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Lupeol: An Ubiquitous Compound for Multiple Ailments

Mirunalini Sankaran[1] , Jayasri.G[2]

[1,2]Department of Biochemistry & Biotechnology, Annnamalai University,

Correspondence Author: **Dr. S. Mirunalini*, M.Sc., M.Phil. Ph.D,**

Assistant Professor , Department of Biochemistry & Biotechnology, Annamalai University, Annamalainagar – 608 002, Tamil Nadu, India.

ABSTRACT: Natural product and herbal remedies used in traditional folklore medicine have been the source of many medically beneficial drugs because they elicit fewer side effect. Lupeol is anatural products have been used as remedies to treat human diseases. It is a found in white cabbage, green pepper, strawberry, olive, mangoes and grapes. It is exhibits an array of biological activities like anticancer, antiprotozoal and cancer chemo preventive in vitro system. Last 15 years have seen tremendous efforts by researchers worldwide to develop this wonderful molecule for its clinical use for the treatment variety of disorder. It have been found to be pharmacological interaver this review highlight. In detail the therapeutic effect of Lupeol for various ailments.

Key word: Lupeol, Anti Inflammation ,Antiprotozoal, Anti diabetic, Antioxident, anti cancer**.**

Introduction:

Triterpenoid

There is a growing interest in natural triterpenoids, also know as phytosterols, due to their wide spectrum of biological activities [1] . Triterpenes are a wide-spread group of natural compounds with considerable practical significance which are produced by arrangement of squalene epoxide in a chair-chair, chai-boat arrangement followed by condensation. Triterpense are important structural components of plant membranes, and free triterpense severe to stabilize bilayers in plant cell membranes just as cholesterol dose in animal cell membrane.[2]

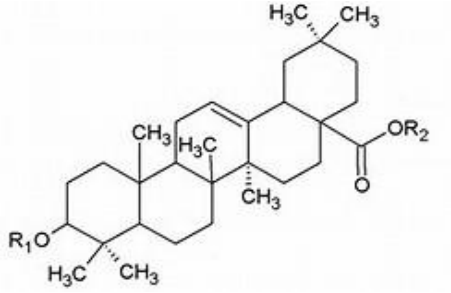

Figure:1 Chemical structure of Triterpenoid

Lupeol

Lupeol has been reported to be present in the diverse species of the plant kingdom. It is found as an active constituent of various medicinal plants used by native people in the treatment of varies skin ailment. There is a growing interest in natural triterpenoids also known as phytosterols, due to their wide spectrum of biological activites. It is a pent acyclic triterpenoid alcohol and secondary metabolic bio synthesisised in the cytosol of eukaryotic cells from the steroid precursors squalence [3].It has been broadly identified in the plant kindom and is abundant in ditary fruits and vegetables such as mango, strawberry, grapes, tomato and cabbage nuts such as hazelnut damirchi and medicinal plants including gingseng and aloe vera. It is a pharmacologically active triterpenoid. It has several potiential medicinal properties. It appeared to block the function of a protein called NF-κB,with assists both healthy and malignant cells in the process of growth and repair.In addition the

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growth and spread of the cancer appeared to be slowed Compared to conviential drugs, lupeol reduced the size of the tumor far faster.In addition ,lupeol did not appear to cause the wasting often associated with chemotherapy. Lupeol is also presention saw palmetto, olive seed and certain vegetables. Triterpenes are awide –spread group of natural compounds with considerable pratical siginificance which are produced by arrangement of squalene epoxide in a chair-chair-boat arrangement followed by condensation [3]. Triterpense are important structural components of plant membrances, and free Triterpenes serve to stabilize phospholipid bilayers in plant cell memberance [3].Most Triterpenes contain 28 or 29 carbons and one or two carbon –carbon double bonds,typically one in the sterol nucleus and sometimes a second in the alkyi-side chain [4]. Triterpenes are natural components of human diets. In the west ,an average of 250 mg per day of Triterpenes ,largely derived from vegetables oils, cerals, fruits and vegetables is consumed [4]. One such compound which has gained wide attention of medical professionals, pharmaceutical marketers and researchers all around the world ,one among the dietary triterpene known as lupeol. The review provides detailed of preclinical studies conducted to determine the utility of lupeol as a therapeutic and prevent the potiential on variance ailment.

