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Review Article

Lupeol as a magical drug

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ABSTRACT

Lupeol, a triterpene 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. Natural products and herbal remedies used in traditional folklore medicine have been the source of many medically beneficial drugs because they elicit fewer side effects, relatively cheap, affordable and claimed to be effective. However, in order to make these remedies acceptable to modern medicine, there is a need to scientifically evaluate them to identify the active principles and to understand their mechanism of action. *Calotropis gigantea* commonly known as milk weed or swallow-wort, is a medicinal plant widely used as a folk medicine in India. It exhibits a wide array of pharmacological activities including wound healing and antimicrobial properties. Lupeol, a pentacyclic triterpenoid was extracted for the first time from the latex of *C. gigantea* and characterized by spectral studies. The presence of lupeol in the latex in appreciable amounts may account for its various biological activities.

Keywords: Anti-inflammatory, Lupeol, Antibacterial activity, HPTLC, Plasmodium falciparum, Gallic acid, Antitumar, *Calotropis gigantea*

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. 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.[2] 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] 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. 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]

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.[4-10]

The list of selected plants which have been reported to possess Lupeol in significant amounts is presented in (Table 1).[6] The quantification of Lupeol in fruits and medicinal plants has been performed and is summarized in (Table 2).[7]

Chemical structure and analysis

The chemical structure of lupeol is presented in [Figure 1].[6] 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-B donor 1, H-B acceptor 1. 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 presence of seven methyl singlets and an olefinic function in the 1H-NMR spectrum revealed that Lupeol is pentacylic triterpenoidal type in nature.[11] 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.[12]

Quantitation estimation of lupeol

- *In U.V* - UV spectra of lupeol display the λ_{max} value was found to be 350nm.[13]

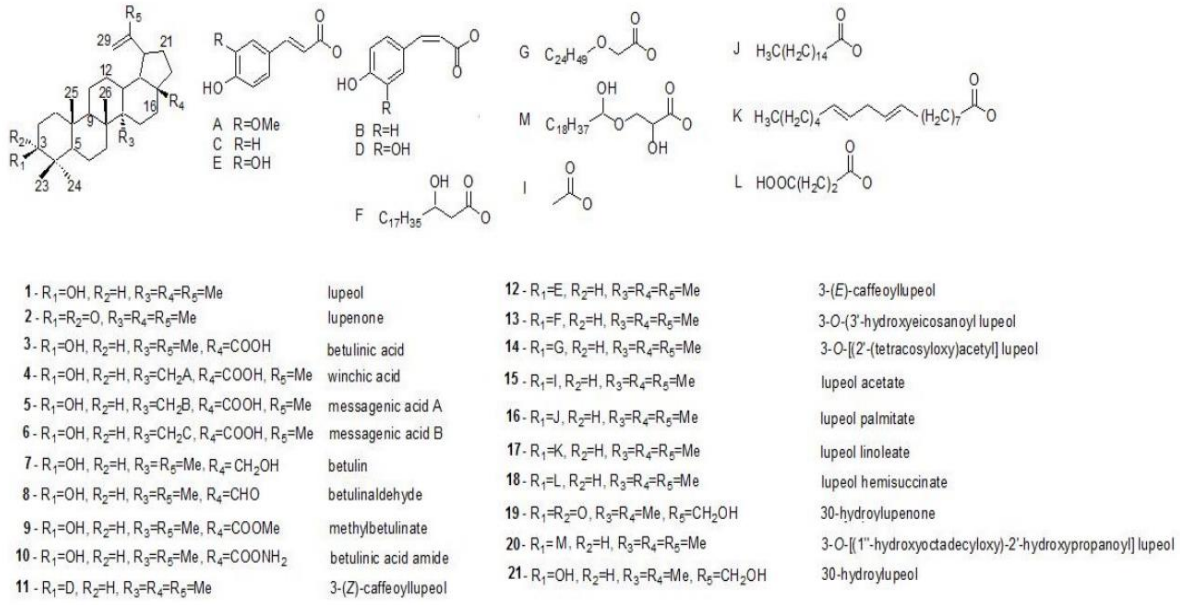

Figure 1: Chemical structure of lupeol.

