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Lupeol, A Novel Anti-inflammatory and Anti-cancer Dietary Triterpene

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Abstract

In the Western world, an average of 250 mg per day of triterpenes (member of phytosterol family), largely derived from vegetable oils, cereals, fruits and vegetables is consumed by humans. During the last decade, there has been an unprecedented escalation of interest in triterpenes due to their cholesterol-lowering properties and evidence of this phenomenon include at least 25 clinical studies, 20 patents and at least 10 major commercially triterpene-based products currently being sold all around the world. Lupeol a triterpene [also known as Fagarsterol] found in white cabbage, green pepper, strawberry, olive, mangoes and grapes was reported to possess beneficial effects as a therapeutic and preventive agent for a range of disorders. Last 15 years have seen tremendous efforts by researchers worldwide to develop this wonderful molecule for its clinical use for the treatment of variety of disorders. These studies also provide insight into the mechanism of action of Lupeol and suggest that it is a multi-target agent with immense anti-inflammatory potential targeting key molecular pathways which involve nuclear factor kappa B (NFκB), cFLIP, Fas, Kras, phosphatidylinositol-3-kinase (PI3K)/Akt and Wnt/β-catenin in a variety of cells. It is noteworthy that Lupeol at its effective therapeutic doses exhibit no toxicity to normal cells and tissues. This mini review provides detailed account of preclinical studies conducted to determine the utility of Lupeol as a therapeutic and chemopreventive agent for the treatment of inflammation and cancer.

1. Introduction

There is a growing interest in natural triterpenoids, also known 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- chair-boat arrangement followed by condensation [2]. Triterpenes are important structural components of plant membranes, and free triterpenes serve to stabilize phospholipid bilayers in plant cell membranes just as cholesterol does in animal cell membranes [2]. 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 alkyl side chain [3]. Triterpenes are natural components of human diets. In the West, an average of 250 mg per day of triterpenes, largely derived from vegetable oils, cereals, fruits and vegetables is consumed [3]. There are reports which suggest that average triterpenoid intake is 30 mg/kg/day in the United States and based upon diet such as olive oil, the intake could reach 400 mg/

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kg/day in Mediterranean countries [3]. During the last decade, there has been an unprecedented escalation of interest in triterpenes. Most of this interest has focused on the cholesterol-lowering properties of triterpenes, and evidence of this phenomenon include at least 25 clinical studies, 20 patents and at least 10 major commercially triterpene-based products currently being sold all around the world [3]. It is estimated that well over 2400 subjects have taken part in clinical studies with different types of triterpenes with dosage up to 25 g or more per day with no adverse effect reported [3].

One such agent which has gained wide attention of medical professionals, pharmaceutical marketers and researchers all around the world, is a dietary triterpene known as Lupeol. This review provides detailed account of preclinical studies conducted to determine the utility of Lupeol as a therapeutic and chemopreventive agent for the treatment of inflammation and cancer.

2. Source of Lupeol

Lupeol, is found in vegetables such as white cabbage, pepper, cucumber, tomato, in fruits such as olive, fig, mango, strawberry, red grapes and in medicinal plants such as American ginseng, Shea butter plant, *Tamarindus indica, Allanblackia monticola, Himatanthus sucuuba, Celastrus paniculatus, Zanthoxylum riedelianum, Leptadenia hastata, Crataeva nurvala, Bombax ceiba and Sebastiania adenophora* used by native people in North America, Latin America , Japan, China, Africa and Caribbean islands [4–14]. The list of selected plants which have been reported to possess 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.

3. Chemical Structure and Analysis

The chemical structure of Lupeol is presented in Figure 1. The chemical formula of Lupeol is $C_{30}H_{50}O$ and its melting point is 215–216 °C. Properties computed from the structure of Lupeol show that it has a molecular weight of 426.7174 [g/mol], H-Bond donor 1, H-Bond acceptor 1, rotatable bond count 1, exact mass 426.386166, mono isotopic mass 426.386166, topological polar surface area 20.2, heavy atom count 31, formal charge 0, complexity 766, isotope atom count 0, defined atom stereo center count 10, and bonded unit count 1 (PubChem, NIH library, Compound ID 259846). The infra-red spectrum of Lupeol shows the presence of a hydroxyl function and an olefinic moiety which show their presence in the spectrum at 3235 and 1640 cm-1, respectively [6]. The molecular formula depicts the presence of six degrees of unsaturation, out of them one can be satisfied by an olefinic function. The presence of seven methyl singlets and an olefinic function in the 1H-NMR spectrum revealed that Lupeol is pentacylic triterpenoidal type in nature [6,15]. Study conducted by Martelanc *et al.,* using high-performance liquid chromatographic (HPLC) method with UV and mass spectrometric [MS] showed that Lupeol exhibits a parent ion peak at m/z 409 [M+H-18][+]] [16].