Source:

Lupeol is found in vegetables such as white cabbage, pepper, cucumber, tomato, fruits such as olive, fig mango, strawberry, red grapes and in medicinal plant.[5] The quantification studies have shown that lupeol is present in olive fruit (3µg/g),Mango fruit(1.80µg/g pulp),Aloe leaf (280µg/g dry leaf),Elm plant(800µg/g),Japanese pear(175µg/g twing bark) and Ginseng oil(15.2mg/100 g of oil).The list of selected plants which have been reported posses lupeol in significant amounts is presented in Table 1.The Quantification of lupeol in fruits and medicinal plants has been performed and is summarized in Table 2.[6]

Table 1: List of selected plants containing Lupeol.

Botanical Name	Common Name	Botanical Name	Common Name
Alove vera	Aloe	Apocynum Cannabinum	Bitterrot
Cajanuscajan	Congo-pea	Calendula offcinalis	Buii's Eyes
Camellia sinensis	Black Tea	Capsicum annuum	Aferica pepper
Cassia fistula	Indian Laburunum	Cociniagrandis	Ivy groud
Cucumissativus	Cucumber	Daususcarota	Carrot
Fiscuscarica	Common fig	Gentianalutea	Bitter root
Glycine max	Soya bean	Glycyrrhizaglabra	Common licorice
Hemidesmusindicus	Indian Sarsaparilla	Juniperus Communis	Common Jupniper
Lawsonia alba	Henna	Lycopersiconesculentum	Tomatto
Morus alba	White mulberry	Olea Europa	Olive
Panax ginseng	Asiatic ginseng	Phonexdactylifera	Date palm

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Table 2: Content of lupeol in fruits and in plants.

Name of plant	Lupeol
Olive fruit	3µg/g of fruit
Mango fruit	1.80µg/g mango pulp
Aloe leaves	2.80µg/g dry leaf
Elm plant	880µg/g bark
Japanese pear(shinko)	175µg/g twing bark
Ginseng oil	15.2 mg/100 g of oil

Chemical structure:

The chemical structure of lupeol is presented.[Figure1]. The chemical formula of lupeol is $C_{30,}H_{50,}O$ and its melting point is 215-216^{o}C. Properties computed from the structure of lupeol show that it has a molecular weight of 426.7174(g/mol).(7)

