The Journal of Phytopharmacology 2022; 11(6):425-431
Online at: www.phytopharmajournal.com

Review Article

ISSN 2320-480X
JPHYTO 2022; 11(6): 425-431
November- December
Received: 03-10-2022
Accepted: 19-11-2022
Published: 20-12-2022

doi: 10.31254/phyto.2022.11609

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Lupeol: An Alternative Approach towards Cancer Treatment

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ABSTRACT

Cancer is a broad word for a group of neoplastic illnesses defined by changes in a cell's structure that cause it to proliferate abnormally. There are about 200 cancers detected in human body. Each type of carcinoma has different indications and symptoms, as well as different treatments. Lupeol 280 mg/g dried leafs is a chemical component found in aloe leaves. Lupeol is a triterpene active in both food and medicine. Over the last decade, an unprecedented massive increase in involvement in triterpene as a result of their cholesterol-lowering properties. The products based on triterpene are commercially over sold in the world due to its heavy demand of use. Fagarsterol another name for the chemical lupeol. It's found in foods like *Brassica oleracea var. capitata, Capsicum annuum Group, Fragaria, Olea europaea, Mangifera indica, Vitis vinifera, Aloe barbandesismiller*, Semaltreeetc. Lupeol was already demonstrated to be an efficient curative and protective constituent for a wide range of disorders. It is an anti-carcinogenic and curative compound. Many developments have been so far with respective lupeol dosage formulation to increase bioavailability and pharmacological effect. This manuscript also provides deep inside of recent patents associated with lupeol in past decade.

Keywords: Cancer, Leukemia, Lymphoma, Myeloma, Lupeol, *Aloe vera*.

INTRODUCTION

Cancer is a pervasive illness that affects people in every nation on the planet. Cancer is the major reason of death rates in all over the world after heart disorders. Every year, 8,00,000 people in the United States are detected with cancer, with India accounting for about half of these cases. Cancer is a word used to describe a group of illnesses known as neoplastic diseases [neos = new, plasma creation], which are defined by alterations in a cell that cause aberrant (unordered and uncontrolled) cell multiplication. In general, neoplastic disorders are classified as benign or malignant

Unlike malignant tumors, adenomas are usually enclosed inside a connective tissue membrane, and histological, all cells seem to be identical and originated from the same tissue source. They are not contagious and do not expand to further sections of body parts. The type of cells and tissues involved in cancer are categorized physiologically. Mostly human cancers are carcinomas, which are characterized as solid tumors that arise from epithelial cells. These include the mucous membranes, dermis, pancreas, thyroid, prostrate, liver, and breast, as well as the colon and derived organs, which include the mucous membranes, dermis, pancreas, thyroid, prostrate, liver, and breast. [1].

There are about 100 kinds of human cancer, with human carcinomas accounting for around 95% of all malignancies, mixed tissue tumors like testes and ovaries accounting for 3% of all malignancies, and sarcomas accounting for the remaining 2%. Sarcomas are solid tumors that develop in connective tissues like that cartilage, muscle, fibrous connective tissues, and bones and are derived from embryonic mesoderm.

Cancer symptoms and indications vary with the kind of cancer, its location, and how far the cells have gone. For example, breast cancer may apparent as a lump in the breast or nipple discharge, on the other way metastatic breast cancer may apparent as discomfort (if it has rises to the bones), severe tiredness (lungs), or convulsions (brain).

Imaging tests are frequently used to assist doctors in finding malignant irregularities in the body. Doctor's use computed tomography, magnetic resonance imaging, ultrasound and X-radiations to examine the body. Depending upon the technology used similar methods like endoscopy, bronchoscopy may allow visualization of highly cancerous cells in the colon, bronchus and throat in difficult to see areas, radio nuclear screening is frequently used. The procedure entails taking or administering an intravenous injection of mildly radiopharmaceutical which can be localized in abnormal tissue and detected. [1,2,3,4,5,39,43].

