidiabetic operators. Hypoglycemic exercises of lupeol and iso-orientin in a rodent model were assessed together. The impact of alloxan was utilizedto promote the blood glucose level of the show. Contaminated rats were administered plant extricates; combined treatment of both extracts (lupeol+iso-orientin) altogether diminished the levels of blood glucose and progressed the antioxidant status as well. The antidiabetic activities of lupeol and iso-orientin altogether decreased blood glucose levels and oxidative stretch and consequently, it may be considered advantageous within the treatment of diabetes. (Malik et al., 2019) Ethno pharmacological action of *Hedera nepalensis*extract and lupeol against alloxan-induced type I diabetes was tested with rodent models. The defensive impacts of *Hedera nepalensis* unrefined extricate, lupeol and n-hexane fraction of the plant (HNN) were explored. Lupeol and HNN fractional together diminished the blood glucose level by expandingaffront level in time dependentway, conjointlyaltogetherexpanded amylase and lipase action in diabetic rats. (Hashmi et al., 2020) Ginsenoside Rh2 is one of the major standards contained in *Panax ginseng* root. Ginsenosides are a series of natural triterpenoids which have a place to oleanane sort saponins, (simple of lupeol).

The discoveries of a present study appear that there's an instrument of ginsenoside Rh2 for the plasma glucose-lowering activity. Wistar rats were infused with the extricate compound intravenously in a think about and appeareddiminished plasma glucose in a dose-dependent way there. (Lee et al., 2006) The impacts of the phytoconstituent polyhydroxylated triterpenoids and sesquiterpene (a nicotinic corrosivesubordinate of lupeol) disconnected

from Eriobotrya japonica was considered in hereditarily diabetic mice and normoglycemic rats. Two subordinate compounds of polyhydroxylated triterpenoids delivered a checked hindrance of glycosuria (having glucose or other sugar in pee). Moreover, they were able to diminish blood glucose levels in normoglycemic rats. (De Tommasi et al., 1991) There are moreovera fewcircuitousdefensiveactivities of lupeol against diabetes. For illustration, it is useful in avoiding diet-induced body fat aggregation and conceivablydecreasing the chance of diabetes and heart malady. Ursolic acid could be a pentacyclic triterpene acid, analoque of lupeol, which is the foremost inexhaustible bioactive compound in C. mas (Cornus mas) natural products. It is utilized to treat diabetes-related disorders in Asia. Since ursolic acid decontaminated from cornus mas natural products have naturalactivities which progressed certain metabolic parameters related with diets high in immersed fats and weight. (Jayaprakasam et al., 2006) Ten lupeol ester derivatives were synthesized and a nicotinic acidsubsidiary was found that shownway better lipid bringing down profile (LLP). But lupeol showed at a dose two times higher impact than them in conjunction with an antihyperglycemic impact. It uncovered the potential of lupeol derivatives and lupeol as a framework for creating drugs focusing ondiabetes. Lipid profile effects diabetes status as increased amount of intracellular lipids leads to hyperglycemia often(Papi Reddy et al., 2009a)

11.1 Mechanism of Actions of Anti-diabetic Effect

Natural triterpenoids have several direct and indirect mechanisms of action of working as anti diabetic medicine. Among the most of the mechanisms of actions molecular mechanisms are responsible. Some direct and indirect mechanisms are:

Mechanisms of actions	Phytochemical	Reference
Stimulation of insulin secretion	Oleanolic acid, ursolic acid. (Pentacyclic triterpenes, derivative of lupeol)	(Lyu et al., 2016)

Reversing insulin resistance • Activation of insulin signaling • Increasing adiponectin level • Inhibiting protein tyrosine phosphatase	lupeol (Lu), lupenone (Lu) betulinic acid (Lu), betulinic acid methyl ester (Lu) (Lu= Lupane type triterpenes) Ursolic acid, corosolic acid, pomolic acid, moronic acid, lupenone, betulinic acid (Pentacyclic triterpenes, derivative of lupeol)	(Lyu et al., 2016)
Increasing the action of AMP-activated protein kinase (AMPK)	Ursolic acid, betulinic acid, oleanolic acid.	(Xu et al., 2009) (Tan et al., 2008) (Ha et al., 2009)
Activation of peroxisome proliferator-activated receptors	Lupeol extracted from *Hibiscus sabdariffa*plant.	(Giacoman-Martínez et al., n.d.)
Promoting glycogen synthesis and inhibiting glycogen degradation	Ursolic acid, Hederagonic acid, ypsogenin, echinocystic acid,oleanolic acid, hederagenin acid and gypsogenic acid, Maslinic acid (Pentacyclic triterpenes, derivative of lupeol)	(Lyu et al., 2016) (Guan et al., 2009)
Suppression of starch hydrolysis and glucose transport in small intestine	Corosolic acid, oleanolic acid, ursolic acid, bartogenic acid, ferulic acid and lupine, Gymnemic acids II, III, and IV, and gymnemoside-f. (Pentacyclic triterpenes, derivative of lupeol) gymnemasaponin V (saponin type lupeol derivative)	(Lyu et al., 2016) (Takagi et al., 2008) (Ali et al., 2006)

Inhibition of gluconeogenesis	Corosolicacid(Pentacyclic triterpenes, derivative of lupeol)	(Yamada et al., 2008)

12 Pharmacokinetic Aspects of Lupeol

Pharmacokinetic considers have demonstrated that retention of lupeol by animals was quickin spite of its nonpolar characteristics, and lupeol has a place to lesson II BCS (biopharmaceutics classification framework) compounds (K. Liu et al., 2021) These compounds of class II show high permeability and low solubility. Herbal drugs as phytochemicals or extracts of this classification have their poor bioavailability. A bioavailability is limited by their solvation rate. (*Biopharmaceutics Classification System (BCS): Development, Implementation, and Growth: Mehta, Mehul: 9781118476611: Amazon.com: Books*, n.d.) However, there are no reports about bioavailability of lupeol. It is known that it has limited water solubility, which impacts on its bioavailability. (Cháirez-Ramírez et al., 2019) To get the qualitative and quantitative pharmacokinetic data of lupeol, the major compound display in *Ficus religiosa L.*extricate, the bioavailability of the compound was evaluated and a medicateconveyancesystem was created which upgrades the bioavailability of it. The framework was known as ‘Solid lipid nanoparticles’ (SLN). (Priyanka et al., 2017) Investigate was done to assess the systemic bioavailability of lupeol with bunches of female CD-1 strain mice. Study of coordinateabsorption and assimilation in different organs (stomach, small digestive tract) appeared critical concentrations of lupeol at prior post organization time, which demonstrated that retention of lupeol by the animals was way better than anticipatedin spite of its nonpolar nature. (Cháirez-Ramírez et al., 2019) Free lupeol may quicklyvanish from plasma due to metabolic shifts or distribution to other organs. In any case, criticaldifferences in pharmacokinetics characteristics and parameters are watched when free lupeol typified within the liposome. Lupeol liposome gradually evacuates from the blood circulation after intravenous organization. The AUC esteem of l lupeol stacked PEGylated liposomes is 3.2 times more than free lupeol. But liposomal definitionsappeared cytotoxicity which is likely due to way better bioavailability. They moreover appeared lower discharge rate and lower IC50 values. (J. Zhang et al., 2019) The poisonous quality levels of lupeol are too known to be exceptionallylow, as lupeol administered orally in a dosage of 2 g/kg body weight has been detailed to deliver no

unfavorable impacts in rats demonstrate, and after perception of 96h no mortality was delivered. (Geetha & Varalakshmi, 2001a)

13 Derivatives of Lupeol

Lupeol and its derivatives have complex pharmacological and comprehensive properties with several potential medicinal effects. These triterpenoids are secondary metabolites determined from plants. New derivatives are being synthesized using oxidation, aldolization, elucidation, carboxylation, SAR modification etc. (Le et al., 2021) Lupane has pulled in much consideration due to their widerange of naturalexercises among all triterpene derivatives. Lupeol is a lupane type pentacyclic triterpene that is principally found in common natural plants products (such as fruit plants). Until now very free oxime derivatives of lupeol have been reported, such as lupeol ketone intermediate. (Le et al., 2021) Moreover, pentacyclic triterpenoids can be further differentiated into lupane, ursane, friedelane,oleane, serratane, and taraxatone category. (Ghante & Jamkhande, 2019)