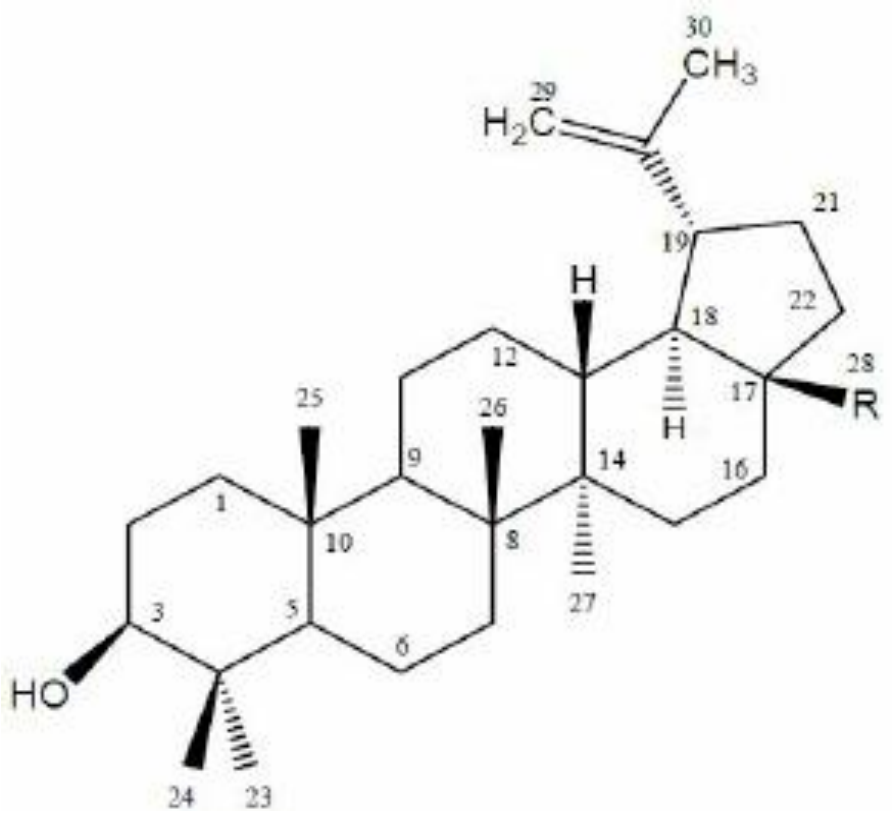

Figure 2: Chemical Structure of Lupeol**.**

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Pharmacological activities of lupeol