CANCER PREVENTIONS

- Tobacco should not be used.
- Eat healthy and nutritious food.
- Maintain a healthy weight and engage in regular physical activity.
- Get your vaccinations immediately.
- Take precautions against the sun.
- Avoid risky behaviors such as needles sharing and protected sex.

CANCER TREATMENT

Various treatments take part in the treatment of cancer like Biomarker testing, chemotherapy, hormone therapy, Hyperthermia, Immunotherapy, photodynamic therapy, surgery, radiation therapy and targeted therapy.

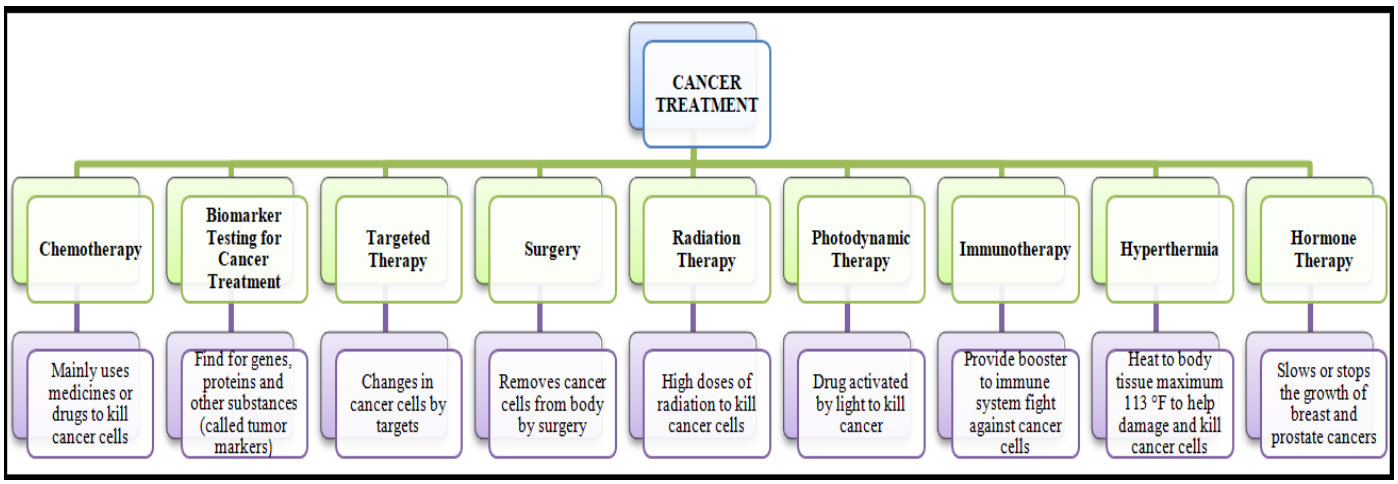

Figure 1: Cancer Treatment

DRAWBACK OF EXISTING TREATMENT

Drawback of chemotherapy

Main drawback of chemotherapy is side effects like weakness, hair loss, bleeding, Low red blood cell counts, nausea, and appetite changes, vomiting, constipation, diarrhea, problems occurs in mouth, tongue and throat like sores and pain during swallowing, peripheral neuropathy and other nerve problem associated with numbness, tingling, and pain, problem occurs in skin dryness and color change, side effects in kidney and bladder associated with urine, mood changes, problems occurs in affect concentration and focus, weight changes, problems in sexual function and fertility problems.