13.1 Anti-cancer Derivative of Lupeol

The confinement of the semi-synthesis of eight lupeol esters and the assessment of their in vitro action against nine strains of cancer cells was detailed. The response of carboxylic acids with Lupeol and DIC/DMAP (dimethylaminopyridine) was utilized to get (1) lupeol stearate (2), lupeol palmitate (3) lupeol miristate (4), and the unused esters lupeol laurate (5), lupeol caprate (6), lupeol caprilate (7), lupeol caproate (8) and lupeol 3’,4’-dimethoxybenzoate. These compounds were distinguishedutilizing FT-IR, 1H, 13C-NMR, CHN examination and XRD information (device to decide the structure) was tried in vitro for expansion of human cancer cell movement. Lupeol miristate appeared a specific development restraint impact on erythro myeloblastic leukemia (K-562) cells in a concentration-dependent way. Lupeol esters 2 - 4 and 7 – 9 appeared a more cytostatic impact than lupeol. Lupeol esters miristate appeared a particular cytostatic impact with low GI50 values. (Silva et al., 2017)One of a derivative compound, lupenone used in 25.4 M is more potent than lupeol used in 38 M, uncovering that the existance of a ketone group at C-3 improved which induced cell differentiation function and thus act like an anti-melanoma cancer agent. (Hayami, 1970) Significant augmentation in anticancer activity of lupeol subsidaries were obtained for ketone 5, which was from 5- to 7-fold more active against all types of tested cell lines than the parent compound lupeol. (Bednarczyk-Cwynar et al., 2016)

13.2 Antioxidant Derivative of Lupeol

Lupeol linoleate is an ester derivative of pentacyclic triterpene, lupeol. Compared to lupeol, lupeol linoleate had a distant impact on the antioxidant reputation of the liver. It is known as hepatoprotective effect of lupeol. It showed activity against the harmful signs of incessant cadmium presentation. Lupeol was supplemented at a dosage coexisting with cadmium administration which displayed a refinement in the antioxidant status. The oral administration of triterpenes switched the tissue redox system by developing the antioxidant status of the liver. (Nagaraj et al., 2000) Lupeol linoleate has Cardioprotective effect on cyclophosphamide (CP) - induced oxidative stress Cyclophosphamide is an alkylating substance utilizing in chemotherapy for cancer that causes deadly cardiac toxicity. The cardioprotective effects of lupeol (50 mg/kg body weight) as well as lupeol linoleate (50 mg/kg body weight) were highlightly observed as antioxidant properties of triterpenes, altering the effect induced by CP. (P. T. Sudharsan et al., 2005) Anotherresearch appeared linoleate ester derivative of lupeol can enhance the oxidative variations of the lipids present in blood. from the normal state within the initial state of hypercholesterolemic atherosclerosis in rodent (Sudhahar et al., 2006)

13.3 Anti-inflammatory Derivative of Lupeol

Lupeol acetic acid derivationincludes the opioid framework by the totalblockade of the opioid enemy naloxone.Thus it induces an anti inflammatory effect. The latex collected from the stem bark of the species *Himatanthus drasticus* contains pentacyclic triterpene lupeol such as lupeol acetate which induces anti-inflammatory effect while tested in-vivo as well as in-vitro. (Lucetti et al., 2010) Lupeol acetate was investigated for having hypotensive activity by reducing cardiac inflammation and thus proved as conceivable preventative specialists in this cardiac clutters and other resulting cardiovascular inflammatory maladies inflammatory diseases. But in the study, it has uncovered its inauspicious impact on the heart, liver and kidneys of mice with a high concentrated dose. (R. Saleem et al., 2003)

13.4 Diverse activities of lupeol derivatives

Other than the utmostparts of being antiprotozoal, anti-inflammatory, antitumor, and chemopreventive operators, lupeol, its subsidiary compounds and related compounds moreoverhave a differentcluster of other exercises. Linoleate ester derivative of lupeol were

demonstrated to be successful antiurolithiatic substance by anticipating the arrangement of blister calculi as well asdiminishing the measure of pre-determined obelisk(Revathi & D, 2012) The combination of betulinic acid and lupeol's antiurolithiatic component of activity were uncovered because of having their capacity to minimizerenal peroxidative changes induced by crystal formation there and ensuing tissue impairement. (Malini et al., 2000) Lupenone and 3- epi-lupeol appeared allelochemical properties. (Macías-Rubalcava et al., 2007) Antioxidant derivative of lupeol moreover provides a work in creams used for anti-aging care, salves, congeal preparations, and lip emollient at quantity of 0.2-3% w/w due to its capacity to preserve skin surface cojointly the keenness by advancing epidermal recovery. (l ZanifɜMcDowel, 2005) Lupeol acetic acid derivation can neutralize snake and cobra poisonexercises as well as potentiated windpoison antiserum activity. (Chatterjee et al., 2006) Some analogs have illustrated the capacityto operate as antifertility agents which were tested with male albino rats. (Gupta et al., 2005) Birch bark has been known as a clinically demonstrated conventional therapeutic cure to accelerate wound recuperating since a long time prior. (Abyshev et al, 2007) A comprehensive birch bark preparation named as TE (triterpene extricate) and and is connected single triterpene betulinportion wound recuperating in human essential keratinocytes. TE advanced keratinocyte relocation as the atomiccomponent of the clinically demonstrated wound recuperating impact of birch. bark. (Ebeling et al., 2014)

14 Safety Evaluation

The safety of lupeol and related agents is must and uncompromisable. (Ghazanfar et al., 2017) Lupeol ester derivatives such as acetyl salicylate, propionate, succinate, isonicotinate and lupeol acetic acid derivation were gottenutilizing an eco-friendly amalgamationmethod. But within the esterification prepare, the frequently utilized dangerous reagents ought to be supplanted by secure ones in this type of synthesis. This is often especially imperative since the compounds gotten are possibly dynamic substances, extraordinarily in skin care formulations. Indeed other followsums of dangerous reagents can have a poisonousimpact on harmed or bothered tissues of skin. (M. Malinowska et al., 2019) In a cytotoxicity evaluation test, lupeol was active at a fixed concentration of 40 µg/mL against drug sensitive leukemia. For this reason, it's not fully safe for leukemia patients. But it displayed considerable cytotoxicity with IC50 values for cancer cells. (Nyaboke et al., 2018) The result of a suschronic toxicity study of triterpene extract (TE) in rat model was shown, triterpenes

showed poor aqueous solubility, safe bioavailability and no toxicity in vivo test. (Jäger et al., 2008)The day by day treatment with lupeol was found secure from the perspective of gastric provocative events and ulcer induction. (De Lima et al., 2013)

15 Conclusion

Common instinctual products have been utilized as cures to remedy or treat sicknesses from the exceptionallybeginning. This convention has been outperformed by the astonishing pharmacological and innovative advancements that have developed with the guarantee of simpler healing. In this context, a noteworthysum of environmentalsubstances have been featured by the analysts due to their inclusive therapeutic possessions. Lupeol may be a common constituent of numerous common plant extracts which shows a wide range of organic exercises and can be utilized to maintain a strategic distance from a few maladies. (Wal et al., 2011) In this review, a novel compound lupeol and its derivatives have been well described. A wide range of bioactivities and bioassays, in-vivo as well as in-vitro study results of lupeol are crtiticized here, along with its convenient medicinal properties and diversity of mechanism of actions against different ailment. Lupeol and its subsidiaries have appeared their work by balancing processes related with xenobiotic biotransformation, SAR adjustment, with the security of cellular components or with the advancement of a more differentiated phenotype in target cells. Since the likelihood of utilizingatomicfocused on dietary specialists like lupeol and its derivatives in see of the reality that their defensive impacts demonstrate to be capableenough. (Chaturvedi et al., 2008). It has been appeared to fortify apoptosis by interceding in a few signaling pathways or signaling cascades. This review also claims that lupeol and its derivatives can be abused as imminent targets for improvement of prose chemotherapeutic operators. It has been estimated that almost one third of all new cancers diagnosed worldwide originates in the skin till now. (Jemal et al., 2008) And numerous in vitro experiments affirmed that lupeol can proceed as an antioxidant, which can be applied in the skin cancer treating agent and medicines. A recent global research report 2021 called **“**Lupeol Market**”** is presenting most valuable insights of lupeol into global market opportunities, business strategies and latest innovations in the chemical and pharmaceutical industry.The report demonstrates an in-depth evaluation of lupeol that is also affective for the market growth and innovation of manufacturer in future. (*Global Lupeol Market - ﷽ Industry Reports*, n.d.)It has been used as a standard for the distinguishing proof and evaluation of triterpenoids by gass chromatography in many analysis processes. Though

neuro protective, hepato protective, and chemo sensitization effects of lupeol is still little bit less defined becase of its complicated molecular mechanism, but these potential effect can be used to search for new class of safe medicines for future generations. Manufacturedchange of plant metabolites or extraction of phytochemical compounds may be aweightyzone of medicinal chemistry that can make modern and latent drugs.