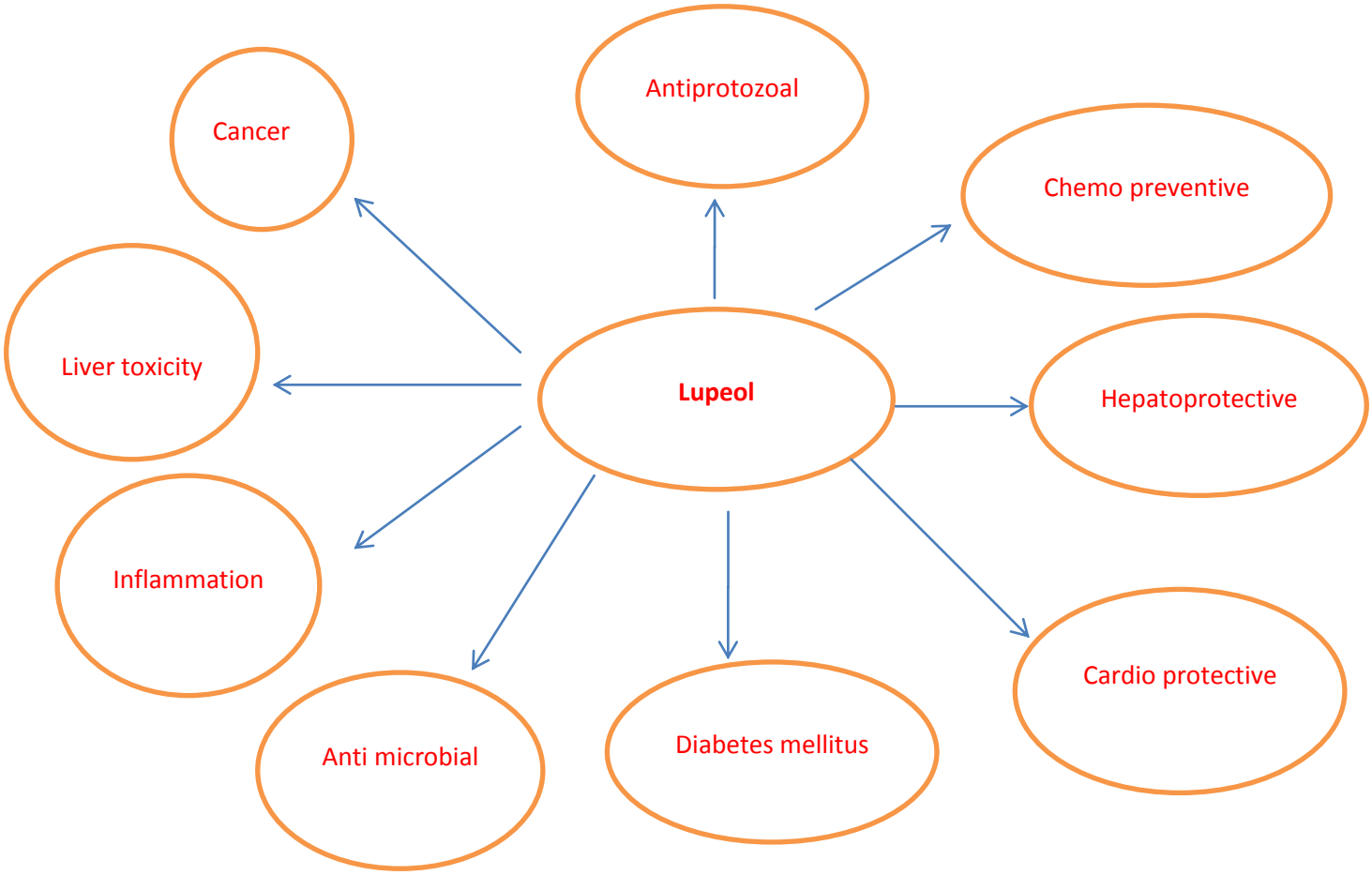

Fig.2. Diagram represents the effect of Lupeol against different types of human diseases

Lupeol and inflammation

Lupeol has been shown to exhibit various pharmacological activities under in vitro and in vivo conditions. These include its beneficial activity against inflammation, cancer, arthritis, diabetes, heart diseases, renal toxicity and hepatic toxicity. Lupeol. The anti-inflammatory potential of lupeol could be assessed from the observation that lupeol pretreatment significantly reduced prostaglandin E2 (PGE2) production in A23187stimulated macrophages. reported for the first time the utility of lupeol to treat or reduce inflammation in a mouse model of arthritis, which is an inflammation associated disease. The beneficial effect of lupeol in treating inflammation in arthritic mice was shown to be associated with its potential to modulate immune system and the generation of inflammatory factors.Another major development in establishing the antiinflammatory potential of lupeol was a recent study by Vasconcelos et al., where lupeol was tested for the treatment of inflammation in a mouse model of bronchial asthma. It is well established that asthma is a chronic inflammatory disease of the airways, associated with a Th2 immune response. This study showed that lupeol administration causes a significant reduction in cellularity and eosinophil levels in the broncho-alveolar fluid. Treatment of lupeol was also found to reduce the

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production of mucus and overall inflammation in the lungsThe anti-inflammatory effect of lupeol was observed to be equal to dexamethasone, a well-known anti-inflammatory agent. The latex from Himatanthus sucuuba is used in popular Amazonian medicine as an anti-inflammatory remedy and lupeol was observed to be an active constituent of this anti-inflammatory plant which at a dose of 100 mg/kg (p.o.) inhibited the edema and the abdominal constrictions by 50–40% and 57.9%, respectively, in animals. Inflammation, which orchestrates the tumor-supporting microenvironment, is a critical component of both tumor promotion and tumor progression and is an indispensable participant in the neoplastic process. It has been established that cancer can be promoted and/or exacerbated by inflammation and infections.

The hypothesis that aberrant induction of cyclooxygenase-2 (COX-2), a conventional marker of inflammation, and up-regulation of the prostaglandin cascade play a significant role in carcinogenesis is consolidated by accumulating body of evidences from molecular, animal, and human investigations, and reciprocally blockade of the process has a strong potential for cancer prevention and therapy. Since nuclear factor kappa B (NF-kB) becomes activated in response to inflammatory stimuli and its constitutive activation has been associated with cancer, in addition to selective modulation of cytokine signaling, interfering with NF-kB activation in tumor cells can further expedite the prevention strategy and may render the cancer cells to elimination by pro-apoptotic cytokines. Lupeol afforded significant inhibition in a time- and dose-dependent manner against TPA-mediated increase in (i) skin edema and hyperplasia, (ii) epidermal ornithines decarboxylase (ODC) activity, and (iii) protein expression of ODC, COX-2, and nitric oxide synthase. An ester derivative of lupeol, lupeol linoleate, also possesses marked anti-inflammatory activity, as shown by oral or intraperitoneal administration of lupeol at a dose of 25–200 mg/kg body weight in acute and chronic inflammation in rats and mice. Lupeol, along with its acetate and palmitate esters, was found to be the main anti-inflammatory constituent in the croton oil induced ear edema test. Furthermore, lupeol hemisuccinate, synthesized from lupeol, exhibited a stronger activity than lupeol. Lupeol from Crataeva religiosa bark has been evaluated for its anti-inflammatory, analgesic, antipyretic effect on rat and mice. It was seen to exert significant dose-dependent effect on acute and chronic inflammatory processes. With lupeol established as a potent anti-inflammatory compound, it is also thought to possess ant carcinogenic attributes. It inhibits cancer growth in vitro and in vivo and ameliorates inefficiency of cancer cells to undergo apoptosis as listed. Lupeol and lupeol linoleate were also investigated for their possible hepatoprotective effect against cadmium-induced toxicity in rats and it was elucidated that the possible mechanism under clad is scavenging of peroxyl radicals by bolstering the levels of antioxidants and antioxidant enzyme system. Another lupane-type terpenoid, 3b,25-epoxy-3ahydroxylup-20(29)-en-28-oic acid, exhibited the strongest inhibitory effect on tumor initiating activity in mouse models initiated with ultraviolet-B (UV-B) and promoted with TPA. Several studies were carried out to understand the molecular mechanism through which lupeol inhibits or abrogates the inflammatory processes under in vitro and in vivo situations and such studies provided several mechanistic facets of anti-inflammatory action of lupeol. Lupeol was reported to modulate several molecules which directly or indirectly play a role in inflammatory process. Lupeol was shown to inhibit the activity