PHYTOCHEMICAL POTENTIAL IN CANCER PREVENTION

The aloe vera plant has long been known for its health, cosmetic, medicinal, and skin-care advantages. Aloe vera is derived from the Arabic phrase 'Alloeh,' which signifies "shining bitter material," and the Latin term vera, which means "truth." Greek scientists approved aloe vera as a universal medication 2000 years ago. [6,7,8] Aloe vera is scientifically known as *"Aloe Barbadensis Miller."* The plant species belongs to *Asphodelaceae* and *Liliaceae* family. It is an evergreen, xerophilous, fleshy and green plant. This plant has triangle leaves, yellow tube-like flowers; sharpe leaves edges and fruit with numerous seeds. Each leaf contains three layers: the outer layer, the middle layer, and the inner layer [9,10,11,12,13,14,15]. An inner translucent gel contains ninety nine percent water and contains various elements such as lipids, amino acids, glucomannans, and vitamins, sterols. Glycosides and Anthraquinones are found in the bitter yellow sap in the interfacial layer of latex. Protective covering rind layer is composed of 15 to 20 cells layers which contain carbohydrates and proteins. It includes antioxidants Vitamin A (beta-carotene), C, and E. There's also vitamin B_{12}, choline and folic acid. Antioxidant works to neutralize free radicals. Among the eight enzymes identified in it are peroxidases, lipases, celluloses, catalases, carboxypeptidases, brady kinase, amylases, alkaline phosphatases, alliances. It contains minerals like K, Ca, Zn, Na, Mg, Cu, Se, Mn and Cr. Sugars contain mono and polysaccharides. Mucopolysaccharides are derived from the mucilaginous covering of plants. Aloe vera gels have recently released alprogen a glycoprotein as well as C-glucosyl chromone, a novel anti-inflammatory molecule. It consists of twelve anthra-quinones, phenolics compounds that have been utilized as enemas in the past. It contains minerals like Ca, Cr, Cu, Mg, Mn, Se, K, Na and Zn. Sugars contain mono and polysaccharides. It comprises Phyto hormones such as cholesterol, camp sterol, beta-sitosterol, and lupeol. They all have Anti-inflammatory properties, while lupeol likewise possess bactericidal and pain-relieving properties. Auxins and gibberellins are anti-inflammatory hormones that help with tissue repair. It has 20 of the 22 amino acids that man required, including 7 of the 8 essential amino acids. There's also salicylic acid, lignin, and saponins.

LUPEOL

Structure

Lupeol (**Figure 2**)

Scientific Name of Lupeol - 3-lup-20(29)-en-3-ol

Rings present-

6 member rings- 4 (total number), contain chair conformation

5 member rings- 1 (total number), contain envelop conformation [27].

It is a kind of terpene develop in plants

Therapeutic potentials

Lupeol act as a carcinoma preventive medium in the treatment of carcinomas and anti-inflammatory. It is found in *Aloe barbandesis miller*, *Brassica oleracea var. capitata*, *Olea europaea*, Semal tree, *Mangifera indica*, *Capsicum annuum Group*, *Fragaria*, *Vitis vinifera*, *Himatanthussucuuba*, and *Celastruspaniculatus* etc.

Chemistry

Lupeol has the chemical formula $C_{30}H_{50}O$ and a melting point of 215-216°C. 426.7174g/mol is its molecular formula (Saleem, 2009)[39].