3. An overview of Lupeol and its beneficial effects

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 [17–75]. In this review, we will present evidence from published and unpublished preclinical studies about the role of Lupeol in alleviating inflammation and cancer. These are discussed as following:

3.1 Lupeol and Inflammation—Lupeol has been extensively studied for its inhibitory effects on inflammation under *in vitro* and in animal models of inflammation. A comprehensive study conducted by Fernández *et al.*, showed that topical application of Lupeol (0.5 and 1 mg/

ear) alleviated 12-0-tetradecanoylphorbol acetate (TPA)-induced inflammation in an ear mouse model [17]. This study showed that topical application of Lupeol decreases myeloperoxidase levels [neutrophil specific marker] thus causing reduction in cell infiltration into inflamed tissues in mice [17]. The anti-inflammatory potential of Lupeol could be assessed from the observation that Lupeol pretreatment significantly reduced prostaglandin E2 (PGE2) production in A23187-stimulated macrophages [17]. Another study by Fernández *et al.*, has shown that Lupeol-rich extract of *Pimenta racemosa* plant (which is widely used by country doctors in Caribbean region to treat inflammatory ailments) exhibits significantly high anti-inflammatory activity in animal models [18]. This study showed that the anti-inflammatory behavior of the Lupeol-rich extract was similar to that exhibited by the selective cyclooxygenase inhibitor, Indomethacin [18].

Several studies were carried out to compare the anti-inflammatory efficacy of Lupeol with known anti-inflammatory agents. A comparative study by Nguemfo *et al.*, for anti-inflammatory potential between Lupeol and a well known phytochemical α-Mangosteen [isolated from superfruit Mangosteen] was conducted in an animal model of carrageenan-induced inflammation [7]. Lupeol treatment (5–9.37 mg/kg) was reported to exhibit anti-inflammatory activity with a maximum inhibition of 57.14% while as α-mangostin at similar dose showed anti-inflammatory activity of 38.70% [7]. Similarly, Lupeol and its derivatives (linoleate, acetate and palmitate) were shown to exhibit higher anti-inflammatory activity than commonly used non-steroidal anti-inflammatory drug indomethacin in rat and mouse models of inflammation [19,20–23].

Geetha *et al.*, 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 [24]. 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 [24]. Lupeol was reported to suppress modulate the phagocytic activity of macrophages and T-lymphocytes, and suppresses CD4+T cell mediated cytokine generation in a mouse model [25]. Oral administration of Lupeol (12.5–200 mg/kg) resulted in the significant reduction in CD4+ T and CD8+ T cell counts and the level of cytokines (IL-2, IFN-gamma and IL-4) in arthritic mice [25]. A similar report by Latha *et al.*, showed that increased activities of lysosomal enzymes and glycoproteins associated with decreased collagen in arthritic animals were significantly altered by Lupeol (50 mg/kg) feeding [26].

Another major development in establishing the anti-inflammatory 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 [27]. 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 [27]. Treatment of Lupeol was also found to reduce the production of mucus and overall inflammation in the lungs [27]. The anti-inflammatory effect of Lupeol was observed to be equal to dexamethasone, a well known anti-inflammatory agent [27]. 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 [8].