Bibliography

A Target Based Therapeutic Approach Towards Diabetes Mellitus Usi...: Ingenta Connect. (n.d.). Retrieved February 21, 2022, from https://www.ingentaconnect.com/content/ben/cdr/2008/00000004/00000004/art00002

Abdollahi, S., & Rad, M. R. S. (2012). On an M/G/1 Queueing Model with k-Phase Optional Services and Bernoulli Feedback. *Journal of Service Science and Management*, *05*(03), 280–288. https://doi.org/10.4236/jssm.2012.53033

Abyshev, A. Z., Agaev, É. M., & Guseinov, A. B. (2007). Studies of the chemical composition of birch bark extracts (Cortex betula) from the Betulaceae family. *Pharmaceutical Chemistry Journal*, *41*(8), 419–423. https://doi.org/10.1007/s11094-007-0091-5

Ali, H., Houghton, P. J., & Soumyanath, A. (2006). α-Amylase inhibitory activity of some Malaysian plants used to treat diabetes; with particular reference to Phyllanthus amarus. *Journal of Ethnopharmacology*, *107*(3), 449–455. https://doi.org/10.1016/j.jep.2006.04.004

Amount of betulin, betulinic acid, lupeol and other triterpenes in... | Download Table. (n.d.). Retrieved February 22, 2022, from https://www.researchgate.net/figure/Amount-of-betulin-betulinic-acid-lupeol-and-other-triterpenes-in-fractions_fig3_302032391

Anas, A., Ahmed, A., Umar, S., Jajere, U. M., Mshelia, E. H., & Natasha, O. (2017). Inhibitory effect of isolated Lupeol from stem bark of *Diospyros mespiliformis* Horsch (Ebenaceae) against some microbial pathogens. *Bayero Journal of Pure and Applied Sciences*, *10*(1), 293. https://doi.org/10.4314/bajopas.v10i1.45

Andrikopoulos, N. K., Kaliora, A. C., Assimopoulou, A. N., & Papapeorgiou, V. P. (2003). Biological activity of some naturally occurring resins, gums and pigments against in vitro LDL oxidation. *Phytotherapy Research*, *17*(5), 501–507.

https://doi.org/10.1002/ptr.1185

Anti-inflammatory and anti-arthritic activities of lupeol and related... | Download Table. (n.d.). Retrieved February 22, 2022, from https://www.researchgate.net/figure/Anti-inflammatory-and-anti-arthritic-activities-of-lupeol-and-related-compounds_tbl1_227878150

Asahina, M., Yamauchi, Y., Hanada, A., Kamiya, Y., Kamada, H., Satoh, S., & Yamaguchi, S. (2007). Effects of the removal of cotyledons on endogenous gibberellin levels in hypocotyls of young cucumber and tomato seedlings. *Plant Biotechnology*, *24*(1), 99–106. https://doi.org/10.5511/plantbiotechnology.24.99

Babu ST. (2019). Study on the Anti Metastatic and Anticancer Activity of Triterpene Compound Lupeol in Human Lung Cancer. *International Journal of Pharmaceutical Sciences and Research*, *4*(2), 763–773. https://doi.org/10.13040/IJPSR.0975-8232.10(2).721-27

Bednarczyk-Cwynar, B., Wiecaszek, T., & Ruszkowski, P. (2016). Cytotoxic activity of some lupeol derivatives. *Natural Product Communications*, *11*(9), 1237–1238. https://doi.org/10.1177/1934578x1601100910

Beserra, F. P., Vieira, A. J., Gushiken, L. F. S., De Souza, E. O., Hussni, M. F., Hussni, C. A., Takahira, R. K., Nóbrega, R. H., Martinez, E. R. M., Jackson, C. J., De Azevedo Maia, G. L., Rozza, A. L., & Pellizzon, C. H. (2020). Erratum: Lupeol, a dietary triterpene, enhances wound healing in streptozotocin-induced hyperglycemic rats with modulatory effects on inflammation, oxidative Stress, and angiogenesis (Oxidative Medicine and Cellular Longevity (2019) 2019 (3182627) DOI: 10. *Oxidative Medicine and Cellular Longevity*, *2020*. https://doi.org/10.1155/2020/3252696

Bhuiyan, F. R., Howlader, S., Raihan, T., & Hasan, M. (2020). Plants Metabolites: Possibility of Natural Therapeutics Against the COVID-19 Pandemic. *Frontiers in Medicine*, *7*(August), 1–26. https://doi.org/10.3389/fmed.2020.00444

Biopharmaceutics Classification System (BCS): Development, Implementation, and Growth: Mehta, Mehul: 9781118476611: Amazon.com: Books. (n.d.). Retrieved February 22, 2022, from https://www.amazon.com/Biopharmaceutics-Classification-System-BCS-Implementation/dp/1118476611

Blom, A., Ekman, E., Johannisson, A., Norrgren, L., & Pesonen, M. (1998). Effects of

xenoestrogenic environmental pollutants on the proliferation of a human breast cancer cell line (MCF-7). *Archives of Environmental Contamination and Toxicology*, *34*(3), 306–310. https://doi.org/10.1007/s002449900322

Bociort, F., Macasoi, I. G., Marcovici, I., Motoc, A., Grosu, C., Pinzaru, I., Petean, C., Avram, S., & Dehelean, C. A. (2021). Investigation of lupeol as anti-melanoma agent: An in vitro-in ovo perspective. *Current Oncology*, *28*(6), 5054–5066. https://doi.org/10.3390/curroncol28060425

Caciagli, P. (2008). Vegetable Viruses. *Encyclopedia of Virology*, 282–290. https://doi.org/10.1016/B978-012374410-4.00650-6

Chaaib, F., Queiroz, E. F., Ndjoko, K., Diallo, D., & Hostettmann, K. (2003). Antifungal and Antioxidant Compounds from the Root Bark of Fagara zanthoxyloides. *Planta Med*, *69*(04), 316–320.

Cháirez-Ramírez, M. H., Gallegos-Infante, J. A., Moreno-Jiménez, M. R., González-Laredo, R. F., & Rocha-Guzmán, N. E. (2019). Absorption and distribution of lupeol in CD-1 mice evaluated by UPLC–APCI + –MS/MS. *Biomedical Chromatography*, *33*(3). https://doi.org/10.1002/bmc.4432

Chatterjee, I., Chakravarty, A. K., & Gomes, A. (2006). Daboia russellii and Naja kaouthia venom neutralization by lupeol acetate isolated from the root extract of Indian sarsaparilla Hemidesmus indicus R.Br. *Journal of Ethnopharmacology*, *106*(1), 38–43. https://doi.org/10.1016/j.jep.2005.11.031

Chaturvedi, P. K., Bhui, K., & Shukla, Y. (2008). Lupeol: Connotations for chemoprevention. *Cancer Letters*, *263*(1), 1–13. https://doi.org/10.1016/j.canlet.2008.01.047

Chaturvedula, V. S. P., Schilling, J. K., Miller, J. S., Andriantsiferana, R., Rasamison, E., & New, D. G. I. K. (2004). *Additions and Corrections 2004*,. *67*, 40162.

Cheng, D. H., Liu, Y., & Wang, L. (2021). Antitumor Effects of Ethanol Extract from Ventilago leiocarpa Benth on Sarcoma 180 Tumor-Bearing Mice and Possible Immune Mechanism. *Chinese Journal of Integrative Medicine*, *27*(12), 905–911. https://doi.org/10.1007/s11655-021-3440-4

Corrêa, R. S., Coelho, C. P., Dos Santos, M. H., Ellena, J., & Doriguetto, A. C. (2009). Lupeol. *Acta Crystallographica Section C: Crystal Structure Communications*, *65*(3).

https://doi.org/10.1107/S0108270109004910

De Lima, F. O., Alves, V., Filho, J. M. B., Da Silva Almeida, J. R. G., Rodrigues, L. C., Soares, M. B. P., & Villarreal, C. F. (2013). Antinociceptive effect of lupeol: Evidence for a role of cytokines inhibition. *Phytotherapy Research*, *27*(10), 1557–1563. https://doi.org/10.1002/ptr.4902

De Tommasi, N., De Simone, F., Cirino, G., Cicala, C., & Pizza, C. (1991). Hypoglycemic effects of sesquiterpene glycosides and polyhydroxylated triterpenoids of Eriobotrya japonica. *Planta Medica*, *57*(5), 414–416. https://doi.org/10.1055/s-2006-960137

Ebeling, S., Naumann, K., Pollok, S., Wardecki, T., Vidal-y-Sy, S., Nascimento, J. M., Boerries, M., Schmidt, G., Brandner, J. M., & Merfort, I. (2014). From a traditional medicinal plant to a rational drug: Understanding the clinically proven wound healing efficacy of birch bark extract. *PLoS ONE*, *9*(1). https://doi.org/10.1371/journal.pone.0086147

Eom, S., Kim, C., Yeom, H. D., Lee, J., Lee, S., Baek, Y. Bin, Na, J., Park, S. I., Kim, G. Y., Lee, C. M., & Lee, J. H. (2020). Molecular regulation of α3β4 nicotinic acetylcholine receptors by lupeol in cardiovascular system. *International Journal of Molecular Sciences*, *21*(12), 1–10. https://doi.org/10.3390/ijms21124329

Favre-Godal, Q., Dorsaz, S., Queiroz, E. F., Marcourt, L., Ebrahimi, S. N., Allard, P. M., Voinesco, F., Hamburger, M., Gupta, M. P., Gindro, K., Sanglard, D., & Wolfender, J. L. (2015). Anti-Candida Cassane-Type Diterpenoids from the Root Bark of Swartzia simplex. *Journal of Natural Products*, *78*(12), 2994–3004. https://doi.org/10.1021/acs.jnatprod.5b00744