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

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

- *In I.R* - IR spectra of lupeol, a very intensely broad band at 3384 cm^{-1} and moderately intense band at 1192 cm^{-1} and 672 cm^{-1} were observed for the O-H bond vibration of hydroxyl group. The out of plane C-H vibrations of the unsaturated part was observed at 826 cm^{-1}. The corresponding C=C vibration was shown around 1654 cm^{-1} was weakly intense band. The stretching and bending vibrations of methyl part were noticed by the intence band 2916 cm^{-1} and medium intensity band at 1460 cm^{-1}.[13]

Natural occurrences

Lupeol is found in a variety of plants, including mango, *Acacia visco* and *Abronia villosa.* It is also found in dandelion coffee.[14]

Synthesis

The first synthesis of lupeol was reported by Gilbert Stork *et al* [15]. In 2009, Surendra and Corey reported a more efficient and enantioselective total synthesis of lupeol, starting from (*1E, 5E*)-8-[(*2S*)-3, 3-dimethyloxiran-2-yl]-2, 6-dimethylocta-1, 5-dienyl acetate by use of a polycyclization.[16]

Isolation of lupeol

Plant material- The botanically identified plant material of *Crataeva nurvala* was used.

Method

C. nurvala stem bark powder was extracted exhaustively with petroleum ether by cold percolation and the resulting extract was eluted successively with hexane, hexane: benzene and benzene. The benzene elute on concentration deposited a white component lupeol which was filtered and recrystallised from methanol: acetone (60:40).[17]

Quantitation and detection

Currently, the use of medicinal plants is massively increasing as a low cost alternative to the pricey industrial drugs and due to more natural treatment requirements that display fewer side effects. Therefore, several products based on plants species are being manufactured in various pharmaceutical forms and are being sold in pharmacies and natural product stores.[18] The development of methods for detection and quantitation of an active substance is fundamental for quality control of either medicinal plants or phytopreparations. Gas chromatography (GS) and High Performance Thin Layer Chromatography (HPTLC) techniques are the most employed methods to quantitate lupeol in medicinal plants. HPTLC is cost efficient, flexible and quick. Silica gel 60 F^{254} is used as the stationary phase; the plate development can be carried out with a variety of solvents system like toluene/methanol (9:1) , n-hexane/ ethyl acetate (5:1) and lupeol is detected and quantified by densitometry after reaction with anisaldehyde- sulfuric acid, Lieberman-Burchard reagent or antimony trichloride.[19,20]

Pharmacological activities of lupeol

Antiprotozoal

Several of the most severe disease in the world are caused by protozoa and primarily distress developing nation's populace. Some of these so called neglected diseases, such as leishmaniasis and malaria, persist without effective treatment either by natural reasons, e.g, resistant strains, or from industrial disinterest due to economics in finding more efficient drugs.[21]

Based on the traditional knowledge.[22] Carried out a photochemical bioassay guided study and found plumbagin as the main active constituent (IC_{50} 5.0 µg/ml) an action of displayed by lupeol against varied strains of Leishmania and trypanosome species (Table 3).[23] Furthermore, the bioassay guided research of a plant used in the treatment of malaria symptom by a pygmy tribe from Cameron led to the isolation of an alkaloid rich fraction along with lupeol and its derivatives 13,14 and 20 (Figure 5).[23] These last four compound displayed low individual potencies against two different strains of plasmodium falciparum (Table-3)[23] and the suggestion of synergic effect among the metabolites.[23] Biological tests aiming for natural antimalarial agents revealed that lupeol moderates in vitro growth inhibition of plasmodium falciparum, but lack activity in an

vivo assay.[24] Since then lupeol and related compounds have been tested by several scientists against different strains of some protozoa species (Table-3).[23]

For example, A 96 member lupeol based library. One of the most promising library members was bioassay on *P. falciparaarum* NF-54 strain (IC_{50} of 14.8 µM) and *P. berghei* and same discrepancy between the in vitro and in vivo activities was observed.[25]

Table 3: Antiprotozoal activities of lupeol and its related compounds.