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 of soybean lipoxygenase-1 (15-sLO) with

IC_{50} equal to 35 μM [28]. Lupeol treatment (10–100 μM) is also shown to decrease the generation of pro-inflammatory cytokines such as tumor necrosis factor α (TNFα) and Interleukin β (ILβ) in lipopolysaccharide-treated macrophages [17]. Recent report by Yamashita *et al.*, suggested that superoxide generation induced by arachidonic acid (AA) is suppressed by Lupeol in N-formyl-methionyl-leucyl-phenylalanine(fMLP)-treated human neutrophils [29]. Further Lupeol treatment was observed to cause a reduction in the inflammation by decreasing levels of type II cytokines IL-4, IL-5 and IL-13 in a bronchial asthma mouse model [27]. Recently, Lupeol was reported to exhibit significantly high wound healing potential in a dead space wound healing mouse model [30]. This study showed that Lupeol exerts its wound healing effect by decreasing the level of monocytes and docking with GSK3β protein [30]. The activation domain of GSK3β consisting 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 [30]. Taken together, these compelling evidences suggest that the therapeutic usefulness of Lupeol for inflammatory conditions is attractive and warrants further investigation.

3.2 Lupeol and Cancer—Recent studies have shown that diets rich in phytochemicals can significantly reduce cancer risk by as much as 20% [2,31–32]. Epidemiological data suggest that the phytosterols content of the diet is associated with a reduction in common cancers including cancers of the colon, breast, and prostate [2,31–32]. 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 [32 and references therein]. Reports suggest that the decreased risk for various cancers associated with high olive oil consumption may be associated with its rich triterpene content [33]. A number of triterpenoids have shown promise as antineoplastic agents and exhibit anti-proliferative activity when tested against various cancer cell lines [2,31–32]. These triterpenoids include members belong to the cycloartane, lupane, friedelane, dammarane, ursane, oleanane, limonoid and cucurbitacin family [2,34–44]. Recent reports showed that triterpenes directly inhibit tumor growth, cell cycle progression, and induce the apoptosis of tumor cells under *in vitro* and *in vivo* situations [32 and references therein]. 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 [45–48]. During the course of tumorigenesis, mutations get accumulated thus transforming neoplastic cells into malignant carcinomas [45–48]. It is noteworthy that Lupeol was reported to exhibit strong anti-mutagenic activity under *in vitro* and *in vivo* systems [49–50 and references therein]. Earlier reports have shown that Lupeol inhibits the chemically-induced DNA damage under *in vitro* conditions [51]. Study by Nigam *et al.*, showed that topical application of Lupeol [200 μg/mouse] prevents 7,12-dimethylbenz[a]anthracene [DMBA]-induced DNA damage [DNA strand breaks] in murine skin [50]. Recently, Lupeol was shown to inhibit the Benzo[a]pyrene [B(a)P], a well-known mutagen-induced genotoxicity in a mouse model [52]. This study showed that pretreatment with Lupeol [1 mg/animal] for 7 days prior to B[a]P administration significantly decreased B[a]P-induced clastogenicity and caused an increase in mitotic index [52].

A broad program has been initiated at the School of Medicine and Public Health, University of Wisconsin-Madison to study the beneficial effects of Lupeol for various cancer types such as prostate, skin, pancreatic and breast cancer. Earlier we provided evidence that Lupeol inhibits tumor promotion in two stage skin carcinogenesis in a mouse model [53]. Topical application of Lupeol [40 mg/kg/3 times a week] for 28 weeks was shown to significantly decrease tumor burden, tumor multiplicity and increase tumor latency period in the mouse model [53]. The anti-tumor promotion effects of Lupeol were observed to be associated with its potential to modulate signaling pathways such as nuclear factor kappa B (NFκB) and the