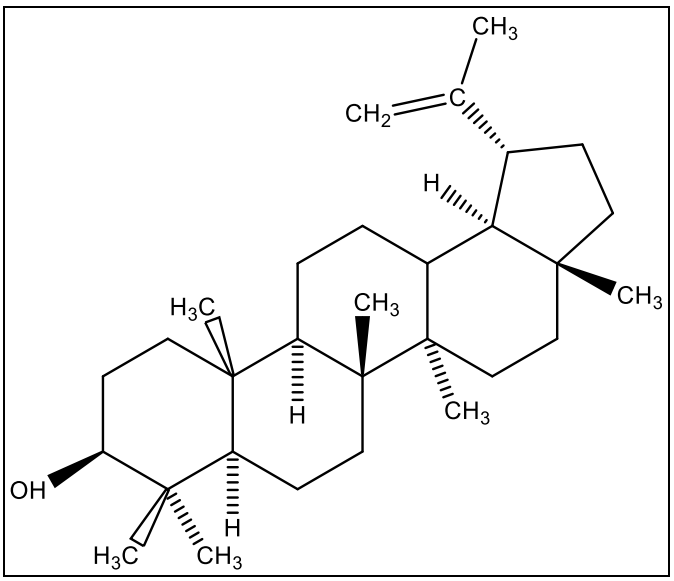

Figure 2: Lupeol Structure

Characteristics of lupeol

Lupeol extracted by the process of esterification. To make lupeol esters, the following carboxylic acids and its anhydrides were utilized as an acylating agents: - acetate, propionate, isonicotinate, succinate, and acetylsalicylate.

Esterificationphenomenon: -1 gram/2.3 mmol of Lupeol + 10 cm^3 oftetrahydrofurane+7.5cm^3 /sigma Aldrich of N-methylmorphine+sigma Aldrich carboxylic acid with anhydride +N,N-dicyclohexylcarbodimide(as catalyst)+4-dimethylaminopyridine (as catalyst) + with 4 hrs reflux.

The thin layer chromatography (TLC) technique had been used to monitor the reactions progression. Thin layer chromatography platesfrom poly-gram Silica gel G with ultraviolet range 254 nanometer and machereysodium gel were utilized. An eluent, a 9:1 v/v mixture of $C_4H_8O_2$ and $CHCl_3$was utilized. TLC plates were sprayed with a 50 percent phosphoric acid water solution with a 10 percent isopropanol vanillin solution. When plates were heated for two-three minutes at the temperature range of 100 degree Celsius the triterpenes appeared evident. The resulting mixture was put into 300 cm^3 of a 10% aqua hydrochloric acid solution in each synthesis. The organic solvent was washed two-three times from twenty percent hydro solution of sodium bicarbonate (50 cm each time) for neutralization. The organic solvent was then evaporated and condensed to 1/3 of its original amount using magnesium sulphate. The pure product was separated out. The powders dried at 37 degree Celsius after the solvent evaporation, and then crystallized from methanol and chloroform.

Quantitation and Detection

Medicinal plant usage is now on the rise. Due to its low cost as compared to the synthetic medicines. The natural treatment has fewer side effects. Active components from herbal plant are responsible for its pharmacological effect, and the quantity of such components may vary significantly depending on different types of variables like herbal plant's cells utilized and the harvest season.

Quality monitoring for phyto-preparations/medicated plant requires advancement in techniques, for detecting and quantifying active substances. GC and HPTLC is the most often used methods for quantifying lupeol as medicinal plant. Low-cost HPTLC method is versatile, and fast. The stationary phase is a silica gel $60F_{254}$, and the plate development may be done using various solvent systems such as (toluene:methanol:9:1:v/v), (toluene:chloroform 10:2 v/v), (ethyl acetate:glacial acetic acid:10:2 v/v), (toluene: ethylacetate: methanol 7.5:1.5:0.7) and (n-hexane:ethyl ,acetate 5:1) [8,54].

For measurement and identification of lupeol in seed oil or plant extract, pre-derivatization of the samples, such as by acetylation or trimethylsilylation, or utilising a silica gel column/liquid-liquid partition is necessary.

Pre-derivatization of the samples, such as by acetylation pr trimethylsilylation, is required for quantification and detection of lupeol in seed oil or plant extract or using silica gel column/liquid-liquid partition is required [16,17,18,19,20]. They have successfully validated a technique to measure quantity of lupeol in Justicia anselliana (the extract produced Finally, Reversed Phase of high-performance liquid chromatographyis the newest and least expensive method for quantifying and determining lupeol (RP-HPLC).