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of soybean lipoxygenase-1 (15-sLO) with an IC50 equal to 35 lM Lupeol treatment (10–100 lM) is also shown to decrease the generation of pro-inflammatory cytokines such as tumor necrosis factor-a (TNF-a) and interleukin-b (IL-b) in lipopolysaccharidetreated macrophages. Recent report by Yamashita et al. suggested that superoxide generation induced by arachidonic acid (AA) is suppressed by lupeol in N-formylmethionyl-leucyl-phenylalanine (fMLP) treated human neutrophils. Further, lupeol treatment was observed to cause a reduction in the inflammation by decreasing the levels of type II cytokines, IL-4, IL-5 and IL-13, in a bronchial asthma mouse model.Recently, lupeol was reported to exhibit significantly high wound healing potential in a dead space wound healing mouse model. This study showed that lupeol exerts its wound healing effect by decreasing the level of monocytes and docking with GSK3b protein.The activation domain of GSK3b consists of Tyr216, with residues Asn64, Gly65, Ser66, Phe67, Gly68, Val70, Lys85, Leu132, Val135, Asp181 in the active pocket, docked with lupeol at the torsional degree of freedom 0.5 units.Taken together, these compelling evidences suggest that the therapeutic usefulness of lupeol for inflammatory conditions is attractive and warrants further investigation.[8]

Lupeol and cancer

Lupeol and cancer Recent studies have shown that diets rich in phytochemicals can significantly reduce cancer risk by as much as 20%. Epidemiological data suggest that the phytosterol content of the diet is associated with a reduction in common cancers including cancers of the colon, breast, and prostate. Data emanating from molecular studies with various tumorigenic models suggest that phytosterols modulate host systems potentially enabling more robust antitumor responses such as enhancing immune recognition of tumor cells, altering hormone-dependent growth of endocrine tumors and modulating sterol biosynthesis. Reports suggest that the decreased risk for various cancers associated with high olive oil consumption may be associated with its rich triterpene content. A number of triterpenoids have shown promise as antineoplastic agents and exhibit antiproliferative activity when tested against various cancer cell lines. These triterpenoids include members belonging to the cycloartane, lupane, friedelane, dammarane, ursane, oleanane, limonoid and cucurbitacin family.Recent reports have shown that triterpenes directly inhibit tumor growth, cell cycle progression, and induce the apoptosis of tumor cells under in vitro and in vivo situations [9]