Fernandes Rodrigues, J., & Souza, W. (2008). Ultrastructural Alterations in Organelles of Parasitic Protozoa Induced by Different Classes of Metabolic Inhibitors. *Current Pharmaceutical Design*, *14*(9), 925–938. https://doi.org/10.2174/138161208784041033

Fernández, M. A., de las Heras, B., Garcia, M. D., Sáenz, M. T., & Villar, A. (2010). New insights into the mechanism of action of the anti-inflammatory triterpene lupeol. *Journal of Pharmacy and Pharmacology*, *53*(11), 1533–1539. https://doi.org/10.1211/0022357011777909

Flekhter, O. B., Boreko, E. I., Nigmatullina, L. R., Pavlova, N. I., Medvedeva, N. I., Nikolaeva, S. N., Ashavina, O. A., Savinova, O. V., Baltina, L. A., Galin, F. Z., &

Tolstikov, G. A. (2004). Synthesis and antiviral activity of lupane triterpenoids and their derivatives. *Pharmaceutical Chemistry Journal*, *38*(7), 355–358. https://doi.org/10.1023/B:PHAC.0000048431.65649.bd

Fotie, J., Bohle, D. S., Leimanis, M. L., Georges, E., Rukunga, G., & Nkengfack, A. E. (2006). Lupeol long-chain fatty acid esters with antimalarial activity from Holarrhena floribunda. *Journal of Natural Products*, *69*(1), 62–67. https://doi.org/10.1021/np050315y

From, A. P., & Clavzflqrum, S. (1994). ANTI-HIV ACTIVITY OF STRUCTURALLY RELATED TRITERPENOIDS En ,. *J Nat Prod*, *57*(2), 243–247.

Geetha, T., & Varalakshmi, P. (2001a). Anti-inflammatory activity of lupeol and lupeol linoleate in rats. *Journal of Ethnopharmacology*, *76*(1), 77–80. https://doi.org/10.1016/S0378-8741(01)00175-1

Geetha, T., & Varalakshmi, P. (2001b). Anti-inflammatory activity of lupeol and lupeol linoleate in rats. *Journal of Ethnopharmacology*, *76*(1), 77–80. https://doi.org/10.1016/S0378-8741(01)00175-1

Ghante, M. H., & Jamkhande, P. G. (2019). Role of pentacyclic triterpenoids in chemoprevention and anticancer treatment: An overview on targets and underling mechanisms. *Journal of Pharmacopuncture*, *22*(2), 55–67. https://doi.org/10.3831/KPI.201.22.007

Ghazanfar, K., Mubashir, K., Dar, S. A., Nazir, T., Hameed, I., Ganai, B. A., Akbar, S., & Masood, A. (2017). Gentiana kurroo Royle attenuates the metabolic aberrations in diabetic rats; Swertiamarin, swertisin and lupeol being the possible bioactive principles. *Journal of Complementary and Integrative Medicine*, *14*(3). https://doi.org/10.1515/jcim-2017-0002

Giacoman-Martínez, A., Alarcón-Aguilar, F. J., Zamilpa, A., Hidalgo-Figueroa, S., Navarrete-Vázquez, G., García-Macedo, R., Román-Ramos, R., & Almanza-Pérez, J. C. (n.d.). *Giacoman-Martínez A et al. Triterpenoids from Hibiscus … Planta Med*.

Global Lupeol Market - ﷺ Industry Reports. (n.d.). Retrieved February 22, 2022, from https://www.kingpinmarketresearch.com/global-lupeol-market-19825558

Guan, T., Li, Y., Sun, H., Tang, X., & Qian, Y. (2009). Effects of maslinic acid, a natural triterpene, on glycogen metabolism in cultured cortical astrocytes. *Planta Medica*,

75(10), 1141–1143. https://doi.org/10.1055/s-0029-1185481

Guiné, R. P. F., & Barroca, M. J. (2012). Effect of drying treatments on texture and color of vegetables (pumpkin and green pepper). *Food and Bioproducts Processing*, *90*(1), 58–63. https://doi.org/10.1016/j.fbp.2011.01.003

Gupta, R. S., Bhatnager, A. K., Joshi, Y. C., Sharma, M. C., Khushalani, V., & Kachhawa, J. B. S. (2005). Induction of antifertility with lupeol acetate in male albino rats. *Pharmacology*, *75*(2), 57–62. https://doi.org/10.1159/000086947

Ha, D. T., Tuan, D. T., Thu, N. B., Nhiem, N. X., Ngoc, T. M., Yim, N. H., & Bae, K. H. (2009). Palbinone and triterpenes from Moutan Cortex (Paeonia suffruticosa, Paeoniaceae) stimulate glucose uptake and glycogen synthesis via activation of AMPK in insulin-resistant human HepG2 Cells. *Bioorganic and Medicinal Chemistry Letters*, *19*(19), 5556–5559. https://doi.org/10.1016/j.bmcl.2009.08.048

Hashmi, W. J., Ismail, H., Jafri, L., & Mirza, B. (2020). Ethnopharmacological activity of hedera nepalensis k. Koch extracts and lupeol against alloxan-induced type i diabetes. *Brazilian Journal of Pharmaceutical Sciences*, *56*, 1–15. https://doi.org/10.1590/s2175-97902019000318406

Hata, K., Hori, K., & Takahashi, S. (2003). Role of p38 MAPK in Lupeol-Induced B16 2F2 Mouse Melanoma Cell Differentiation. *Journal of Biochemistry*, *134*(3), 441–445. https://doi.org/10.1093/jb/mvg162

Hayami, I. (1970). NII-Electronic Library Service. *Chemical Pharmaceutical Bulletin*, *43*, 2091. http://www.mendeley.com/research/geology-volcanic-history-eruptive-style-yakedake-volcano-group-central-japan/

Hishiya, A., & Takayama, S. (2008). Molecular chaperones as regulators of cell death. *Oncogene*, *27*(50), 6489–6506. https://doi.org/10.1038/onc.2008.314

Hodges, L. D., Kweifio-Okai, G., & Macrides, T. A. (2003). Antiprotease effect of anti-inflammatory lupeol esters. *Molecular and Cellular Biochemistry*, *252*(1–2), 97–101. https://doi.org/10.1023/A:1025569805468

Howes, M. J. R. (2017). Phytochemicals as anti-inflammatory nutraceuticals and phytopharmaceuticals. In *Immunity and Inflammation in Health and Disease: Emerging Roles of Nutraceuticals and Functional Foods in Immune Support*. Elsevier Inc. https://doi.org/10.1016/B978-0-12-805417-8.00028-7

Important Microbiology Terms, Glossary, and Definitions. (n.d.). Retrieved February 21, 2022, from https://microbenotes.com/microbiology-terms/

Jäger, S., Laszczyk, M. N., & Scheffler, A. (2008). A preliminary pharmacokinetic study of betulin, the main pentacyclic triterpene from extract of outer bark of birch (Betulae alba cortex). *Molecules*, *13*(12), 3224–3235. https://doi.org/10.3390/molecules13123224

Jang, M. H., Piao, X. L., Kim, J. M., Kwon, S. W., & Park, J. H. (2008). Inhibition of cholinesterase and amyloid-&bgr; aggregation by resveratrol oligomers from Vitis amurensis. *Phytotherapy Research*, *22*(4), 544–549. https://doi.org/10.1002/ptr

Javed, S., Mahmood, Z., Khan, K. M., Sarker, S. D., Javaid, A., Khan, I. H., & Shoaib, A. (2021). Lupeol acetate as a potent antifungal compound against opportunistic human and phytopathogenic mold Macrophomina phaseolina. *Scientific Reports*, *11*(1), 1–11. https://doi.org/10.1038/s41598-021-87725-7

Jayaprakasam, B., Olson, L. K., Schutzki, R. E., Tai, M. H., & Nair, M. G. (2006). Amelioration of obesity and glucose intolerance in high-fat-fed C57BL/6 mice by anthocyanins and ursolic acid in cornelian cherry (Cornus mas). *Journal of Agricultural and Food Chemistry*, *54*(1), 243–248. https://doi.org/10.1021/jf0520342

Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., Murray, T., & Thun, M. J. (2008). Cancer Statistics, 2008. *CA: A Cancer Journal for Clinicians*, *58*(2), 71–96. https://doi.org/10.3322/ca.2007.0010

Käßmeyer, S., Plendl, J., Custodis, P., & Bahramsoltani, M. (2009). New insights in vascular development: Vasculogenesis and endothelial progenitor cells. *Journal of Veterinary Medicine Series C: Anatomia Histologia Embryologia*, *38*(1), 1–11. https://doi.org/10.1111/j.1439-0264.2008.00894.x

l ZanifəMcDowel. (2005). *No Title*6–1 .وسترتيغى تعليم اللغة العربية.