Compound	Protozoan (strain)	Activity	Plant species	Plant family
1	*Plasmodium berghei*	I[a] *in vivo* at 15 mg/kg	*Vernonia brasiliana*	Asteraceae
	Plasmodium. falciparum (BHz26/86)[b]	45% GI[c] *in vitro* at 25 µg/mL		
	Trypanosoma brucei brucei (TF)[d]	IC_{50}[e] *in vitro* 19.3 µg/mL	*Strychnos spinosa*	Loganiaceae
	Trypanosoma cruzi[f]	IC_{90}[g] *in vitro* >100 µg/mL	*Pera benensis*	Euphorbiaceae
	P. falciparum (FCR-3)[h]	IC_{50}[e] *in vitro* 41 µg/mL	*Holahrrena floribunda*	Apocynaceae
	P. falciparum (3D7)[i]	IC_{50}[e] *in vitro* 45 µg/mL		
	P. falciparum (3D7)[i]	IC_{50}[e] *in vitro* 11.8 µg/mL	*Rinorea ilicifolia*	Violaceae
	P. falciparum (K1)[j]	I[a] *in vitro* at 10 and 20.0 µg/mL	*Gardenia saxatilis* *Ziziphus cambodiana*	Rubiaceae Rhamnaceae
	P. falciparum (K1)[j]	IC_{50}[e] *in vitro* 5.0 µg/mL	*Cassia siamea*	Fabaceae
	Leishmania[k]	IC_{90}[g] *in vitro* 100 µg/mL	*Pera benensis*	Euphorbiaceae
2	*P. falciparum* (K1)[j]	I[a] *in vitro* 20.0 µg/mL	*Gardenia saxatilis*	Rubiaceae
3	*P. falciparum* (K1)[j]	IC_{50}[e] *in vitro* 19.6 µg/mL	*Uapaca nitida*	Euphorbiaceae
	P. falciparum (K1)[j]	I[a] *in vitro* 10.0 µg/mL	*Ziziphus cambodiana*	Rhamnaceae
	P. falciparum (3D7)[i]	IC_{50}[e] *in vitro* 6.3 µg/mL	*Zataria multiflora*	Lamiaceae
	P. falciparum (T9-96)[l]	IC_{50}[e] *in vitro* 25.9 µg/mL	*Uapaca nitida*	Euphorbiaceae
	P. berghei	I[a] *in vivo* at 250 mg/kg/day		
	T. brucei brucei (TF)[d]	IC_{50}[e] *in vitro* 14.9 µg/mL	*Strychnos spinosa*	Loganiaceae
4	*P. falciparum* (K1)[j]	I[a] *in vitro* at 20.0 µg/mL	*Gardenia saxatilis*	Rubiaceae
5	*P. falciparum* (K1)[j]	IC_{50}[e] *in vitro* 1.5 µg/mL	*Gardenia saxatilis*	Rubiaceae
6	*P. falciparum* (K1)[j]	IC_{50}[e] *in vitro* 3.8 µg/mL	*Gardenia saxatilis*	Rubiaceae
7	*P. falciparum* (K1and T9-96)[j,l]	I[a] *in vitro* 500 µg/mL	*Uapaca nitida*	Euphorbiaceae
	T. brucei brucei (TF)[d]	IC_{50}[e] *in vitro* 4.0 µg/mL	*Strychnos spinosa*	Loganiaceae
	P. falciparum (3D7)[i]	IC_{50}[e] *in vitro* < 12 µg/mL	Synthetic	-
8	*P. falciparum* (K1)[j]	IC_{50}[e] *in vitro* 6.5 µg/mL	*Ziziphus cambodiana*	Rhamnaceae
	P. falciparum (3D7)[i]	IC_{50}[e] *in vitro* 6.2 µg/mL	*Ziziphus vulgaris*	Rhamnaceae

Table 4: Plants containing lupeol with anti-inflammatory use.