phosphatidylinositol 3-kinase [PI3K] /Akt (protein kinase B pathway), which are reported to play an important role during tumorigenesis [53 and references therein]. Tumor promoters {such as 12-O-tetradecanoylphorbol 13-acetate (TPA)} are known to activate NFκB signaling thus resulting in the translocation of activated NFκB to the nucleus where it acts as a transcriptional factor [53–54 and references therein]. NFκB is known to activate several target genes which are required for the tumor growth [54 and references therein]. Lupeol was shown to significantly inhibit the NFκB translocation and its DNA binding activity in a mouse model of skin tumorigenesis [53]. Recent studies have shown the emergence of PI3K/Akt signaling as a potential molecular target for chemotherapeutic and chemopreventive agents [55]. We provided evidence that Lupeol ameliorates TPA-induced PI3K/Akt signaling in murine skin [53]. Further, Lupeol was observed to significantly inhibit the activity of ornithine decarboxylase (ODC) protein which is a well known biomarker of tumor promotion [53, 56 and references therein]. These data suggested the chemopreventive potential of Lupeol against the development of skin cancer. We extended these studies to investigate the chemotherapeutic potential of Lupeol for treating human skin cancer under preclinical settings. For this purpose, Lupeol was tested against human melanoma tumor cells *in vitro* and in a xenograft athymic nude mouse model [57]. We showed that Lupeol inhibits growth of highly metastatic tumors of human melanoma origin by modulating ratio of Bcl-2 and Bax protein levels *in vitro* and *in vivo* [57]. 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. The data emanating from recent ongoing work in Dr. Hasan Mukhtar's laboratory (University of Wisconsin, Madison, WI) show that Lupeol significantly inhibits the growth of metastatic melanoma cells harboring constitutive activation of Wnt/β-catenin signaling (H. Mukhtar, personal communication). The potential of Lupeol to inhibit the growth or metastatic spread of melanoma cells is supported by a study conducted by Hata *et al.*, where Lupeol was shown to significantly inhibit the migration of human melanoma cells through disassembling the actin cytoskeleton [58]. These studies suggest that Lupeol itself being non-toxic to normal cells could be used as a chemopreventive as well chemotherapeutic agent against skin cancer.

Recently studies have been carried out to investigate the structure–activity relationships of Lupeol in various human cancer cell lines [59–61]. A study conducted by Aratanechemuge *et al.*, showed that Lupeol induces apoptosis of human promyelotic HL-60 leukemia cells [59]. This study showed that Lupeol induces the formation of hypodiploid nuclei and fragmentation of DNA [a characteristic of apoptosis] in a dose and time dependent manner [59]. Recently, Cmoch *et al.*, showed that Lupeol induces death of cancer cell lines of various histopathological origins, including T-lymphoblastic leukemia CEM (IC_{50} =50 μM), breast carcinoma MCF-7 [IC_{50} =50 μM], lung carcinoma A-549 (IC_{50} =50 μM), multiple myeloma RPMI 8226 (IC_{50} =50 μM), cervical carcinoma HeLa (IC_{50} =37 μM), and malignant melanoma G361 (IC_{50} =50 μM) when treated for 72 h [60]. Lupeol is also reported to inhibit the proliferation of the ERα-negative breast cancer cells MDA-MB-231 [61]. In our ongoing program (which is focused on anti-cancer activity of Lupeol), we observed that Lupeol inhibits the growth of both ER+ ve and ER−ve types of breast cancer cells in a dose and time dependent manner [Saleem *et al.*, unpublished data]. We also observed that Lupeol inhibits the growth of HER2 +ve breast cancer cells (Saleem *et al.*, unpublished data).

Neo-angiogenesis is a hallmark of cancer invasion and metastasis [62 and references therein]. It is noteworthy that Lupeol (50- 30 μg/ml) is shown to exhibit anti-angiogenic property in an *in vitro* tube formation model of human umbilical venous endothelial cells [63]. Study by Hata *et al.*, showing that Lupeol strongly inhibit the migration of human neuroblastoma and lung adenocarcinoma cells, further strengthen the belief that Lupeol could be developed as a broad-based anti-cancer agent [58]. Recently, Lupeol was shown to induce apoptotic death of pancreatic cancer cells harboring varied *Kras* status *viz*., Panc-1, BxPC-3 and AsPC-1 [64]. It is important to note that Lupeol exhibited more specificity towards highly malignant and

invasive pancreatic cancer cells possessing mutated *Kras* (AsPC-1 and Panc-1) than lesser aggressive Bx-PC-3 harboring wild type *Kras* [64]. These data are significant because it is well established that more than 90% of pancreatic cancers harbor *Kras* mutation resulting in activation of intracellular signaling pathways which leads to proliferation of pancreatic cancer cells [64 and references]. The failure of known chemotherapeutic agents such as gemcitabine, cisplatin and TRAIL in against established tumors is known to stem from the upregulation of multiple molecular pathways. Ras oncoprotein was reported to activate the NF-κB/PI3K/Akt/MAPK signaling network thus conferring chemoresistance to pancreatic carcinoma cells [65 and references therein]. Lupeol has been shown to inhibit the PI3K/Akt and NFκB signaling network in pancreatic cancer cells [65]. We observed that Lupeol decreases the activity of Ras protein (GTP-bound Ras) in pancreatic cancer cells (Saleem *et al.*, unpublished data).