Lakshmi, V., Mahdi, A. A., Ahmad, M. K., Agarwal, S. K., & Srivastava, A. K. (2015). Antidiabetic Activity of Lupeol and Lupeol Esters in Streptozotocin- Induced Diabetic Rats. *Bangladesh Pharmaceutical Journal*, *17*(2), 138–146. https://doi.org/10.3329/bpj.v17i2.22330

Le, H. T. T., Chau, Q. C., Duong, T. H., Tran, Q. T. P., Pham, N. K. T., Nguyen, T. H. T., Nguyen, N. H., & Sichaem, J. (2021). New derivatives of lupeol and their biological activity. *MolBank*, *2021*(4), 5–9. https://doi.org/10.3390/M1306

Lee, W. K., Kao, S. Te, Liu, I. M., & Cheng, J. T. (2006). Increase of insulin secretion by ginsenoside Rh2 to lower plasma glucose in Wistar rats. *Clinical and Experimental Pharmacology and Physiology*, *33*(1–2), 27–32. https://doi.org/10.1111/j.1440-1681.2006.04319.x

Lerma-Torres, J. M., Navarro-Ocaña, A., Calderón-Santoyo, M., Hernández-Vázquez, L., Ruiz-Montañez, G., & Ragazzo-Sánchez, J. A. (2019). Preparative scale extraction of mangiferin and lupeol from mango (Mangifera indica L.) leaves and bark by different extraction methods. *Journal of Food Science and Technology*, *56*(10), 4625–4631. https://doi.org/10.1007/s13197-019-03909-0

Liu, K., Zhang, X., Xie, L., Deng, M., Chen, H., Song, J., Long, J., Li, X., & Luo, J. (2021). Lupeol and its derivatives as anticancer and anti-inflammatory agents: Molecular mechanisms and therapeutic efficacy. *Pharmacological Research*, *164*, 105373. https://doi.org/10.1016/j.phrs.2020.105373

Liu, Y., Bi, T., Shen, G., Li, Z., Wu, G., Wang, Z., Qian, L., & Gao, Q. (2016). Lupeol induces apoptosis and inhibits invasion in gallbladder carcinoma GBC-SD cells by suppression of EGFR/MMP-9 signaling pathway. *Cytotechnology*, *68*(1), 123–133. https://doi.org/10.1007/s10616-014-9763-7

Lucetti, D. L., Lucetti, E. C. P., Bandeira, M. A. M., Veras, H. N. H., Silva, A. H., Leal, L. K. A. M., Lopes, A. A., Alves, V. C. C., Silva, G. S., Brito, G. A., & Viana, G. B. (2010). Anti-inflammatory effects and possible mechanism of action of lupeol acetate isolated from Himatanthus drasticus (Mart.) Plumel. *Journal of Inflammation*, *7*, 1–11. https://doi.org/10.1186/1476-9255-7-60

Lupien, M., Meyer, C. A., Bailey, S. T., Eeckhoute, J., Cook, J., Westerling, T., Zhang, X., Carroll, J. S., Rhodes, D. R., Liu, X. S., & Brown, M. (2010). Growth factor stimulation induces a distinct ERα cistrome underlying breast cancer endocrine resistance. *Genes and Development*, *24*(19), 2219–2227. https://doi.org/10.1101/gad.1944810

Lyu, H., Chen, J., & Li, W. L. (2016). Natural triterpenoids for the treatment of diabetes mellitus: A review. *Natural Product Communications*, *11*(10), 1579–1586. https://doi.org/10.1177/1934578x1601101037

Macías-Rubalcava, M. L., Hernández-Bautista, B. E., Jiménez-Estrada, M., Cruz-Ortega, R., & Anaya, A. L. (2007). Pentacyclic triterpenes with selective bioactivity from

Sebastiania adenophora leaves, euphorbiaceae. *Journal of Chemical Ecology*, *33*(1), 147–156. https://doi.org/10.1007/s10886-006-9208-7

Majumder, S., Ghosh, A., & Bhattacharya, M. (2020). Natural anti-inflammatory terpenoids in Camellia japonica leaf and probable biosynthesis pathways of the metabolome. *Bulletin of the National Research Centre*, *44*(1). https://doi.org/10.1186/s42269-020-00397-7

Malik, A., Jamil, U., Butt, T. T., Waquar, S., Gan, S. H., Shafique, H., & Jafar, T. H. (2019). In silico and in vitro studies of lupeol and iso-orientin as potential antidiabetic agents in a rat model. *Drug Design, Development and Therapy*, *13*, 1501–1513. https://doi.org/10.2147/DDDT.S176698

Malini, M. M., Lenin, M., & Varalakshmi, P. (2000). Protective effect of triterpenes on calcium oxalate crystal-induced peroxidative changes in experimental urolithiasis. *Pharmacological Research*, *41*(4), 413–418. https://doi.org/10.1006/phrs.1999.0601

Malinowska, M. A., Sikora, E., Stalińska, J., Ogonowski, J., & Drukała, J. (2021a). The effect of the new lupeol derivatives on human skin cells as potential agents in the treatment of wound healing. *Biomolecules*, *11*(6), 1–16. https://doi.org/10.3390/biom11060774

Malinowska, M. A., Sikora, E., Stalińska, J., Ogonowski, J., & Drukała, J. (2021b). The Effect of the New Lupeol Derivatives on Human Skin Cells as Potential Agents in the Treatment of Wound Healing. *Biomolecules 2021, Vol. 11, Page 774*, *11*(6), 774. https://doi.org/10.3390/BIOM11060774

Malinowska, M., Miroslaw, B., Sikora, E., Ogonowski, J., Wojtkiewicz, A. M., Szaleniec, M., Pasikowska-Piwko, M., & Eris, I. (2019). New lupeol esters as active substances in the treatment of skin damage. *PLoS ONE*, *14*(3), 1–15. https://doi.org/10.1371/journal.pone.0214216

Martelanc, M., Vovk, I., & Simonovska, B. (2007). Determination of three major triterpenoids in epicuticular wax of cabbage (Brassica oleracea L.) by high-performance liquid chromatography with UV and mass spectrometric detection. *Journal of Chromatography A*, *1164*(1–2), 145–152. https://doi.org/10.1016/j.chroma.2007.06.062

McAuley, J. L., Gilbertson, B. P., Trifkovic, S., Brown, L. E., & McKimm-Breschkin, J. L. (2019). Influenza virus neuraminidase structure and functions. *Frontiers in*

Microbiology, *10*(JAN). https://doi.org/10.3389/fmicb.2019.00039

Memon, A. A., Memon, N., & Bhanger, M. I. (2010). Micelle-mediated extraction of chlorogenic acid from Morus laevigata W. leaves. *Separation and Purification Technology*, *76*(2), 179–183. https://doi.org/10.1016/j.seppur.2010.10.005

Min, T. R., Park, H. J., Ha, K. T., Chi, G. Y., Choi, Y. H., & Park, S. H. (2019). Suppression of EGFR/STAT3 activity by lupeol contributes to the induction of the apoptosis of human non-small cell lung cancer cells. *International Journal of Oncology*, *55*(1), 320–330. https://doi.org/10.3892/ijo.2019.4799

Moriarity, D. M., Huang, J., Yancey, C. A., Zhang, P., Setzer, W. N., Lawton, R. O., Bates, R. B., & Caldera, S. (1998). Lupeol is the cytotoxic principle in the leaf extract of Dendropanax cf. querceti. *Planta Medica*, *64*(4), 370–372. https://doi.org/10.1055/s-2006-957454

Nagaraj, M., Sunitha, S., & Varalakshmi, P. (2000). Effect of lupeol, a pentacyclic triterpene, on the lipid peroxidation and antioxidant status in rat kidney after chronic cadmium exposure. *Journal of Applied Toxicology*, *20*(5), 413–417. https://doi.org/10.1002/1099-1263(200009/10)20:5<413::AID-JAT706>3.0.CO;2-Y

Nguyen, T. D., MacNevin, G., & Ro, D. K. (2012). De novo synthesis of high-value plant sesquiterpenoids in yeast. In *Methods in Enzymology* (1st ed., Vol. 517). Elsevier Inc. https://doi.org/10.1016/B978-0-12-404634-4.00013-9

Norsuzila Ya'acob, M., Abdullah, M., Ismail, Medina, M., Talarico, T. L., Casas, I. A., Chung, T. C., Dobrogosz, W. J., Axelsson, L., Lindgren, S. E., Dobrogosz, W. J., Kerkeni, L., Ruano, P., Delgado, L. L., Picco, S., Villegas, L., Tonelli, F., Merlo, M., Rigau, J., … Masuelli, M. (1989). We are IntechOpen , the world ' s leading publisher of Open Access books Built by scientists , for scientists TOP 1 %. *Intech*, *32*, 137–144. http://www.intechopen.com/books/trends-in-telecommunications-technologies/gps-total-electron-content-tec- prediction-at-ionosphere-layer-over-the-equatorial-region %0AInTec

