BENEFICIAL HEALTH EFFECTS OF LUPEOL TRITERPENE AND ITS MEDICINAL PROPERTIES

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Contents

Summary

Natural products-based treatment for human diseases has been popular in earlier civilizations due to its inexpensive properties and easy availability. Lupeol, a triterpene, is one of the most extensively studied phytosterols found in edible fruits, vegetables, and medicinal plants. Detailed *in vitro* and *in vivo* studies suggest that Lupeol has important pharmacological activities, such as anti-inflammatory, anti-protozoal, anti-invasive, anti-microbial, and anti-proliferative, etc.. Lupeol is also effective in wound healing, hyperglycemia, heart diseases, renal diseases, and auto-immune disorders. Lupeol is a class II biochemical compound in a bio-pharmaceutical classification system that is readily absorbed in the body and has high therapeutic efficacy. The most notable property of Lupeol is that it selectively targets the diseased cell while sparing the healthy cells. Research findings from the authors' and others' labs confirmed the pharmacological efficacy of Lupeol by targeting various cell signaling pathways. In this chapter, we discuss the medicinal properties of Lupeol against multiple diseases, including cancer.

1. Introduction

1.1. Phytochemicals

Phytochemicals, also known as phytobiotics or phytogenics, are naturally occurring bioactive secondary metabolites produced by plants that give them their odor and color while also defending them against pathogens, herbivores, and other dangers. The inherent biological activities of the phytochemicals produced in plants may be suitable for the plants, but they may adversely affect other organisms. However, not all secondary metabolites produced by plants are harmful to other organisms. As it turns out, some of the phytochemicals are propitious in a variety of human ailments. In numerous biological reactions, phytochemicals operate as enzyme substrates, cofactors, or inhibitors. They can also act as ligands for the receptors, catalytic scavengers of reactive oxygen and nitrogen species, and substances that increase nutrient bio-absorption and promote a healthy gut by promoting the growth of beneficial microbiota.

Recently, the use of phytochemicals as therapeutic agents against different diseases has been on trend, and much research is being conducted in this area. In traditional medicine, many plants have therapeutic characteristics due to the phytochemicals produced by them. Research on phytochemicals proved that different phytochemicals affect multiple signaling pathways that play important roles in different diseases. Phytochemicals are broadly classified into six major subclasses: carbohydrates, lipids, terpenoids, phenolic acids, and nitrogen-containing metabolites. A large subclass of phytochemicals belongs to triterpenoids in the the class terpenoids, a group of secondary metabolites derived from squalene. Triterpenoids contain six isoprene units and are usually non-polar compounds. Triterpenoids benefit animals/humans due to their diverse biological activities and ease of availability. Notably, triterpenes are abundant in foods such as vegetable oils, grains, and fruits. Humans can safely consume up to 25 g of triterpenes per day, with daily consumption ranging from 250 mg in Western countries to 400 mg in Mediterranean countries. Recently, several preclinical studies showed very encouraging results, culminating in several patents and clinical

studies, which led to a flood of triterpene-based supplementals and cosmetic products filling the shelves of pharmaceutical stores.