Mutations that occur through DNA strand breaks have been shown to form the precursors of cancer development, and cells harboring mutations are at high risk to transform into neoplastic phenotype. During the course of tumorigenesis, mutations get accumulated, thus transforming neoplastic cell into malignant carcinomas. It is noteworthy that lupeol was reported to exhibit strong anti-mutagenic activity under in vitro and in vivo systems and references therein. Earlier reports have shown that lupeol inhibits the chemically induced DNA damage under in vitro conditions. Study by Nigam et al. showed that topical application of inhibits the chemically induced DNA damage under in vitro conditions. We showed that lupeol inhibits growth of highly metastatic tumors of human melanoma origin by modulating the ratio of Bcl-2 and Bax protein levels in vitro and in vivo.The most important observation in this study was that no toxic effect on normal human melanocytes was observed at a dose at which lupeol kills malignant melanoma cells. Recently, studies have been carried out to

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investigate the structure–activity relationships of lupeol in various human cancer cell lines. A study conducted by Aratanechemuge et al. showed that lupeol induces apoptosis of human promyelotic HL-60 leukemia cells.This study showed that lupeol induces the formation of hypo diploid nuclei and fragmentation of DNA (a characteristic of apoptosis) in a dose- and time-dependent manner. Lupeol has been found to induce differentiation and inhibits the cell growth of mouse melanoma and human leukemia cells. Besides lupeol, lupenone, which is obtained from A. mellifera, has been shown to exhibit significant cytotoxicity against non–small-cell lung carcinoma-N6 (NSCLC-N6) cell line.In another study, lupeol, betulin, methyl betulinate, and glycosides (b-D-glucosides, a-L-rhamnosides, and a-D-arabinosides) were synthesized and tested in vitro for cytotoxicity against three cancerous cell lines: human lung carcinoma (A-549), human colon adenocarcinoma (DLD-1) and mice melanoma (B16-F1).Lupane-type terpenoids also exhibited cytotoxicity against human hepatocellular carcinoma (Hep-G2) and human epidermoid carcinoma (A-431), while they did not affect the growth of tumor cell lines such as human melanoma (MEL-2), human lung carcinoma (A-549), and murine melanoma (B16-F10).Lupeol has been reported as a differentiation-inducing compound in B16 2F2 cells, up-regulating the melanogenesis of these cells. The cytotoxicity profiles of lupane triterpene against human cancer cells showed that its cytotoxic effect against lung cancer cell lines is the strongest, while it is very weak against osteosarcoma, breast cancer and urinary bladder cancer cells. Synergistic cytotoxic effects of lupeol with chemotherapy drug, cisplatin, have been observed in vitro, resulting in chemo sensitization of head and neck squamous cell carcinoma (HNSCC) cell lines with high NF-kB activity. DNA topoisomerases (Topos) are ubiquitous enzymes that play a crucial role in many aspects of DNA metabolism such as replication, transcription on, recombination and chromosome segregation during mitosis. Topos have therefore been identified for anticancer chemotherapeutic drug development. Topo-II inhibitors are mainly characterized into two groups according to their inhibitory mechanism. One group, termed "poisonous", stabilizes covalent intermediates named cleavable complexes, and the other one referred to as "catalytic inhibitors" targets some other step during the catalytic cycle without formation of cleavable complexes. Topo-II is an essential enzyme in the DNA replication process and is the primary cellular target or many of the widely used and effective anticancer agents. Naturally occurring lupane-type triterpenoids isolated from the bark of Phyllanthus flexuosus were screened for human Topos-I and -II inhibitory activities. It revealed that lupeol and betulin are selective catalytic inhibitors of human Topo-II activity with IC50 values in the range of 10–39 lM.[10]

Lupeol as an antimicrobial agent

Several of the most severe diseases in the world are caused by protozoans and primarily distress developing nations' populace .Some of these so called neglected disease, such as leishmaniasis and malaria ,persist without effective treatment either by natural reason, e.g, resistant,or form industrial disinterest due to economics in finding more efficient drug.[11]

Lupeol as Cancer Chemopreventive agent

The first report about lupeol as a cancer chemopreventive agent involved the induction of Epstein Barr virus early antigen (EBV-EA) by the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA), in lymphocytes. Lupeol treatment