Plant species	Plant family	Studied extract	Folk medicinal use
Bridelia scleroneura	Euphorbiaceae	Stem bark	Abdominal pain, contortion, arthritis and inflammation
Leptadenia hastata	Asclepiadaceae	Latex	Anti-inflammatory, wound healing agent
Diplotropis ferruginea	Fabaceae	Stem bark	Inflammation, vaginal and external ulcers
Pimenta racemosa	Myrtaceae	Leaves	Several inflammatory processes
Millettia versicolor	Fagaceae	Leaves	Analgesic, anti-rheumatic and anti-inflammatory
Strobilanthus callosus, S. ixiocephala	Acanthaceae	Roots	Inflammatory disorders
Himathanthus sucuuba	Apocynaceae	Stem bark	Gastritis, hemorrhoids, anemia, arthritis, verminosis and cancer
Euclea natalensis	Ebenaceae	Root bark	Bronchitis, pleurisy and chronic asthma
Croton pullei	Euphorbiaceae	Leaves	Inflammation (the genus)
Anemone raddeana	Ranunculaceae	Rhizome	Rheumatism and neuralgia

Table 5: Anticancer activity of betulinic acid.

Cell line	Derivation	Activity[a]
MEL-1	Human melanoma	1.1 µg/mL[b]
MEL-2	Human melanoma	2.0 µg/mL[b]
MEL-3	Human melanoma	2.7 µM[c]
MEL-4	Human melanoma	4.8 µg/mL[c]
G 361	Human malignant melanoma	> 50 µM[i]
B16	Mouse melanoma	30.5 µM[c]
		53.5 µmol/L[j]
B16-F1	Mouse melanoma	16.1 µM[h]
B16F	Metastatic mouse melanoma	4.6 µM[c]
MDA231	Human breast cancer	10.4 µg/mL[d]
MDL13E	Human breast cancer	11.5 µg/mL[d]
BC-1	Human breast cancer	>20 µg/mL[b]
HBL100	Human breast cancer	5.0 µg/mL[f]
MCF-7	Human breast cancer	194 µM[c]
		NR[e]
		>>50 µM[i]
BT474	Human breast cancer	12.1 µg/mL[d]
BT483	Human breast cancer	12.8 µg/mL[d]
BT549	Human breast cancer	5.5 µg/mL[d]
		>250 µM[c]
MDA-MB-238	Human breast cancer	195 µM[c]
SKBR3	Human breast cancer	16.2 µg/mL[d]
T47D	Human breast cancer	13.0 µg/mL[d]
		2.4 µM[g]
ZR-75-1	Human breast cancer	NR[e]

Table 6: Antibacterial activity of lupeol, betulinic acid and betulinaldehyde.

Bacteria species	Lupeol MIC µg/mL	Betulinic acid MIC µg/mL	Betulinaldehyde MIC µg/mL
Pseudomonas aeruginosa ATCC 27853	250	250	NT
Escherichia coli ATCC 25922	250	250	NT
Straphylococcus aureus ATCC 29213	250	250	NT
Enterococcus faecalis ATCC 29212	63	16	NT
Staphylococcus aureus ATCC 25923	> 200	NT	NT
Salmonella typhi ATCC 0232	> 200	NT	NT
Vibrio cholera	> 200	NT	NT
Escherichia coli ATCC 35218	> 200	NT	NT
Shigella spp. batch 0.57 (*S. dysentery*; *S. flexneri*; *S. sonnei*; *S. boydii*)	> 200	NT	NT
Mycobacterium tuberculosis	Inactive	25	25

NT = not tested

Anti- inflammatory

Inflammation is a cascade of biochemical events, involving the local vascular system and the immune system, characterized by five basic symptoms: rubor (redness), calor (heat), tumor (swelling), dolor (pain), and loss of function. It happens as a response to either injurious agents such as chemical irritants, toxins, pathogens, and burns.[26] The synthesis and release of several inflammatory mediators by different types of defense cells are involved in the process, which regulated by diverse enzyme.

In general, the monocytes differentiate into macrophages that synthesize various signaling molecules, among them the protein interleukin 1β, which triggers a second wave of cytokines responsible for the migration of the neutrophils to the injured tissue. Macrophages also produce reactive intermediates of oxygen such as hydrogen peroxide, and nitric oxide, important agents in edema development.[27] The uncontrolled release of many of those signaling molecules is the basis for the development of different type of inflammatory diseases like asthma and arthritis.