Nyaboke, O. H., Moraa, M., Omosa, K. L., Mbaveng, A. T., Nchiozem-Ngnitedem, V.-A., Masila, V., Okemwa, E., Heydenreich, M., Efferth, T., & Kuete, V. (2018). Cytotoxicity of Lupeol from the Stem Bark of Zanthoxylum gilletii against Multi-factorial Drug Resistant Cancer Cell Lines. *Investigational Medicinal Chemistry and Pharmacology*,

1(1), 10. https://investchempharm.com/

Ogiwara, K., & Hata, K. (2009). Melanoma cell differentiation induced by lupeol separates into two stages: Morphological and functional changes. *Journal of Natural Medicines*, *63*(3), 323–326. https://doi.org/10.1007/s11418-009-0319-7

Okusa, P. N., Penge, O., Devleeschouwer, M., & Duez, P. (2007). Direct and indirect antimicrobial effects and antioxidant activity of Cordia gilletii De Wild (Boraginaceae). *Journal of Ethnopharmacology*, *112*(3), 476–481. https://doi.org/10.1016/J.JEP.2007.04.003

Okusa, Philippe N., Stévigny, C., Névraumont, M., Gelbcke, M., Van Antwerpen, P., Braekman, J. C., & Duez, P. (2014). Ferulaldehyde and lupeol as direct and indirect antimicrobial compounds from Cordia gilletii (Boraginaceae) root barks. *Natural Product Communications*, *9*(5), 619–622. https://doi.org/10.1177/1934578x1400900506

Osbourn, A. E., & Lanzotti, V. (2009). Plant-derived natural products: Synthesis, function, and application. *Plant-Derived Natural Products: Synthesis, Function, and Application*, 1–597. https://doi.org/10.1007/978-0-387-85498-4

Oyeka, C. A., Amasiani, R. N., & Ekwealor, C. C. (2019). Mycotoxins contamination of maize in Anambra State, Nigeria. *Food Additives and Contaminants: Part B Surveillance*, *12*(4), 280–288. https://doi.org/10.1080/19393210.2019.1661528

Pan, W. H., Xu, X. Y., Shi, N., Tsang, S. W., & Zhang, H. J. (2018). Antimalarial activity of plant metabolites. *International Journal of Molecular Sciences*, *19*(5). https://doi.org/10.3390/ijms19051382

Papi Reddy, K., Singh, A. B., Puri, A., Srivastava, A. K., & Narender, T. (2009a). Synthesis of novel triterpenoid (lupeol) derivatives and their in vivo antihyperglycemic and antidyslipidemic activity. *Bioorganic and Medicinal Chemistry Letters*, *19*(15), 4463–4466. https://doi.org/10.1016/j.bmcl.2009.05.034

Papi Reddy, K., Singh, A. B., Puri, A., Srivastava, A. K., & Narender, T. (2009b). Synthesis of novel triterpenoid (lupeol) derivatives and their in vivo antihyperglycemic and antidyslipidemic activity. *Bioorganic and Medicinal Chemistry Letters*, *19*(15), 4463–4466. https://doi.org/10.1016/J.BMCL.2009.05.034

Parsaeimehr, A., Martinez-Chapa, S. O., & Parra-Saldívar, R. (2017). Medicinal Plants Versus Skin Disorders. *The Microbiology of Skin, Soft Tissue, Bone and Joint Infections*,

205–221. https://doi.org/10.1016/b978-0-12-811079-9.00013-6

Pentacyclic triterpenoic acids: new chemoprotective compounds. Minireview - PubMed. (n.d.). Retrieved February 21, 2022, from https://pubmed.ncbi.nlm.nih.gov/15640935/

Petrovska, B. B. (2012). Historical review of medicinal plants' usage. *Pharmacognosy Reviews*, *6*(11), 1–5. https://doi.org/10.4103/0973-7847.95849

Phan, H. V. T., Duong, T. H., Pham, D. D., Pham, H. A., Nguyen, V. K., Nguyen, T. P., Nguyen, H. H., Nguyen, N. H., Sam-ang, P., Phontree, K., & Sichaem, J. (2021). Design and synthesis of new lupeol derivatives and their α-glucosidase inhibitory and cytotoxic activities. *Natural Product Research*, *36*(1), 1–7. https://doi.org/10.1080/14786419.2020.1758095

Pisha, E., Chai, H., Lee, I. S., Chagwedera, T. E., Farnsworth, N. R., Cordell, G. A., Beecher, C. W. W., Fong, H. H. S., Kinghorn, A. D., Brown, D. M., Wani, M. C., Wall, M. E., Hieken, T. J., Gupta, T. K. D., & Pezzuto, J. M. (1995). Discovery of betulinic acid as a selective inhibitor of human melanoma that functions by induction of apoptosis. *Nature Medicine*, *1*(10), 1046–1051. https://doi.org/10.1038/nm1095-1046

Pitchai, D., Roy, A., & Ignatius, C. (2014). In vitro evaluation of anticancer potentials of lupeol isolated from Elephantopus scaber L. on MCF-7 cell line. *Journal of Advanced Pharmaceutical Technology and Research*, *5*(4), 179–184. https://doi.org/10.4103/2231-4040.143037

Plant Life: Metabolites: Primary vs Secondary. (n.d.). Retrieved February 21, 2022, from http://lifeofplant.blogspot.com/2011/03/metabolites-primary-vs-secondary.html

Prabhu, B., Balakrishnan, D., & Sundaresan, S. (2016). Antiproliferative and anti-inflammatory properties of diindolylmethane and lupeol against N -butyl- N -(4-hydroxybutyl) nitrosamine induced bladder carcinogenesis in experimental rats. *Human and Experimental Toxicology*, *35*(6), 685–692. https://doi.org/10.1177/0960327115597985

Prasad, S., Kalra, N., & Shukla, Y. (2007). Hepatoprotective effects of lupeol and mango pulp extract of carcinogen induced alteration in Swiss albino mice. *Molecular Nutrition and Food Research*, *51*(3), 352–359. https://doi.org/10.1002/mnfr.200600113

Prasad, S., Kalra, N., & Shukla, Y. (2008). Induction of apoptosis by lupeol and mango extract in mouse prostate and LNCaP cells. *Nutrition and Cancer*, *60*(1), 120–130.

https://doi.org/10.1080/01635580701613772

Prasad, S., Nigam, N., Kalra, N., & Shukla, Y. (2008a). Regulation of signaling pathways involved in lupeol induced inhibition of proliferation and induction of apoptosis in human prostate cancer cells. *Molecular Carcinogenesis*, *47*(12), 916–924. https://doi.org/10.1002/mc.20442

Prasad, S., Nigam, N., Kalra, N., & Shukla, Y. (2008b). Regulation of signaling pathways involved in lupeol induced inhibition of proliferation and induction of apoptosis in human prostate cancer cells. *Molecular Carcinogenesis*, *47*(12), 916–924. https://doi.org/10.1002/MC.20442

Preetha, S. P., Kanniappan, M., Selvakumar, E., Nagaraj, M., & Varalakshmi, P. (2006). Lupeol ameliorates aflatoxin B1-induced peroxidative hepatic damage in rats. *Comparative Biochemistry and Physiology - C Toxicology and Pharmacology*, *143*(3), 333–339. https://doi.org/10.1016/j.cbpc.2006.03.008

Priyanka, K., Kosuru, R., Sharma, R. P., Sahu, P. L., & Singh, S. (2017). Assessment of pharmacokinetic parameters of lupeol in Ficus religiosa L. extract after oral administration of suspension and solid lipid nanoparticles to Wistar rats. *Journal of Drug Delivery Science and Technology*, *41*, 58–67. https://doi.org/10.1016/j.jddst.2017.06.019

Qiao, W., Zhou, Z., Liang, Q., Mosongo, I., Li, C., & Zhang, Y. (2019). Improving lupeol production in yeast by recruiting pathway genes from different organisms. *Scientific Reports*, *9*(1), 1–8. https://doi.org/10.1038/s41598-019-39497-4

Ramu, R., Shirahatti, P. S., Nanjunda, S. S., Zameer, F., Dhananjaya, B. L., & Nagendra Prasad, M. N. (2016). Assessment of in vivo antidiabetic properties of umbelliferone and lupeol constituents of Banana (Musa sp. var. Nanjangud Rasa Bale) Flower in Hyperglycaemic Rodent Model. *PLoS ONE*, *11*(3), 1–17. https://doi.org/10.1371/journal.pone.0151135

Rangari, V. D., & Agarwal, R. B. (2003). *ANTIINFLAMMATORY AND ANTIARTHRITIC ACTIVITIES OF LUPEOL AND 19α-H LUPEOL Indian Journal of Pharmacology 2003; 35: 384-387 SHORT COMMUNICATION ANTIINFLAMMATORY AND ANTIARTHRITIC ACTIVITIES OF LUPEOL AND 19α-H LUPEOL ISOLATED FROM STROBILANTHUS CALLOSUS AND*. *165206*, 384–387.