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of mice before benzo-pyrene-induced clastogenicity reduced aberrant cells, micronuclei presence and cytotoxicity in the bone marrow cells as well as caused an increase in the mitotic index, revealing the lupeol's antigen toxic potential . The modulating effect of lupeol on antioxidant enzymes, lipid per oxidation and GLUT athione levels was also observed in assay models using the ubiquitous carcinogen benzoyl peroxide and testosterone-induced oxidative stress. A methanolic extract of Careya arborea bark, containing lupeol and betulinic acid, increased the antioxidant and hepatoprotective parameters as well as the superoxide dismutase and catalase enzymes levels in liver and kidney tissues of Erlich ascites carcinoma tumor bearing mice . Lately, it was demonstrated that lupeol, when coadministered with the carcinogen DMBA, was capable of preventing alterations on cell proliferation in mouse skin by inducing p53 and cyclin B-mediated G2/M cell cycle arrest, and targeting apoptosis by activation of caspases .[12]

Hepatoprotective effect of lupeol

Lupeol and analogues have also displayed hepatoprotective effects. Lupeol showed some effectiveness in lessening the action of aflatoxin B1 , a secondary fungal metabolite known for its hepatotoxic and hepatocarcinogenic effects. In this study, rats pretreated with lupeol had the serum and liver enzyme levels restored to almost normal at the same time that the activities of enzymatic antioxidants and the non-enzymatic antioxidants GSH, vitamin C, and vitamin E levels were brought back to those of the control. Additionally, treatment with lupeol substantially normalized degenerative alterations in the hepatocytes with granular cytoplasm. Lupeol also re-established antioxidant enzyme activities in mouse liver affected by 7,12-dimethylbenzanthracene (DMBA)-induced oxidative stress. Noteworthy, the observed decrease in ROS levels along with restoration of mitochondrial transmembrane potential, reduction in DNA fragmentation and subsequent inhibition of apoptosis indicated a divergent mechanism that lupeol plays when acting as an anticancer agent . Lupeol treatment induced growth inhibition and apoptosis in hepatocellular carcinoma SMMC7721 cells by down-regulation of the death receptor 3 (DR3) expressions. Therefore, lupeol was revealed as a promising chemo preventive agent for that type of cancer .[13]

Cardioprotective effect of lupeol

Lupeol has been investigated for its cardioprotective effects and was demonstrated to provide 34.4% protection against in-vitro LDL oxidation . Lupeol and lupeol acetate have also shown hypotensive activity, which may make them possible preventative agents in cardiovascular diseases. In addition, supplementation of lupeol or lupeol linoleate was effective against the cardiac oxidative injury caused by cyclophosphamide, a drug used in the treatment of cancer and autoimmune disorders . A study showed lupeol and lupeol linoleate can ameliorate the lipidemic-oxidative abnormalities in the early stages of hypercholesterolemia atherosclerosis in rats. corroborated this effect and revealed the triterpene's mode of action by a restoration of several transmembrane enzymes, total cholesterol, triglycerides and phospholipids to normal levels, preventing hypertrophic cardiac histology. Reddy and collaborators, also demonstrated lupeol's antidyslipidemic activity in hamster at 100 mg/kg. b. wt. In addition, they synthesized 10 lupeol ester derivatives and found a nicotinic acid derivative that exhibited better lipid lowering profile at a dosage twice lower than lupeol along

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with an antihyperglycemic effect, which revealed the lupeol's potential as a scaffold for developing drugs targeting coronary diseases and diabetes [14]