Several plants employed in folk medicine to treat inflammatory symptoms have been show to contain lupeol as one of their active principle (Table 4),[28] corroborating the popular uses. Lupeol decreases the IL-4 (interleukin 4) production by Th2 cells (T-helper type 2).[28]

Potent anti-inflammatory activity of lupeol in an allergic airway inflammation model as evidenced by significant reduction in eosinophils infiltration and in Th2 associated cytokines (IL-4, IL-5, IL-13) levels that trigger the immune response in asthma.[29] Lupeol reduced the LPS-induced IL-6 secretion to 27.6% at a concentration of 1 µM. The topical anti-inflammatory activity of *Pimenta racemosa* extract containing lupeol was associated with the reduction of neutrophils into the inflamed tissues.[30]

Antitumor

Cancer is a disease recognized by seven hallmarks.[31]

1. Unlimited growth of abnormal cells
2. Self- sufficiency in growth signals
3. Insensitivity to growth inhibitors
4. Evasion of apoptosis
5. Sustained angiogenesis
6. Inflammatory microenvironment
7. Eventually tissue invasion and metastasis

Antitumor activity began in the 1970 when the cancer chemotherapy national service centre reported the tumor inhibiting effects of an extract from *Hyptis emoryi* containing betulinic acid as its main constituent.[32] Betulin is also a lupeol analogue isolated from the roots of *Sarracenia flava*, demonstrated antitumor activity against human epidermoid carcinoma of the nasopharynx while lupeol isolated from the same plants displayed antitumor activity against lymphocytic leukemia P-388 cells.[33,34]

Shortly after, betulinic acid isolated from *Vauquelinia corymbosa* also demonstrated antitumar activity against p-388 cells.[35] When the betulinic acid was screened in vitro against a panel of human cancer cell lines, strong inhibition was show against several human melanoma lines with ED_{50} value ranging from 1 to 5 µg/ml.[36]

Antimicrobial

First tested against *Mycobacterium tuberculosis*, lupeol did not show any antibacterial activity. Betulinaldehyde and betulinic acid both presented minimal inhibitory concentration of 25µg/ml.[37] Lupeol and betulinic acid were inactive against three bacterial species but revealed MIC of 63 and 16 µg/ml against *Enterococcus faecalis*.

Lupeol was also inactive against eight bacteria species displaying MIC >200 µg/ml.[38] Lupeol showed significant zones of inhibition in the culture of 18 strains of the gram negative bacteria *Pseudomonas aeruginosa* and *Klebsiella pneumonia* at a concentration of 30 µg/100 µl.[39] Zone of inhibition were observed in *Pseudomonas aeruginosa*, *Salmonella typhi* and *Escherichia coli* cultures using lupeol, betulinic acid, betulinic acid impregnated disks at a concentration of 10 µg/ml.[40] While lupeol acetate did not display any activity against gram

negative bacteria and fungi but displayed a strong antimicrobial effect against gram positive bacteria.[41]

Conclusions

Triterpenoid, lupeol (3ˇ-hydroxylup-20(29)-ene), 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. Lupeol, a phytosterol and triterpene, is widely found in edible fruits, and vegetables. Extensive research over the last three decades has revealed several important pharmacological activities of lupeol. Various in vitro and preclinical animal studies suggest that lupeol has a potential to act as an anti-inflammatory, anti-microbial, anti-protozoal, anti-proliferative, anti-invasive, anti-angiogenic 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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References