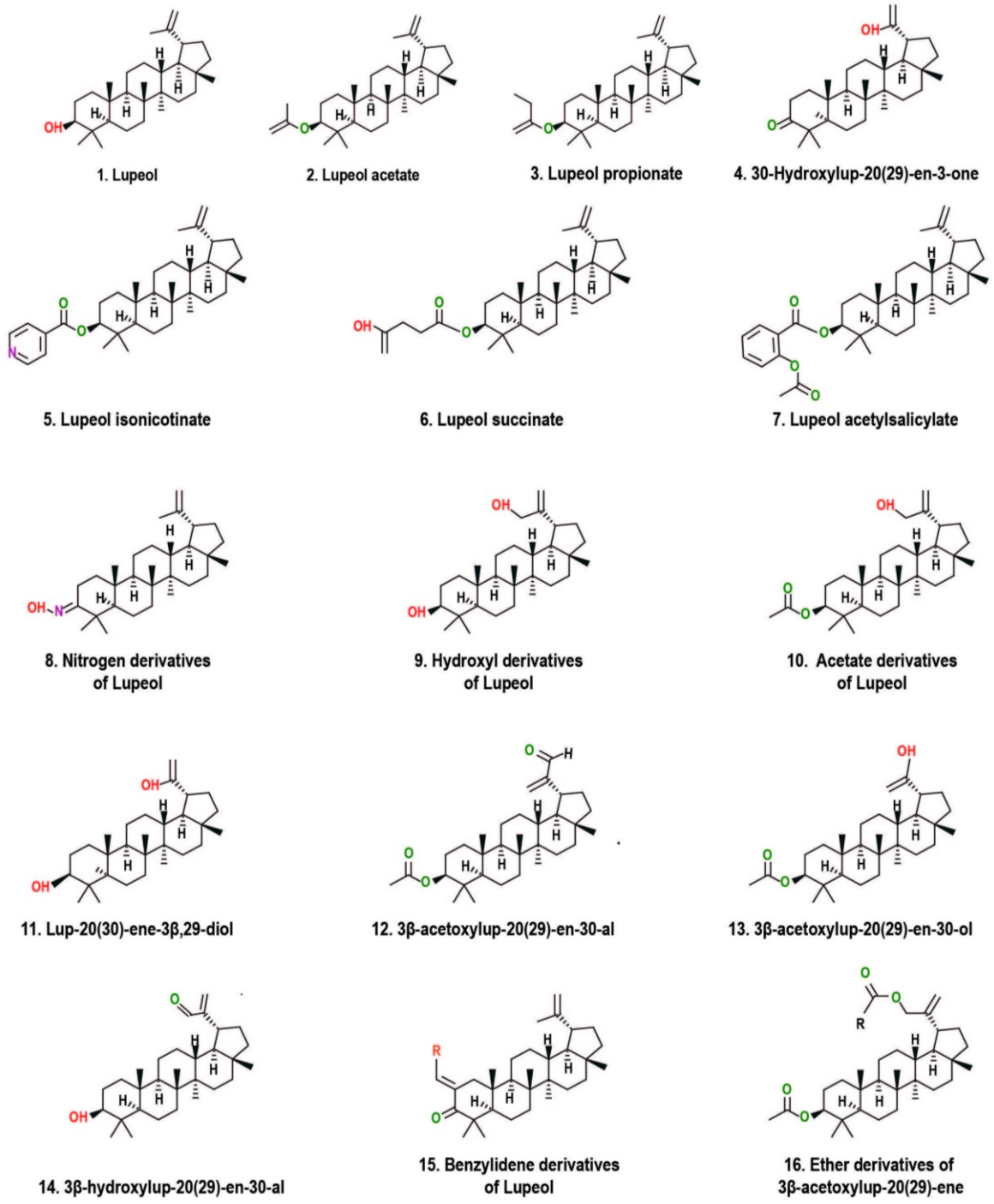

Figure 1. Chemical structure of Lupeol and its derivatives

1.2. Lupeol

Lupeol [Lup-20(29)-en-3b-ol] is one of the pharmacologically active triterpenoids found in various edible fruits, vegetables, and medicinal plants and is effective against a

wide range of diseases. Lupeol has attracted the attention of medical practitioners, researchers, and pharmaceutical marketers for its wide-ranging pharmacological activities. According to many experts, Lupeol is a multitarget agent since it affects the functioning of multiple proteins, and the literature is available in the public domain. In this context, several investigations have been conducted to identify the pharmacological properties of Lupeol using dogs, rodents, and cancer cell lines as test models. Moreover, isolated, semi-modified, and synthetic Lupeol derivatives also demonstrated potent pharmacological and pharmaco-kinetic activity. Common biologically active Lupeol derivatives (synthetically or semi-synthetically modified of 3-beta alcohol moiety) are Lupeol acetate, Lupeol stearate, Lupeol myristate, Lupeol laurate, and Lupeol palmitate. The pharmacological activities of Lupeol and its derivatives are characterized by anti-oxidant, anti-inflammatory, anti-diabetic, anti-mutagenic, anti-asthmatic, anti-arthritic, cardioprotective, hepato-protective, nephron-protective, and anti-carcinogenic properties.

A number of derivatives are synthesized in the lab that possesses the same carbon skeleton as Lupeol. H: Hydrogen; N: Nitrogen; O: Oxygen; OH: Hydroxy group.

1.3. Properties of Lupeol

Lupeol is a pentacyclic triterpenoid Lupane, with a hydroxyl group at the 3-beta position in place of hydrogen. The chemical formula of Lupeol is $C_{30}H_{50}O$ and is soluble in organic solvents such as ethanol, acetone, and chloroform. Lupeol has a lower solubility in water, an exact mass of 426.7 g/mol, and a density of 0.9457 g/cubic cm at 218° C. The melting point of Lupeol is 215-216° C, and specific optical rotation of +27.2 deg at 20° C/D. Furthermore, results from Lupeol's high-performance liquid chromatography (HPLC) and mass spectrometry (MS) show a parent ionic peak at m/z 409 [M+H—18]. [+].