Rao, S. D., Rao, B. N., Devi, P. U., & Rao, A. K. (2017). Isolation of lupeol, design and synthesis of lupeol derivatives and their biological activity. *Oriental Journal of Chemistry*, *33*(1), 173–180. https://doi.org/10.13005/ojc/330119

Regulation of the levels of health promoting compounds: lupeol, mangiferin and phenolic acids in the pulp and peel of mango fruit: a review. (n.d.). Retrieved February 22, 2022, from https://1library.net/document/yndkp90z-regulation-levels-health-promoting-compounds-lupeol-mangiferin-phenolic.html

Revathi, S., & D, D. R. M. (2012). International Journal of Health and Pharmaceutical Sciences Review Article. *Ijhpsonline.Com*, *1*, 37–45. http://ijhpsonline.com/pdf/2012_1(2)/6_109_36-41.pdf

Richards, L. A., Glassmire, A. E., Ochsenrider, K. M., Smilanich, A. M., Dodson, C. D., Jeffrey, C. S., & Dyer, L. A. (2016). Phytochemical diversity and synergistic effects on herbivores. *Phytochemistry Reviews*, *15*(6), 1153–1166. https://doi.org/10.1007/s11101-016-9479-8

Riedl, S. J., & Shi, Y. (2004). Molecular mechanisms of caspase regulation during apoptosis. *Nature Reviews Molecular Cell Biology*, *5*(11), 897–907. https://doi.org/10.1038/nrm1496

Roychoudhury, S., Chakraborty, S., Sinha, A., Kosgi, R., & Mandal, S. C. (2022). Herbal antilithiatic biomolecules. *Herbal Biomolecules in Healthcare Applications*, 573–590. https://doi.org/10.1016/B978-0-323-85852-6.00023-8

Saleem, M. (2009). Lupeol, a novel anti-inflammatory and anti-cancer dietary triterpene. *Cancer Letters*, *285*(2), 109–115. https://doi.org/10.1016/j.canlet.2009.04.033

Saleem, M., Kaur, S., Kweon, M. H., Adhami, V. M., Afaq, F., & Mukhtar, H. (2005). Lupeol, a fruit and vegetable based triterpene, induces apoptotic death of human pancreatic adenocarcinoma cells via inhibition of Ras signaling pathway. *Carcinogenesis*, *26*(11), 1956–1964. https://doi.org/10.1093/carcin/bgi157

Saleem, M., Kweon, M. H., Yun, J. M., Adhami, V. M., Khan, N., Syed, D. N., & Mukhtar, H. (2005). A novel dietary triterpene lupeol induces fas-mediated apoptotic death of androgen-sensitive prostate cancer cells and inhibits tumor growth in a xenograft model. *Cancer Research*, *65*(23), 11203–11213. https://doi.org/10.1158/0008-5472.CAN-05-1965

Saleem, M., Maddodi, N., Zaid, M. A., Khan, N., Bin Hafeez, B., Asim, M., Suh, Y., Yun, J. M., Setaluri, V., & Mukhtar, H. (2008). Lupeol inhibits growth of highly aggressive human metastatic melanoma cells in vitro and in vivo by inducing apoptosis. *Clinical Cancer Research*, *14*(7), 2119–2127. https://doi.org/10.1158/1078-0432.CCR-07-4413

Saleem, M., Murtaza, I., Tarapore, R. S., Suh, Y., Adhami, V. M., Johnson, J. J., Siddiqui, I. A., Khan, N., Asim, M., Hafeez, B. Bin, Shekhani, M. T., Li, B., & Mukhtar, H. (2009). Lupeol inhibits proliferation of human prostate cancer cells by targeting β-catenin signaling. *Carcinogenesis*, *30*(5), 808–817. https://doi.org/10.1093/carcin/bgp044

Saleem, R., Ahmad, S. I., Ahmed, M., Faizi, Z., Zikr-Ur-Rehman, S., Ali, M., & Faizi, S. (2003). Hypotensive activity and toxicology of constituents from Bombax ceiba stem bark. *Biological and Pharmaceutical Bulletin*, *26*(1), 41–46. https://doi.org/10.1248/bpb.26.41

Sánchez-Burgos, J. A., Ramírez-Mares, M. V., Gallegos-Infante, J. A., González-Laredo, R. F., Moreno-Jiménez, M. R., Cháirez-Ramírez, M. H., Medina-Torres, L., & Rocha-Guzmán, N. E. (2015). Isolation of lupeol from white oak leaves and its anti-inflammatory activity. *Industrial Crops and Products*, *77*, 827–832. https://doi.org/10.1016/j.indcrop.2015.09.056

Sassa, H., Takaishi, Y., & Terada, H. (1990). The triterpene celastrol as a very potent inhibitor of lipid peroxidation in mitochondria. *Biochemical and Biophysical Research Communications*, *172*(2), 890–897. https://doi.org/10.1016/0006-291X(90)90759-G

Sauriasari, R., Azizah, N., & Basah, K. (2017). Tyrosinase inhibition, 2,2-diphenyl-1-picrylhydrazyl radical scavenging activity, and phytochemical screening of fractions and ethanol extract from leaves and stem bark of matoa (Pometia pinnata). *Asian Journal of Pharmaceutical and Clinical Research*, *10*(Special Issue October), 85–89. https://doi.org/10.22159/ajpcr.2017.v10s5.23105

Sawai, S., & Saito, K. (2011). Triterpenoid biosynthesis and engineering in plants. *Frontiers in Plant Science*, *2*(JUN), 1–8. https://doi.org/10.3389/fpls.2011.00025

Shahlaei, M., Ghanadian, S. M., Ayatollahi, A. M., Mesaik, M. A., Abdalla, O. M., Afsharypour, S., & Rabbani, M. (2013). Molecular modeling, structure activity relationship and immunomodulatory properties of some lupeol derivatives. *Medicinal Chemistry Research*, *22*(4), 1795–1803. https://doi.org/10.1007/s00044-012-0183-y

Shai, L. J., McGaw, L. J., Aderogba, M. A., Mdee, L. K., & Eloff, J. N. (2008). Four pentacyclic triterpenoids with antifungal and antibacterial activity from Curtisia dentata (Burm.f) C.A. Sm. leaves. *Journal of Ethnopharmacology*, *119*(2), 238–244. https://doi.org/10.1016/j.jep.2008.06.036

Shedoeva, A., Leavesley, D., Upton, Z., & Fan, C. (2019). Wound healing and the use of medicinal plants. *Evidence-Based Complementary and Alternative Medicine*, *2019*(Figure 1). https://doi.org/10.1155/2019/2684108

Siddique, H. R., Mishra, S. K., Karnes, R. J., & Saleem, M. (2011). Lupeol, a novel androgen receptor inhibitor: Implications in prostate cancer therapy. *Clinical Cancer Research*, *17*(16), 5379–5391. https://doi.org/10.1158/1078-0432.CCR-11-0916

Silva, A. T. M. E., Magalhães, C. G., Duarte, L. P., Mussel, W. da N., Ruiz, A. L. T. G., Shiozawa, L., de Carvalho, J. E., Trindade, I. C., & Filho, S. A. V. (2017). Lupeol and its esters: Nmr, powder xrd data and in vitro evaluation of cancer cell growth. *Brazilian Journal of Pharmaceutical Sciences*, *53*(3), 1–10. https://doi.org/10.1590/S2175-97902017000300251

Soares, D. C. F., de Paula Oliveira, D. C., Barcelos, L. S., Barbosa, A. S., Vieira, L. C., Townsend, D. M., Rubello, D., de Barros, A. L. B., Duarte, L. P., & Silva-Cunha, A. (2017). Antiangiogenic activity of PLGA-Lupeol implants for potential intravitreal applications. *Biomedicine and Pharmacotherapy*, *92*, 394–402. https://doi.org/10.1016/j.biopha.2017.05.093

Srivastava, P., Jyotshna, Gupta, N., Maurya, A. K., & Shanker, K. (2014). New anti-inflammatory triterpene from the root of Ricinus communis. *Natural Product Research*, *28*(5), 306–311. https://doi.org/10.1080/14786419.2013.861834

Sudhahar, V., Kumar, S. A., Sudharsan, P. T., & Varalakshmi, P. (2007a). Protective effect of lupeol and its ester on cardiac abnormalities in experimental hypercholesterolemia. *Vascular Pharmacology*, *46*(6), 412–418. https://doi.org/10.1016/j.vph.2006.12.005

Sudhahar, V., Kumar, S. A., Sudharsan, P. T., & Varalakshmi, P. (2007b). Protective effect of lupeol and its ester on cardiac abnormalities in experimental hypercholesterolemia. *Vascular Pharmacology*, *46*(6), 412–418. https://doi.org/10.1016/J.VPH.2006.12.005

Sudhahar, V., Kumar, S. A., & Varalakshmi, P. (2006). Role of lupeol and lupeol linoleate on lipemic-oxidative stress in experimental hypercholesterolemia. *Life Sciences*, *78*(12),