According to the recent published reports, cFLIP has emerged as an important molecule other than NFκB that has gained prominence in conferring chemoresistance to cancer cells [64,66]. Recently, Muratza *et al.*, showed that Lupeol decreases the transcriptional activation of cFLIP gene as well its translational levels in pancreatic cancer cells [64]. Lupeol was shown to sensitize pancreatic cancer cells to TRAIL therapy [64]. This study showed that Lupeol treatment (40 mg/kg; 3 times/week) inhibits the growth of tumors originated from human pancreatic cancer cells (AsPC-1) implanted in a xenograft mouse model [64]. This study showed that the tumor growth inhibitory potential of Lupeol is associated with its ability to decrease the expression level of cFLIP protein in tumors under *in vivo* conditions [64]. Since Lupeol was shown to overcome the chemoresistance offered by cancer cells under *in vivo* condition, this study bears high relevance for human disease. Recently Lee *et al.*, showed that Lupeol alone or in combination (with chemotherapeutic agents) could prove beneficial in the treatment of head and neck cancer in a mouse model [67]. Lee *et al.*, showed that Lupeol preferentially caused the death of head and neck cancer cells but spared normal tongue fibroblast cells [64]. Lupeol [2 mg/animal] was not only found to suppress the tumor growth, but also to impair head and neck cancer cell invasion by targeting NFκB signaling [67]. Further, Lupeol was shown to significantly sensitize head and neck cancer cells to cisplatin chemotherapy in an orthotopic metastatic nude mouse model of oral tongue squamous cell carcinoma [67]. Lupeol treatment was shown to dramatically suppressed local metastasis and that this effect was more than cisplatin alone [67].

Published reports from our laboratory and others suggested the efficacy of Lupeol against the growth of prostate cancer cells *in vitro* and *in vivo* [68–70]. We showed that Lupeol preferentially kills prostate cancer cells while spares normal prostate epithelial cells [68]. Recently, we showed that Lupeol (5–50 μM) inhibits the rate of proliferation of human prostate cancer cells irrespective of their androgen receptor status [69]. We also showed that Lupeol treatment (40 mg/kg) inhibits the growth of prostate cancer tumors of human origin implanted in a xenograft mouse model [68]. Notably, Lupeol was shown to decrease the serum-PSA levels [a clinical biomarker for prostate cancer] in mice implanted with human prostate tumors of human origin [68]. Computer based-chemical-protein interaction modeling studies have shown that Lupeol docks at the ligand binding domain of androgen receptor [Saleem M *et al.*, unpublished data]. Androgens are the key factors in the initiation or progression of prostate cancer and are known to induce oxidative stress which is marked by the generation of reactive oxygen species (ROS) and depletion in the levels of antioxidant enzymes [70]. Lupeol has been shown to inhibit the generation of ROS and restore the depleted antioxidant levels within prostatic tissue of androgen pretreated mice [70]. Studies with various cancer cells have shown that Lupeol adopts multipronged strategy to inhibit the growth of human cancer cells and by inducing apoptosis [68–69]. The mechanistic pathways targeted by Lupeol in prostate cancer cells are Wnt/β-catenin signaling and Fas-apoptotic machinery [68–69]. Lupeol was reported to decrease the expression level of several genes which are directly or indirectly associated with Wnt/β-catenin signaling in prostate cancer cells [69]. Lupeol was observed to target axin,

GSK3β, MMP-2, ERBB-2 and c-myc [69]. Our ongoing studies have shown that Lupeol modulates the microtubule assembly and the protein level of its regulatory molecules such as Stathmin and Survivin in prostate cancer cells thus causing G2/M cell cycle arrest (Saleem *et al.*, unpublished data). Our findings are supported by a recent study by Prasad *et al.*, showing that Lupeol induces G2/M cell cycle arrest in cancer cells by inhibiting the cyclin regulated signaling pathway [71]. The chemotherapeutic potential of Lupeol was also tested against the human hepatocellular carcinoma cell SMMC7721 cells [72]. Lupeol treatment was shown to inhibit the growth and induce the apoptotic death of SMMC7721 cells [72]. This study showed that Lupeol-induced growth inhibition and apoptosis is due to down-regulation of DR3 expression in SMMC7721 cells [72].