Mathe *et al*., developed a resversed phase HPTLC technique to find out lupeol and other 14 penta-cyclic triterpenes in a way to differentiate botanical and geographical origin of comerricial oleo-gum resins frankincense, using acetonitrile and water both contain phosphoric acid (0.01%) as mobile phase and UV range at 210 nm. To assess the presence of lupeol in white cabbage epicuticle wax, Martelanc *et al*., 2007 employed reversed phase HPTLC with ultra-visible and mass spectrometer detectors. [29].

Using a 15 cm C18 column and (ACN: water 4:1) as mobile phase, Li *et al*., 2008 devised an RP-HPLC way to estimate lupeol in ilex cornuta. Martelanc *et al*., 2009 devised a technique for detecting lupeol in triterpenoid isomeric combinations from plant extracts using a mix of complimentary chromatography technologies. They got high resolution for amyrin, lupenone, cycloartenol, lupeol, lupeol acetateand cycloartenol acetate using an HPLC coupled to UV at 220 nm and an ion trap LCQ. Positive mode LCQ MS/MS system with ACPI ion source and CID- collision induced dissociation ion trap. They also discovered that RP-HPTLC can accomplish better separation of isomeric combinations than regular HPTLC, and that (acetone: ACN: 5:1 v/v) ratio is provide good solvent for lupeol. [27,29].

Pharmacological application of Lupeol

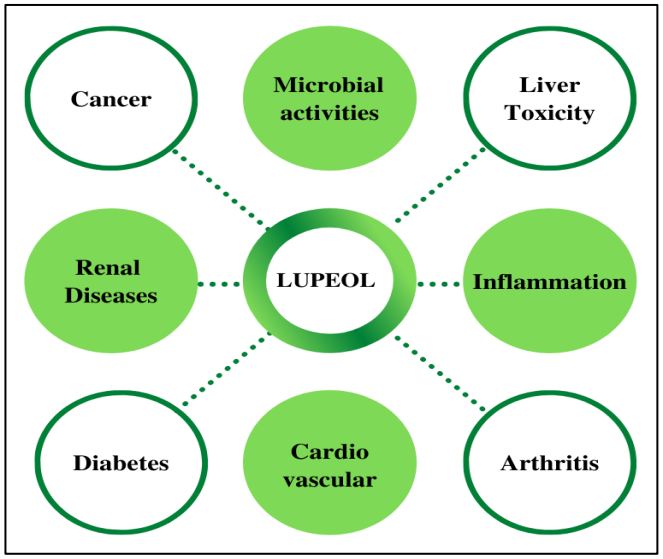

Figure 3: Therapeutics uses of Lupeol

Antiangiogenic Activity

Active principle was isolated via methanol successively. The successive solvents areCH_2Cl_2, $C_4H_8O_2$, C_6H_{14}, $C_4H_{10}O$.A test indicate dichloromethane fraction had antiangiogenic activity. At both 50 gram per milliliter and 30 gram per milliliter concentrations tested, the CH_2Cl_2 extract was significantly inhibitive of HUVEC tube formation. In 50 grams per milliliter CH_2Cl_2 extract, HUVEC tube formation was suppressed above 80 percent. Even at a lesser dosage of 30 grams per millilitre, a significant impact was detected with a suppression rate of forty to sixty percent. Silica gel coloumn used to chromatograph the extract, yielding eight fractions, the most potent of which was fraction five, which inhibited more than eighty percent of the enzyme at 50 gram per milliliter.

This fraction was examined using thin layer chromatography and showed one large area that responded favorably with a triterpenoid detection reagent (Carre-Price). After repeated crystalizations of fraction five from methanol,1.3-gram, BX-1 white color pin like crystals were produced. BX-1's H-NMR spectra revealed a triterpene pattern and two wide singlet peaks at 4.69 ppm and 4.56 ppm. Two distinct peaks emerged in the ^{13}C-NMR spectra at 150.9 ppm and 109.3 ppm. An isopropenyl group was responsible for peaks results. Following that, thorough comparisons of different spectrum mentioned in literature revealed BX-I to be lupeol [21].Other plants that contain lupeol include *Pterocarpus santalinus, Betula alnoides*, *Parkia biglobosa* and *Ventilagoleiocarpa* [22,23,24,2539].