1.4. Sources of Lupeol

Lupeol is found in variable amounts in a wide range of terrestrial and marine plants. The common sources of Lupeol are:

- mango pulp,
- mulberries,
- strawberries,
- white cabbage,
- soybean,
- black tea,
- pepper,
- carrot,
- cucumber,
- pea,
- tomato,
- hazelnuts,
- olive oil,
- figs,

- red grapes,
- guava, ivy gourd, and
- date palm.

Lupeol is also found in:

- *Senegalia visco* (Fabaceae),
- *Strobilanthes callosa* (Acanthaceae),
- *Gossampinus malabarica* (Malvaceae),
- *Abronia villosa* (Nyctaginaceae),
- *Zanthoxylum monogynum,*
- *Gueira senegalensis*,
- *Bombax ceiba*, and
- dandelion coffee.

The sources of Lupeol are found in all the major continents, including North America, South America, Africa, and Asia.

1.5. Bioavailability of Lupeol

It is critical to understand how long it takes for a compound to enter the systemic circulation and reach the site of action. In its natural state, Lupeol has low bioavailability as the serum level of Lupeol was recorded to be 3.08 and 5.22 μM after 4 h and 8 h when treated with the single treatment of Lupeol (200 mg/Kg). However, various Lupeol derivatives isolated from natural plants or synthesized in the lab have shown improved water solubility, absorption, distribution, bioavailability, and potency. In Table 1, the quantity of Lupeol isolated from different edible plants has been documented. Consumption of fruits or vegetables rich in Lupeol can help alleviate various physiological problems, but the amount found in edible fruits is relatively less. Consumption of 1 kg of olive fruits provides 3 g of Lupeol to the body, whereas 1kg of mango pulp contains 180 g of Lupeol. Moreover, the biosynthesis of Lupeol in the lab can significantly increase the titer produced per liter. Recently, the Lupeol biosynthesis pathway was engineered in *E. coli*, and approximately 200.1 mg/L Lupeol was obtained after 72 h of culture.

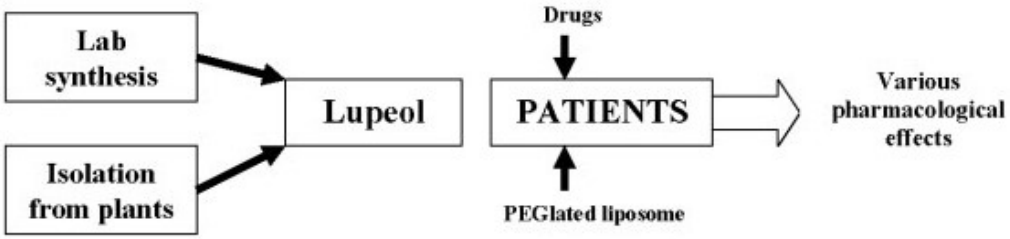

Figure 2. Sources and bioavailability of Lupeol.

Lupeol is a secondary metabolite found in fruits, vegetables, and medicinal plants. Lupeol can be isolated from plants or synthesized in lab. Lupeol has various levels of pharmacological efficiency and can target multiple diseases.

SN	Name of the Plant	Amount	References
1.	Olive fruit	3 μg/g	Siddique et al., 2011
2.	Mango fruit	1.80 μg/g pulp	Siddique et al., 2011
3.	Aloe leaf	280 μg/g dry leaf	Siddique et al., 2011
4.	Elm plant	800 μg/g bark	Siddique et al., 2011
5.	Japanese Pear	175 μg/g twig bark	Siddique et al., 2011
6.	Ginseng oil	15.2 mg/100 g of oil	Siddique et al., 2011
7.	*Derris scandens*	32.79mg/ 100 g Ethanolic extract	Somwong et al., 2021
8.	*Diospyros rhodocalyx*	40.72mg/100g Ethanolic extract	Somwong et al., 2021
9.	*Albizia procera*	21.44 mg/ 100 g Ethanolic extract	Somwong et al., 2021
10.	*Hibiscus deflersii*	7.47 μg/mg of dried weight	Alam et al., 2018
11.	*Hibiscus micranthus*	5.37 μg/mg of dried weight	Alam et al., 2018
12.	*Calotropis gigantea*	0.473 mg/100 mg of dried leaves	Loice et al., 2018
13.	*Crateva nurvala*	0.29% (w/w) in stem bark	Sadhwani et al., 2020

Table 1. Quantity of Lupeol present in different edible and medicinal plants

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Bibliography

Butera G, Pacchiana R, Donadelli M. (2017). Autocrine mechanisms of cancer chemoresistance. *Seminars in Cell & Developmental Biology* 8, 3-12. doi: 10.1016/j.semcdb.2017.07.019. [A comprehensive article detailing and discussing the regulation of secreted molecules by cancer cells that helps in evading drug onslaughts]

Fatma H, Siddique HR. (2021). Pluripotency inducing Yamanaka factors: role in stemness and chemoresistance of liver cancer. *Expert Reviews on Anticancer Therapy* 21(8), 853-864. doi: 10.1080/14737140.2021.1915137. [This review discusses in detail about the role of set of transcription factors involved in cancer stem cells and their role in chemoresistance].