4. Lupeol and Toxicity studies

Lupeol has been reported to exhibit no toxicity in animal studies [76 and references therein]. Lupeol administered orally in a dose of 2 g/kg has been reported to produce no adverse effects in rats and mice, and after 96 hours of observation no mortality was recorded (76 and references therein]. Lupeol tested at doses 40–200 mg/kg under various protocols (long or short-term treatment) did not show any systemic toxicity effect in animals [12, 53, 76 and references therein]. Lupeol (2 mg/animal, equivalent to 80 mg/kg) applied topically (3 times /week) for 28 weeks did not produce any toxicity in mice [53]. Al-Rehaily *et al.*, performed acute toxicity study of Lupeol and reported that mice receiving oral administration of Lupeol (0.5– 40 mg/kg) for seven consecutive days did register no mortality or other toxic signs [77]. Oral administration of Lupeol (50 mg/kg) for consecutive 18 days did not produce any mortality or systemic toxicity in rats [12]. Recent studies showed that mice receiving intraperitoneal administration of Lupeol (40 mg/kg) did not show any sign of toxicity or mortality [54,64, 67–68]. A recent study by Sudhahar *et al.*, showed that mice fed on Lupeol-supplemented diet (50 mg/kg/day) for 15 consecutive days did not produce any systemic toxicity [19]. Preetha *et al.*, showed that oral administration of Lupeol (100 mg/kg) for 7 days did not cause mortality or any systemic toxicity in mice [78]. Taken together, these studies provide convincing evidence that Lupeol is a non-toxic but highly potent chemopreventive and chemotherapeutic agent.

5. Concluding Remarks

Several factors must be taken into consideration when the evidence for the inhibition of carcinogenesis and alleviation of other diseases by Lupeol is examined. These include the effective dose used and the time of exposure. Although animal studies have enhanced our understanding of the possible action of Lupeol in decreasing carcinogenesis and ameliorating inflammation, one must apply caution in extrapolating the information obtained in animal studies to humans, because of species differences. In order to evaluate the overall implications of Lupeol as a chemopreventive and chemotherapeutic agent, further studies are needed to fully identify its protective effects, as well as possible detrimental effects.