Anti diabetics effect of lupeol

Diabetes mellitus is a worldwide epidemic that has created a crisis for the health care system and society. Diabetes was described over 2000 years ago and for the past 200 years it has occupied a predominant place in medical history. In India, medicinal plants have been used as natural medicine since the days of Vedic glory. Many of these medicinal plants and herbs are part of our diet as spices, vegetables and fruits. Historically, in Diabetes mellitus is a global metabolic epidemic disease affecting essential biochemical activities in almost every age group. In India, the prevalence rate of diabetes is estimated to be high among rural population. About 3,17,05,000 people suffered from diabetes in India in the year 2000 and the number is expected to be doubled to 7,94,41,000 in 2030, which would make India to have the most number of people with diabetes mellitus in the world . The reasons for this rise include increase in sedentary lifestyle, consumption of energy-rich diet, obesity, higher life span, etc. . Most of these cases will be type-2 diabetes, which is strongly associated with a sedentary lifestyle and high calorie nutrition and obesity. 'Atharva-Veda' (about 200 B.C.) description of medicinal plants was made under a separate chapter 'Ayurveda'. Sushruta (about 400 B.C.) compiled the classification of 700 herbal drugs under 37 classes in 'Sushruta Samhita' (A compendium of ancient Indian surgery). Charak (about 600 B.C.) made the scientific classification of herbal drugs based on remedial properties in his renowned treatise 'Charaka Samhita' (A compendium of general medicine) in which he described 50 classes of herbal remedies comprising 500 crude drugs. The medicinal values of plants have been tested by trial and error method for a long time. World ethno botanical information about medicinal plants reports almost 800 plants used in the control of diabetes mellitus .The plants and plant products can directly stimulate insulin secretion or action and improve insulin action and binding. It is a big challenge to fully exploit medicinal biodiversity to look for phytochemicals with insulin mimetic property. [15]

One of the well-regulated homeostatic mechanisms in vertebrates is the maintenance of stable levels of glucose in blood. Glucose concentration in the blood affects every cell in the body. Its concentration is, therefore, strictly controlled within the range 80-100mg/dl, and very low level (hypoglycemia) or very high levels (hyperglycemia) are both serious and can lead to death . Skeletal muscle has a fundamentally important role in the maintenance of normal glucose homeostasis and in regulating whole body carbohydrate metabolism. It is the major target tissue for insulin-mediated glucose uptake, metabolism and utilization in humans. Indeed, impaired insulin action in skeletal muscle is responsible for the majority of decreased levels of non-oxidative glucose disposal that are in subjects presenting with the metabolic syndrome, obesity and type-2 diabetes. Splanchnic tissues immediately take up one third of the ingested carbohydrate . Of the remaining two thirds of the ingested carbohydrate that enters the systemic circulation, some is extracted by liver, but peripheral tissues take up the most . Skeletal muscle is the predominant site for about one fourth of the ingested carbohydrate .[16]

Insulin is the most potent anabolic hormone known and is essential for appropriate tissue

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development, growth and maintenance of whole body tissue homeostasis. This hormone is secreted by the β-cells of the pancreatic islets of Langerhans in response to increased circulating levels of glucose and amino acids after a meal. Insulin regulates glucose homeostasis in many sites by reducing hepatic glucose output (via decreased gluconeogenesis and glycogenolysis) and increasing rate of glucose uptake, primarily into striated muscle and adipose tissue . In a highly coordinated fashion, insulin promotes an anabolic state of storage of carbohydrates and lipids, and synthesis of proteins . Insulin acts on three main target tissues, the liver, muscle and adipose tissue.[17].

Adverse effect:

Several factors must be taken into consideration when the evidence for the inhibition of carcinogenesis and allevtions of other diseases by Lupeol is examined. These include the erective dose used and the time of exposure. In order to evaluate the overall implication of Lupeol as a chemo preventive and chemotherapeutic agent, further studies are needed to fully identify its protective effects, as well as possible detrimental effects.

Conclusions

lupeol is an immense bioactive compound present in different medicinal plants. A wide range of bioactivities and bioassays of lupeol are reviewed, which suggest its useful medicinal properties with diversity of action against different diseases. Natural products have been used as remedies to treat human diseases. Various in vitro and preclinical animal studies suggest that lupeol has a potential to act as an anti-inflammatory, anti-microbial, antiprotozoal, anti-proliferative, anti-invasive, antiangiogenic and cholesterol lowering agent. Employing various in vitro and in vivo models, lupeol has also been tested for its therapeutic efficiency against conditions including wound healing, diabetes, cardiovascular disease, kidney disease, and arthritis. Lupeol has been found to be pharmacologically effective in treating various diseases under preclinical settings (in animal models) irrespective of varying routes of administration viz. topical, oral, intra-peritoneal and intravenous. It is noteworthy that lupeol has been reported to selectively target diseased and unhealthy human cells, while sparing normal and healthy cells.

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