1329–1335. https://doi.org/10.1016/j.lfs.2005.07.011

Sudharsan, P. T., Mythili, Y., Selvakumar, E., & Varalakshmi, P. (2005). Cardioprotective effect of pentacyclic triterpene, lupeol and its ester on cyclophosphamide-induced oxidative stress. *Human and Experimental Toxicology*, *24*(6), 313–318. https://doi.org/10.1191/0960327105ht530oa

Sudharsan, P T, Mythili, Y., Sudhahar, V., & Varalakshmi, P. (2010). Role of lupeol and its ester on cyclophosphamide-induced hyperlipidaemic cardiomyopathy in rats. *Journal of Pharmacy and Pharmacology*, *57*(11), 1437–1444. https://doi.org/10.1211/JPP.57.11.0009

Sudharsan, Periyasamy Thandavan, Mythili, Y., Selvakumar, E., & Varalakshmi, P. (2006). Lupeol and its ester ameliorate the cyclophosphamide provoked cardiac lysosomal damage studied in rat. *Molecular and Cellular Biochemistry*, *282*(1–2), 23–29. https://doi.org/10.1007/s11010-006-1169-1

Suksamrarn, S., Panseeta, P., Kunchanawatta, S., Distaporn, T., Ruktasing, S., & Suksamrarn, A. (2006). Ceanothane- and lupane-type triterpenes with antiplasmodial and antimycobacterial activities from Ziziphus cambodiana. *Chemical and Pharmaceutical Bulletin*, *54*(4), 535–537. https://doi.org/10.1248/cpb.54.535

Surendra, K., & Corey, E. J. (2009). A short enantioselective total synthesis of the fundamental pentacyclic triterpene lupeol. *Journal of the American Chemical Society*, *131*(39), 13928–13929. https://doi.org/10.1021/ja906335u

Takagi, S., Miura, T., Ishibashi, C., Kawata, T., Ishiara, E., Gu, Y., & Ishida, T. (2008). Effect of corosolic acid on the hydrolysis of disaccharides. *Journal of Nutritional Science and Vitaminology*, *54*(3), 266–268. https://doi.org/10.3177/jnsv.54.266

Tamanoi, F., Kato-Stankiewicz, J., Jiang, C., Machado, I., & Thapar, N. (2001). Farnesylated proteins and cell cycle progression. *Journal of Cellular Biochemistry*, *84*(SUPPL. 37), 64–70. https://doi.org/10.1002/jcb.10067

Tan, M. J., Ye, J. M., Turner, N., Hohnen-Behrens, C., Ke, C. Q., Tang, C. P., Chen, T., Weiss, H. C., Gesing, E. R., Rowland, A., James, D. E., & Ye, Y. (2008). Antidiabetic Activities of Triterpenoids Isolated from Bitter Melon Associated with Activation of the AMPK Pathway. *Chemistry and Biology*, *15*(3), 263–273. https://doi.org/10.1016/j.chembiol.2008.01.013

Taylor, P., Gupta, R., Sharma, A. K., & Sharma, M. C. (2011). *Natural Product Research : Formerly Natural Product Letters Evaluation of antidiabetic and antioxidant potential of lupeol in experimental hyperglycaemia*. *October 2012*, 37–41.

The historical use of medicinal plants in traditional and scientific medicine - PubMed. (n.d.). Retrieved February 21, 2022, from https://pubmed.ncbi.nlm.nih.gov/29278625/

Thirumalaisamy, R., Ameen, F., Subramanian, A., Selvankumar, T., Alwakeel, S. S., & Govarthanan, M. (2020). In-Vitro and In-Silico Anti-inflammatory Activity of Lupeol Isolated from Crateva adansonii and Its Hidden Molecular Mechanism. *International Journal of Peptide Research and Therapeutics*, *26*(4), 2179–2189. https://doi.org/10.1007/s10989-019-10006-5

Tsai, F. S., Lin, L. W., & Wu, C. R. (2016). Lupeol and its role in chronic diseases. In *Advances in Experimental Medicine and Biology* (Vol. 929). https://doi.org/10.1007/978-3-319-41342-6_7

VIncent P.K. Titanji, D. Z. and M. N. N. (2008). Review Paper THE ANTIMALARIAL POTENTIAL OF MEDICINAL PLANTS USED FOR THE TREATMENT. *African Journal of Tradtional Complementary and Alternative Medicine*, *5*, 302–321.

Vithana, M. D. K., Singh, Z., & Johnson, S. K. (2019). Regulation of the levels of health promoting compounds: lupeol, mangiferin and phenolic acids in the pulp and peel of mango fruit: a review. *Journal of the Science of Food and Agriculture*, *99*(8), 3740–3751. https://doi.org/10.1002/jsfa.9628

Wada, S. I., Iida, A., & Tanaka, R. (2001). Screening of triterpenoids isolated from Phyllanthus flexuosus for DNA topoisomerase inhibitory activity. *Journal of Natural Products*, *64*(12), 1545–1547. https://doi.org/10.1021/np010176u

Wal, P., Wal, A., Sharma, G., & Rai, A. K. (2011). Biological activities of lupeol. *Systematic Reviews in Pharmacy*, *2*(2), 96–103. https://doi.org/10.4103/0975-8453.86298

Wang, H., Xu, C., Kong, X., Li, X., Kong, X., Wang, Y., Ding, X., & Yang, Q. (2019). Correction: TRAIL resistance induces epithelial-mesenchymal transition and enhances invasiveness by suppressing PTEN via miR-221 in breast cancer (PLoS ONE (2019) 9:6 (e99067) DOI: 10.1371/journal.pone.0099067). *PLoS ONE*, *14*(3), 4–7. https://doi.org/10.1371/journal.pone.0214433

WO2014147581A1.pdf. (n.d.).

Xu, A., Wang, H., Hoo, R. L. C., Sweeney, G., Vanhoutte, P. M., Wang, Y., Wu, D., Chu, W., Qin, G., & Lam, K. S. L. (2009). Selective elevation of adiponectin production by the natural compounds derived from a medicinal herb alleviates insulin resistance and glucose intolerance in obese mice. *Endocrinology*, *150*(2), 625–633. https://doi.org/10.1210/en.2008-0999

Yamada, K., Hosokawa, M., Fujimoto, S., Fujiwara, H., Fujita, Y., Harada, N., Yamada, C., Fukushima, M., Ueda, N., Kaneko, T., Matsuyama, F., Yamada, Y., Seino, Y., & Inagaki, N. (2008). Effect of corosolic acid on gluconeogenesis in rat liver. *Diabetes Research and Clinical Practice*, *80*(1), 48–55. https://doi.org/10.1016/j.diabres.2007.11.011

Yasumoto, S., Seki, H., Shimizu, Y., Fukushima, E. O., & Muranaka, T. (2017). Functional characterization of CYP716 family P450 enzymes in triterpenoid biosynthesis in tomato. *Frontiers in Plant Science*, *8*(JANUARY). https://doi.org/10.3389/fpls.2017.00021

Yi, J. E., Obminska-Mrukowicz, B., Yuan, L. Y., & Yuan, H. (2010). Immunomodulatory effects of betulinic acid from the bark of white birch on mice. *Journal of Veterinary Science*, *11*(4), 305–313. https://doi.org/10.4142/jvs.2010.11.4.305

You, Y. J., Nam, N. H., Kim, Y., Bae, K. H., & Ahn, B. Z. (2003). Antiangiogenic activity of lupeol from Bombax ceiba. *Phytotherapy Research*, *17*(4), 341–344. https://doi.org/10.1002/ptr.1140

Zafrul Azam, A. T. M., Al Hasan, A., Uddin, M. G., Masud, M. M., & Hasan, C. M. (2012). Antimicrobial, antioxidant and cytotoxic activities of Glochidion multiloculare (Roxb. ex Willd.) Müll. Arg. (Euphorbiaceae). *Dhaka University Journal of Pharmaceutical Sciences*, *11*(2), 117–120. https://doi.org/10.3329/dujps.v11i2.14560

Zhang, J., Liang, H., Yao, H., Qiu, Z., Chen, X., Hu, X., Hu, J., & Zheng, G. (2019). The preparation, characterization of Lupeol PEGylated liposome and its functional evaluation in vitro as well as pharmacokinetics in rats. *Drug Development and Industrial Pharmacy*, *45*(7), 1052–1060. https://doi.org/10.1080/03639045.2019.1569038

Zhang, L., Zhang, Y., Zhang, L., Yang, X., & Lv, Z. (2009). Lupeol, a dietary triterpene, inhibited growth, and induced apoptosis through down-regulation of DR3 in SMMC7721 cells. *Cancer Investigation*, *27*(2), 163–170. https://doi.org/10.1080/07357900802210745

Ziegler, H. L., Stærk, D., Christensen, J., Hviid, L., Hägerstrand, H., & Jaroszewskil, J. W. (2002). In vitro Plasmodium falciparum drug sensitivity assay: Inhibition of parasite growth by incorporation of stomatocytogenic amphiphiles into the erythrocyte membrane. *Antimicrobial Agents and Chemotherapy*, *46*(5), 1441–1446. https://doi.org/10.1128/AAC.46.5.1441-1446.2002