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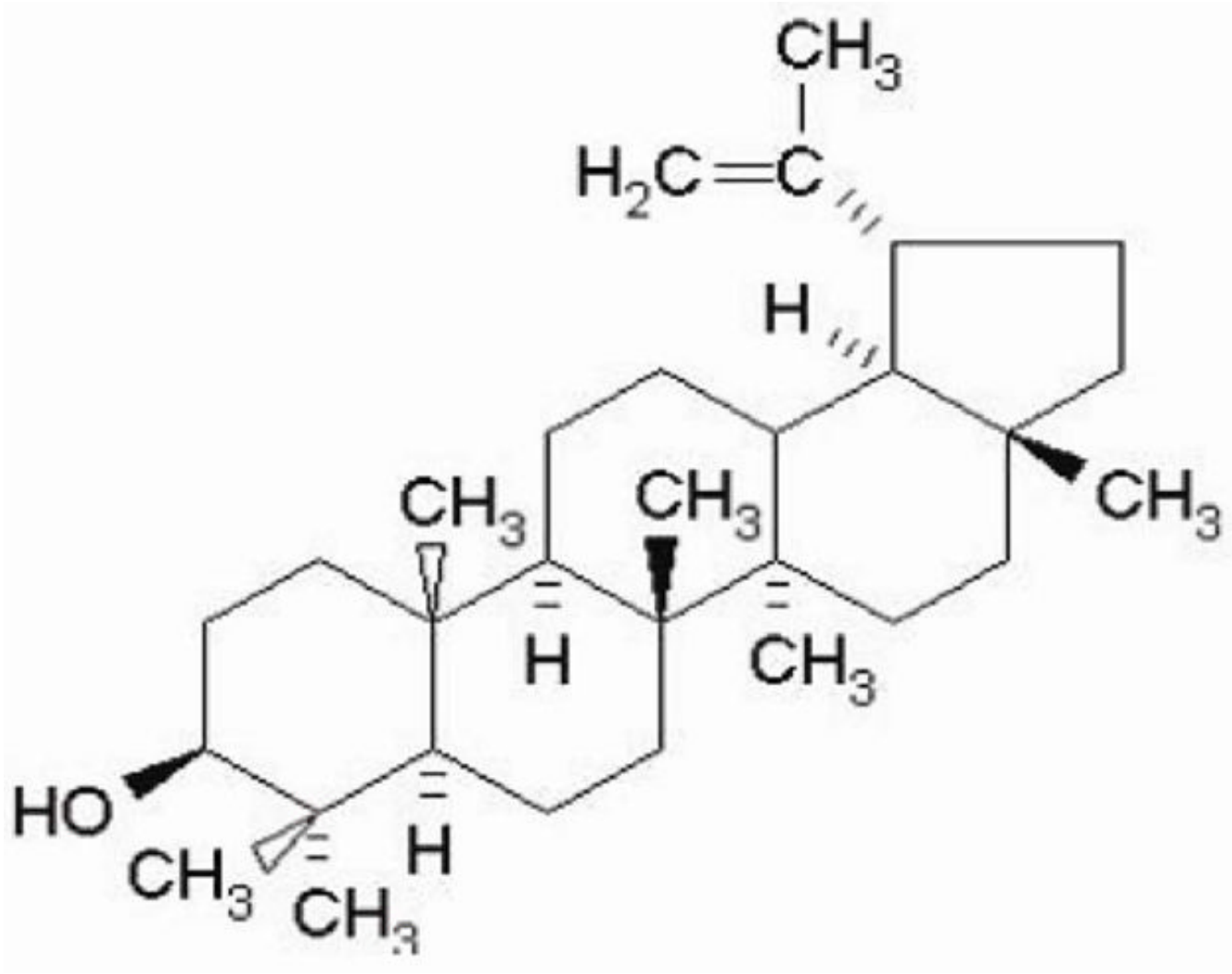

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Table 1

List of Selected Plants Containing Lupeol

Botanical Name	**Common Name**	**Botanical Name**	**Common Name**
Aloe vera	Aloe	*Hemidesmus indicus*	Indian Sarsaparilla
Apocynum cannabinum	Bitterroot	*Juniperus communis*	Common Juniper
Cajanus cajan	Congo-pea	*Lawsonia alba*	Henna
Calendula officinalis	Bull's Eyes	*Lycopersicon esculentum*	Tomato
Camellia sinensis	Black Tea	*Morus alba*	White mulberry
Capsicum annuum	African Pepper	*Olea Europa*	Olive
Cassia fistula	Indian Laburnum	*Panax ginseng*	Asiatic ginseng
Coccinia grandis	Ivy gourd	*Phoenix dactylifera*	Date Palm
Cucumis sativus	Cucumber	*Pisum sativum*	Common pea
Daucus carota	Carrot	*Psidium guajava*	Common guava
Ficus carica	Common fig	*Trilisa odoratissima*	Vanilla plant
Gentiana lutea	Bitter root	*Vitis vinifera*	common grapevine
Glycine max	Soya bean	*Vitellaria paradoxa*	bambouk-buttertree Shea
Glycyrrhiza glabra	Commom Licorice	*Helianthus annuus*	Annual Sunflower

Referenced from Dr. Duke's Phytochemical and Ethnobotanical Databases; US DA. ARS, National Genetic Resources Program.

Phytochemical and Ethnobotanical Databases. [Online Database] National Germplasm Resources Laboratory, Beltsville, Maryland. 2005

Table 2

Content of Lupeol in Fruits and in Plants

Name of Plant	Lupeol (μg/g)
Olive Fruit	3 μg / g of fruit
Mango fruit	1.80 μg/ g mango pulp
Aloe Leaves	280 μg / g dry leaf
Elm Plant	880 μg/ g bark
Japanese Pear (shinko)	175 μg/g twig bark
Ginseng Oil	15.2.mg/100 g of oil