Ganaie A. A., Siddique H. R., Sheikh I.A., Parray A., Wang L., Panyam J., Villalta P.W., Deng Y., Konety B.R., Saleem M. (2020). A novel terpenoid class for prevention and treatment of KRAS-driven cancers: Comprehensive analysis using in situ, in vitro, and in vivo model systems. *Molecular Carcinogenesis* 59(8), 886–896. https://doi.org/10.1002/mc.23200. [This put forward the approach to target specific signaling pathway by Lupeol to inhibit cancer progression]

Hanahan D. (2022). Hallmarks of Cancer: New Dimensions. Cancer Discovery, 12(1), 31–46. https://doi.org/10.1158/2159-8290.CD-21-1059. [This is an interesting and informative perspective that explains the notion of hallmarks that are commonly observed in cancer].

Maurya S.K., Shadab G, Siddique H.R. (2020). Chemosensitization of Therapy Resistant Tumors: Targeting Multiple Cell Signaling Pathways by Lupeol, A Pentacyclic Triterpene. *Current pharmaceutical design*, 26(4), 455–465. https://doi.org/10.2174/1381612826666200122122804 [A comprehensive review discusses Lupeol's role in chemosensitization of various drug-resistant cells].

Siddique H. R., Sarwat M (Eds). (2022). *Herbal Medicine: A boon for Healthy human life*. pp1-718. Elsevier, Amsterdam. [This book discussed the role of herbal medicine and natural plants against various diseases].

https://www.cancer.gov/about-cancer/causes-prevention/risk/diet/cruciferous-vegetables-fact-sheet. [The website provides information on diets that have chemopreventive activity].

https://www.cancer.gov/about-cancer/causes-prevention/risk/diet/tea-fact-sheet. [This website reveals the chemopreventive property of Tea].

Ruiz-Rodríguez M.A., Vedani A., Flores-Mireles A.L., Cháirez-Ramírez M.H., Gallegos-Infante J.A., González-Laredo R.F. (2017). In Silico Prediction of the Toxic Potential of Lupeol. *Chemical Research in Toxicology* 30(8), 1562-1571. doi: 10.1021/acs.chemrestox.7b00070. [The paper observed that in silico analysis of Lupeol and its derivative bring forwards a moderate toxic effect of Lupeol].

Saha S., Profumo E., Togna A.R., Riganò R., Saso L., Buttari B. (2020). Lupeol Counteracts the Pro-inflammatory Signaling Triggered in Macrophages by 7-Keto-Cholesterol: New Perspectives in the Therapy of Atherosclerosis. *Oxidative Medicine and Cell Longevity* 2020, 1232816. doi: 10.1155/2020/1232816. [This paper presents the anti-inflammatory role of Lupeol by counteracting the macrophages mediated pro-inflammatory signaling].

Saleem M. (2009) Lupeol, a novel anti-inflammatory and anti-cancer dietary triterpene. *Cancer letters* 285, 109-115. Doi: 10.1016/j.canlet.2009.04.033. [An interesting paper that discusses the role of Lupeol against inflammation and cancer].

Sharma N., Palia P., Chaudhary A., Shalini., Verma K., Kumar I. (2020) A Review on Pharmacological Activities of Lupeol and its Triterpene Derivatives. *Journal of Drug Delivery and Therapeutics* 10(5), 325-332. Doi: 10.22270/jddt.v10i5.4280. [A detailed article describing the mode of action, uses, and effects of Lupeol and its derivative].

Siddique H.R., Maurya S.K. (2021). Lupeol chemosensitize the cancer stem cells for enzalutamide and ameliorate the enzalutamide induced toxicity in prostate cancer. Proceedings: *American Association of Cancer Annual Meeting* 2021; April 10-15, 2021 and May 17-21, 2021; Philadelphia, PA. Cancer Research. 1(13), 13_Suppl):Abstract nr 276. DOI: 10.1158/1538-7445.AM2021-276. [The author presented the chemo-sensitizing role of Lupeol against prostate cancer].