Table 1: Anti-cancer perspectives of lupeol.

Anti-cancer activity	Findings	Reference
Antimetastatic	Lupeol suppress invasive colorectal cancerous tissues through modifying actin cytoskeleton by rho-associated, protein kinase-1 pathway suppression that give strong strength to lupeol may provide an effective anti-metastatic agent for CRC patients.	[40]
Antitumor	Lupeol inhibits tumor growth and metastasis by limiting macrophage M2 polarisation and inhibiting the urge of macrophages towards cancerous cells. This study gives information regarding M2 polarization of macrophages.	[41]
Antileukemic activity	The cytotoxic lupeol derivatives demonstrated high blood compatibility in a hemolysis assay, indicating that intravenous incorporation of lupeol derivatives has the potential to develop antileukemic medications.	[42]
Antihyperglycemic	Lupeols derivatives was synthesized, evaluated for their alpha-glucosidase inhibitory and cytotoxic activities. Benzylidene chain has good potential against alpha-glucosidase.	[43]

Table 2: Pharmacological application of the Lupeol

Pharmacological Activity	Findings	Reference
Anti-inflammatory	*In vitro* and silico screening of lupeol molecule have five targets side TNFα (PDBID: 2AZ5), COX-2 (PDB ID: 4COX), IL6 (PDBID: 7 PM), IL1β (PDBID" 1T4Q) and MPO (PDB ID: 3ZS0) which are capable for the anti-inflammatory activity and their auto dock results (-11.6, -9.0, -9.9, -7.5, -9.0 kcal/mol) showed that lupeol have maximum binding affinity.	[40]
Anti-Diabetic	Lupeol study identified the effects on antioxidant enzymes, it act on enzymic antioxidants superoxide dismutase (SOD), catalase (CAT), and non-enzymic antioxidant (Vitamin C) in type-2 diabetic adult male rats and decrease the levels of antioxidant enzymes (SOD, Vitamin C and CAT) in gastrointestinal part i.e. liver of the type-2 diabetic rats. Lupeol showed similar effects of metformin and regulates the antioxidant enzymes.	[41]
Cardioprotective	Lupeol reduces the activities of farnesyl- diphosphate farnesyl transferase-1, sterol regulatory element-binding protein-1c and -2, 3-hydroxy-3-methylglutaryl-Coenzyme A synthetase-1 and fatty acid synthase and decreases cholesterol, triglyceride secretion from HepG2-Lipo human hepatoma cells. Lupeol inhibited apolipoproteinB-100 present in the cells at the mRNA level.	[42,43]
Skin protective	Lupeol supressIκBα phosphorylation and degradation, of Lupeol on NF-κB/p65 is through the suppression of proteolysis and IκBα.	[43]
Antimicrobial agents	Lupeol exhibits antimicrobial activity against Gram-negative, Gram-positive bacteria especially against C. Albicans.	[44]
Antiviral	Lupeol has been reported to anti-viral activity towards infection of Herpes simplex virus- 1 (HSV1) or (HSV-2) infection.	[45]
	Lupeol inhibited HIV-1 reverse transcriptase (RT)-associated RNA-dependent DNA polymerase (RDDP) activity as well as the antiviral activities of drugs targeting -glucosidase.	[46]
Nephroprotective agent	Lupeol has effects on SKRC-45 (an RCC cell line) and has potential against RCC within mitochondrial dynamics. Lupeol decreased the crystal deposition of uric acid and calcium, oxalate in the kidneys and lowered the concentration of inhibitors, like glycosaminoglycans and magnesium deposition.	[47,48]
	Lupeol's antiurolithiatic activity was tested *in vitro* for 30 minutes at different doses of extract/fractions (0.04–3 mg/mL) to inhibit calcium oxalate and nucleation combination.	[49]