1. Ovesna Z, Vachalkova A, Horvathova K, Tothova D. Pentacyclic triterpenoic acids: new chemoprotective compounds; Minireview. Neoplasma. 2004;51:327–33.
2. Liby KT, Yore MM, Sporn MB. Triterpenoids and rexinoids as multifunctional agents for the prevention and treatment of cancer. Nat Rev Cancer. 2007;357–69.
3. Moreau RA, Whitaker BD, Hicks KB. Phytosterols, phytostanols, and their conjugates in foods: structural diversity, quantitative analysis, and health-promoting. Prog Lipid Res.2002;41:457–500.
4. Beveridge TH, Li TS, Drover JC. Phytosterol content in American ginseng seed oil. Food Chem. 2002;50:744–50.
5. Alander J, Andersson A. The shea butter family – the complete emollient range for skin care Formulations. Cos Toil Man Worldwide. 2005:28–32.
6. Imam S, Azhar I, Hasan MM, Ali MS, Ahmed SW. Two triterpenes lupanone and lupeol isolated and identified from Tamarindus indica linn. Pak J Pharm Sci. 2007;20:125–7.
7. Nguemfo EL, Dimo T, Dongmo AB, Azebaze AG, Alaoui K, Asongalem AE. Anti-oxidative and anti-inflammatory activities of some isolated constituents from the stem bark of Allanblackia monticola. Inflammopharmacology. 2009;17:37–41.
8. De Miranda AL, Silva JR, Rezende CM, Neves JS, Parrini SC, Pinheiro ML. Anti-inflammatory and analgesic activities of the latex containing triterpenes from Himatanthus sucuuba. Planta Med. 2000;66:284–6.
9. Harish BG, Krishna V, Santosh Kumar HS, Khadeer Ahamed BM, Sharath R, Kumara Swamy HM. Wound healing activity and docking of glycogen-synthase-kinase-3-beta-protein with isolated triterpenoid lupeol in rats. Phytomedicine. 2008;15:763–7.
10. Lima LM, Perazzo FF, Tavares Carvalho JC, Bastos JK. Anti-inflammatory and analgesic activities of the ethanolic extracts from Zanthoxylum riedelianum leaves and stem bark. J Pharm Pharmacol. 2007;59:1151–8.
11. Du SJ, Gariboldi P, Jommi G. Constituents of Shashen (Adenophora axilliflora). Planta Med. 1986;52:317–20.
12. Martelanc M, Vovk I, Simonovska B. Determination of three major triterpenoids in epicuticular wax of cabbage (Brassica oleracea L.) by high-performance liquid

chromatography with UV and mass spectrometric detection. J Chromatogr. 2007;1164:145–52.
13. Moreau RA, Whitaker BD, Hicks KB. Phytosterols, phytostanols and their conjugates in food: structural diversity, quantitative analysis and health – promating uses. Prog Lipid Res. 2002;41:457-500.
14. Starks CM, Williams RB, Norman VL, Lawrence JA, Goering MG, O'Neil-Johnson Rice SM, et al. Abronione, a rotenoid from the desert annual Abronia villosa. Phytochemistry letters. 2011;4:72–4.
15. Gilbert S, Shoichiro U, Wakamatsu T, Grieco P, Labovitz J. Total synthesis of lupeol. Journal of the American Chemical Society. 1971;19:45-9.
16. Surendra K, Corey EJ. A short enantioselective total synthesis of the fundamental pentacyclic triterpene lupeol. Journal of the American Chemical Society. 2009;39:13928–9.
17. Badami S, Manohararеddy S A, Mathew N, Suresh B. Distribution and biological activities of lupeol. Indian Drugs; 2003; 255.
18. Anandjiwala S, Srinivasa H, Rajani M. Isolation and TLC densitometric quantification of lupeol, gallicin, gallic acid from bergia suffruticosa. A hitherto unexplored plant. Chromatographia. 2007;66:725-34.
19. Padashetty SA, Mishra SH. An HPTLC method for the evaluation of two medicinal plants commercially available in the Indian market under the common trade name Brahmadandi. Chromatographia. 2007;66:447-9.
20. Shailajan S, Menon SN. Simultaneous quantitation of lueol and beta- sitosterol from the whole plant powder of Asteracantha longifolia Nees. Analytical chemistry. 2009;8;77-81.
21. Fournet A, Angelo A, Munoz V, Roblet F, Hocquemiller R, Cave A. Biological and chemical studies of Pera benensis, a bolivian plant used in flok medicine as a treatment of cutaneous leishmaniasis. Journal of ethnopharmacology. 1992;37:159-64.
22. Fotie J, Bohle DS, Leimanis ML, Georges E, Rukunga G, Nkengfack AE. Lupeol long chain fatty acid esters with antimalarial activity from Holarrhena floribunda. Journal of natural product. 2006;69:62-7.
23. Alves TMA, Nagem TJ, Carvalho LH, Krettli AU, Zani CL. Antiplasmodial triterpene from vernonia brasiliana" Planta medica. 1996;63:554-5.
24. Srinivasan T, Srivastava GK, Pathak A, Batra S, Raj K, Singh K, Purib SK, Kundua B "Solid phase synthesis and bioevaluation of lupeol based libraries as antimalarial agents. Bioorganic and medicinal chemistry letters. 2002;12:2803-6.
25. Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008;454:428-35.
26. Bensinger SJ, Tontonoz P. Integration of metabolism and inflammation by lipid-activated nuclear receptors. Nature. 2008;454:470-7.
27. Bani S, Kaul A, Khan B, Ahmad SF, Suri KA, Gupta BD, et al. Suppression of T lymphocyte activity by lupeol isolated from crataeva religiosa. Phytotherapy research. 2006;20:279-87.
28. Vasconcelos JF, Teixeira MM, Barbosa Filho JM, Almeida JRGS, Queiroz LP, Ribeirodos santos R, et al. The triterpenes on urinary risk factor o stone formation in a murine model. International immunopharmacology. 2008;8:1216-21.
29. Ding Y, Nguyen HT, Kim SI, Kim HW, Kim YH. The regulation of inflammatory cytokine secretion in macrophage cell line by the chemical constituents of Rhus sylvestris. Bioorganic and medicinal chemistry letters; 2009;19:3607-10.
30. Mantovani A. Inflaming metastasis. Nature. 2009;457:36-7.
31. Sheth K, Jolad S, Wiedhopf R, Cole JR. Tumor inhibitory agent from Hyptis emoryi. Journal of pharmaceutical science. 1972;61:1819.
32. Miles DH, Kokpol U. Tumor inhibitors II: constituents and antitumor activity of Sarracenia flava. Journal of Pharmaceutical Science. 1976;65:284-5.
33. Miles DH, Kokpol U, Zalkow LH, Steindel SJ, Nabors JB. Tumor inhibitors I: preliminary investigation of antitumor