Siddique H.R., Mishra S.K., Karnes R.J., Saleem M. (2011) Lupeol, a novel androgen receptor inhibitor: implications in prostate cancer therapy. *Clinical Cancer Research* 17(16):5379-91. doi: 10.1158/1078-0432.CCR-11-0916. [An interesting article discussing the role of Lupeol as androgen receptor inhibitor against prostate cancer].

Siddique H.R., Saleem M. (2011). Beneficial health effects of Lupeol triterpene: a review of preclinical studies. *Life Science* 88(7-8), 285-93. doi: 10.1016/j.lfs.2010.11.020. [This is a detailed review discussing the biological efficacy of Lupeol].

Siddique H.R., Saleem M. (2012). Role of BMI1, a stem cell factor, in cancer recurrence and chemoresistance: preclinical and clinical evidences. *Stem cells* 30(3), 372-8. doi: 10.1002/stem.1035. [This is an interesting review discussing the role of cancer stem cells and BMI as a stem cell factors in cancer recurrence and chemoresistance].

Sung H., Ferlay J., Siegel R.L., Laversanne M., Soerjomataram I., Jemal A., Bray F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: a Cancer Journal for Clinicians* 71(3), 209-249. doi: 10.3322/caac.21660. [A comprehensive report on the cancer burden, incidence, and mortality all over the globe].

Tsai F.S., Lin L.W., Wu C.R. (2016). Lupeol and Its Role in Chronic Diseases. In: Gupta, S., Prasad, S., Aggarwal, B. (eds) *Drug Discovery from Mother Nature. Advances in Experimental Medicine and Biology*, Springer, Cham. Berlin. 929, pp. 145-175. https://doi.org/10.1007/978-3-319-41342-6_7. [The

chapter describes anti-diabetic, anti-inflammatory, anti-cancer, hepatoprotective property of Lupeol in detail].

Biographical Sketches

Dr. Hifzur R. Siddique: Dr. Siddique is working as a Senior Assistant Professor at Aligarh Muslim University (AMU), India. He obtained his Ph.D. in 2008 from the Indian Institute of Toxicology Research, India, and got post-doctoral trainings at the University of Wisconsin, University of Minnesota & University of S. California, USA. His research specializations are Cancer Biology, Pharmacology, and Toxicology. He is now the Programme Director of Molecular Cancer Genetics and Translational Research program at AMU. He is, so far, published more than 101 original research papers (average impact factor-7.0 per publication) in journals like Nature Communications, Hepatology, Stem Cells, Clinical Cancer Research, Cancer Research, Genes and Cancer, Seminars in Cancer Biology, Seminars in Cell and Developmental Biology, ACS Nanomaterials, Coordination Chemistry Reviews, Life Sciences, Molecular Cancer Therapeutics, etc. He also published 16 book chapters and edited two book "Herbal Medicines- A boon for healthy human life" and Genes, Diseases, Immunity and Immunogenomics. His work on therapy-resistant cancer was selected as one of the best among three "Featured Prostate Cancer Research works by the USA, Department of Defence in 2014.He is the recipient of several academic awards and member of several scientific societies/associations. He regularly delivers invited talks, filed four patents, and 38-awards/honors to his credit. Further, he serves as an editorial member of ten Journals such as Frontiers in Oncology, Frontiers in Genetics etc. and reviewers of more than 70 reputed international journals. Multiple Government Agencies of India support his ongoing research. His brief biography with key achievements has featured in the prestigious journal Recent Patents on Anti-Cancer Drug Discovery in 2020. His current research predominates but not limited to discovering the role of natural phytochemicals in cancer chemo-sensitization and chemoprevention.

Ms. Homa Fatma: She earned her bachelor's and master's degrees from Aligarh Muslim University in Aligarh, India. She has completed her Ph.D. under the guidance of Dr. Hifzur R. Siddique at Aligarh Muslim University, Aligarh, India. She has published 14 papers, 05 book chapters, two popular articles and one technical article during her doctoral degree. She has published her work in Seminars in Cancer Biology, Life Sciences, Toxicology and Applied Pharmacology, Expert Review of Anticancer Therapy, *In Silico* Pharmacology, Drug and Chemical Toxicology, Advances in Protein Chemistry and Structural Biology, Recent Patents on Anticancer Drug Discovery etc. Her research activity includes studying the role of Lupeol against Liver cancer both *in vitro* and *in vivo*. In her master's degree, she was awarded gold medals for achieving the highest grades in her Department and Faculty.