Antiprotozoal Activity

Protozoa is the the world's most serious illnesses, which mainly affect the people of poor countries. The afflicted people's poor buying power and remote habitation regions force them to seek treatment in plants, which are closer and more accessible resources. People of Bolivia's in Amazonian area cure cutaneous leishmaniasis using poultices of stem and bark of plant *Perabenensis*, till the skin sores are completely healed. Fournet *et al.* (1992) conducted researchon the basis of ethnobotanical information and discovered plumbagin is major component, with lupeol having a mild effect against several Trypanosoma and leishmania species. [30,31,32,33,34].

(Srinivasan *et al.* 2002) investigated lupeol-based library with 96 members. Assayed on *Plasmodiumfalciparum*NF-54 strain and *P. berghei*. (Ziegler *et al*., 2002, 2004) showed lupeol permanently modified shape of erythrocyte cells. Dose is equal to the dose of antiplasmodial in-vitro doses. IC_{50} values explains antimalarial activity of lupane-type triterpenes.

They provided a SAR for the studies component's membrane effects and the manner in which they assimilate onto the erythrocyte cell wall based on the carbon twenty-eight group capability of hydrogen donation, and related their molecular mechanism to that of a certain amphiphatic substitute. Rather than having a specific noxious effect on parasite organelles or metabolic pathways, the antiplasmodial activity of these components is related to changes in the host cell's wall structure, rulling them out as lead compounds for antiplasmodial drug development.

Some triterpenes have anti-trypanocidal activity *in vitro*, and structural characteristics necessary for invitro anti-plasmodial action. Trypansoma species have a different life cycle than plasmodium species, more exploration is needed to completely find out the mechanism of action of lupine series teriterpenes against this protozoan genus [35,36].

Anti-inflammatory Activity

Inflammation is defined by five fundamental symptoms are rashes, heat, swelling, discomfort, and loss of function. It involves a sequence of metabolic reactions including the immune function and circulatory function. Chemical irritants, poisons, infections, burns, and splinters are examples of external elements which lead to this reaction. The process involves the production of numerous inflammatory mediators by various kinds of defence cells, which handled by various stimuli.

Mast cells develop from monocytes, which produce signals, including inter-lukin-1 (IL-1) that initiates another phase of cytokinin'sthat cause neutrophils to migrate to the damaged tissue. Furthermore, IL-1 penetrates the bloodstream and travels via brain,here it binds to BBB cells' surface receptors, causing them to generate prostaglandins E-2. This mediator penetrates BBB, activating neuron and receptor of microglia, triggering the acute phase of inflammation.

Macrophages also generate reactive oxygen intermediates including H_2O_2-nhydrogen peroxidesand NO- nitic oxide which are essentialgrowth of edema. Leukotrienes are created by the enzymes 5-Lipoxygenase, which works on a arachidonic acid in neutrophils to make leukotrienes. They producedand manufacture histamines. Lymphocytes like beta cells and thymocyte produce IG antibodies with receptors that allow them to identify antigens, which interact with macrophages and other lymphocytes. Lupeol with their linoleate and palmitate esters, are non-competitive as well as competitive suppressions of serine protease trypsin and chymotrypsin. [28.29,30].

Furthermore, lupeol had no effect on osteosarcoma cell collagenase release and esters of linoleate and palmitate reduced it by 78-97 percent, respectively. It suppressed cAMP-dependent protein kinases (cAK, IC_{50} values of 4-9 M) more effective. [25.26,27]. Eventually, suppressing serine proteases minimizes protease-mediated cellular injury, whereas suppressing cAK helps to stop the yield of PGE2 and Bcells growth, damping the extravagant immune function seen in these inflammatory conditions that would describe why cartilage and subchondral bone were spared. Sudhahar *et al*., 2007 has revealed reduction indamage and stress cells tissues of kidney and heart of rats when treatment is given by lupeol with ester of three linoleate, denoting that they an anti-inflammatory effect.