activity of Sarracenia flava. Journal of pharmaceutical Science. 1974;63:613-5.

34. Trumball ER, Bianchi E, Eckert DJ, Wiedhopf RM, Cole JR. Tumor inhibitory agents from Vauquelinia corymbosa. Journal of pharmaceutical Science. 1976;65:1407-8.
35. Pisha E, Chai H, Lee I, Chagwedera TE, Farnsworth NR, Coredell GA, et al. Discovery of betulinic acid as a selective inhibitor of humn melanoma tha function by induction of apoptosis. Nature medicine. 1994;1:1046-51.
36. Suksamran A, Panseeta P, Kunchanawatta S, Distaporn T, Ruktasing S, Suksamrarn A. Ceanothan and lupine type triterpenes with antiplasmodial and antimycobacterial activites from Ziziphys cambodiana. Chemical and pharmaceutical bulletin. 2006;54:535-7.
37. Shai LJ, McGaw LJ, Ambrosis SR, Crotti AEM, Lopes NP, Turatti ICC, et al. Biotransformation of lupeol by penicillium roqueforti. Planta Medica. 2008;74:1161.
38. Mathabe MC, Hussein AA, NIkolova RV, Basson AE, Meyer JJM, Lall N. Antibacterial activities and cytotoxicity of terpenoids isolated from Spirostachyus Africana. Journal of ethnopharmacology. 2008;116:194-7.
39. Ahamed BKM, Krishna V, Gowdru HB, Rajanaika H, Kumar aswamy HM, Rajshekarappa S, et al. Isolation of bactericidal constituents from the steam bark extract of Grewia tiliaefolia Vahl. Research journal of medicinal plant. 2007;1:72-82.
40. Lutta KP, Bii C, Akenga AT, Cornelius WW. Antimicrobial marine natural product from the sponge Axinella infundibuliformis. Records of Natural Products. 2008;2:116-7.
41. Freire MFI, Carvalho Mario G, Berbara RLL, Freire RB. Antimicrobial activity of lupeol acetate from Vernonia scorpioides Pers. Asteraceae Revista Brasileirade Farmacia. 2008;83:83-7.