Antitumor Activity of Lupeol

Limitless expansion of abnormal cells, self-sufficiency in growth factors, lack of sensitivity to growth inhibitors, apoptotic avoidance, prolonged angiogenesis, and tissue penetration are the sevensignatures mark of cancer. According to WHO inbetween 2005 to 2015, 84 million people died of cancer. In a variety of cell lines, lupeol and related compounds have been found to have anticancer effects.

The present study of lupeol is reported as anticancer activity. Lupeol has been potential to act against different types of tumors like human prostate, breast cancer skin, liver and blood cancer. Different types of cancer have different cell lines like normal human breast cell line (MCF-10A) and cancer line MCF-7. A compound of lupeol induced in the cell line and changes the cell viability of MCF-7 with its IC50 concentration as 80 µM. The various striking observation of lupeol does not cause any noxious effect on a human cell it kills only cancerous cells. [50]

Vasculogenic mimicry and tumor microcirculation is found in many cancers stem-like cells. Recently anticancer of lupeol, a novel physiochemical with Dacarbazine both are *in vivo* and *in vitro*. Lupeol can become a more power full anticancer agent that treated the B16-F10 cell line and inhibit the vasculogenic mimicry with inducing Dacarbazine drug resistance. [51,52,53,54]

The research and assessment of novel lupeol compounds is used to treat lung cancer. Effects of lupeol on lung cancer A427 cells and normal MRC-5 cells MTT test is used to see if the treatment is inhibiting lung cancer cell growth. [37,38].

Lupeol has been shown to have anticancer activity and inhibitory activity in human cervical carcinoma (HeLa) cells by inducing S-phase cell cycle arrest and apoptosis.[53]

Lupeol decreased the phosphorylation of epithelial growth factor receptor and prevented the development of NSCLC cells in human non-small cell lung cancer (NSCLC) (EGFR).[54]

Patents associated with Lupeol

S. No.	Patent Number & Year	Country	Patent Title
1	CA2767642A1 & 2011	Canada	Lupeol-type triterpene derivatives as antivirals
2	US 8,618,082 B2 & 2013	United States Patent	Lupeol anti-tumor agent and uses Thereof
3	EP2454270A2 & 2012	Europe	Lupeol-type triterpene derivatives as antivirals
4	US 20040072807A1 & 2004	United States Patent	Methods of treating antifungal infections using lupeol

CONCLUSION AND FUTURE PERSPECTIVES

• Present treatment of cancer shows various drawbacks with various adverse effects. • The review is based on the lupeol and it's contained number of conventional and verified biological qualities, as well as utilized for prevention of cardiovascular disorders, liver, cancer disorders.• It is found in various plants, hence components easily obtained. It has the capacity to interact with various molecular targets, influencing and regulating and useful in inflammation, cancer.• Lupeol had not toxicity towards normal cells worked synergistically in combination treatments; make this a promising candidate for usage as an adjuvant to currently utilized anticancer and anti-inflammatory drugs.• In this regard, proteomics studies should be conducted to identify different conjugated proteins, during treatments, with the goal of discovering novel targets and therapeutic effectiveness indicators.• In addition, pharmacokinetic research on lupeol should be conducted to enhance its miscibility properties, systemically available and absorbed.• Lupeol do not appear to be an effective antiprotozoal drug, it has proven to be a valuable for the synthesis of more powerful antimicrobial variants.

Acknowledgement

The author thanks the college administration, principal, teachers, and coworkers for their help and support.

Conflicts of Interest

No conflict of interest is declared.

Funding Information

No agency provided funds.

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HOW TO CITE THIS ARTICLE
Sharma D, Gupta N. Lupeol: An Alternative Approach towards Cancer Treatment. J Phytopharmacol 2022; 11(6):425-431. doi: 10.31254/phyto.2022.11609