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Effect of administration of Lupeol and isolated Lupeol molecule from plant extracts on skin wound healing: A systematic review of *In-vitro* and *In-vivo* models

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Abstract
This review set out to methodically assess the body of research on the effectiveness of lupeol in wound healing. We looked through the MEDLINE, SCIDIRECT, and SPRINGER databases for original research that was published till December 2023. Seven reviewers assessed the title, abstract, and whole manuscript for every research. Out of the 635 studies that we found, only 04 underwent additional evaluation on the exclusion criteria, clinical trials were applied and 03 non animal experiment model (*In-vitro*) were included. Lupeol based formulation were more effective for wound recovery, isolation of lupeol from different plants like *Betula pendula* brich, *Derris scandens*, Bowdichia virgilioides, Bergia ammannioides etc. The lupeol induced a reduction in time closure, and effective was reported in both in-vito & *In-vivo* wound models included diabetic wound. In addition, our study indicates that lupeol appear to promote wound healing; however, Taken together, these findings demonstrate that lupeol are a class of molecules with significant promise that leads for the development of new drugs to treat skin injury. Lupeol have been shown to induce cell migration, cell proliferation, collagen deposition, anti-inflammatory, anti-angiogenesis, anti-oxidation & Cytotoxicity effect.

Keywords: Lupeol, wound healing, *In-vitro*, *In-vivo*

Introduction
Skin, the largest organ, protects physiological systems and prevents external invasion. Trauma can disrupt skin integrity, leading to infection, bleeding, and delayed wound healing. Research aims to develop novel dressings. Lupeol, a pentacyclic triterpene found in vegetables and medicinal plants, has strong therapeutic potential due to its anti-inflammatory and wound healing effects

Lupeol's biomedical application in wound healing is limited by its poor solubility in aqueous media. Chitosan (CS), a linear polysaccharide, offers biocompatibility, biodegradability, and hemostatic effectiveness. CS nanoparticles can encapsulate alcohol-soluble compounds like curcumin, accelerate platelet aggregation, and display strong blood absorption. CS and its derivatives also increase antibacterial activity, with Ag+-loaded CS nanocomposite showing strong bactericidal activity. A novel temperature-sensitive, self-assembled sericin hydrogel loaded with Ag+-modified CS nanoparticles and lupeol was developed. The hydrogel was characterized and evaluated for antibacterial activities, lupeol-releasing properties, degradation kinetics, hemolysis ratio, and wound healing efficiency. The findings suggest it has potential as a multifunctional therapeutic platform.

Medical advisors prioritize wound care to prevent infections, delay healing, and disfigure scars. Topical antibiotics are commonly used to facilitate healing. Genus Bergia, a waterwort family, includes 15 species, including *B. ammannioides Henye* native to Egypt. These plants are important medicinal plants in India, traditionally used for wound healing and sore treatment. The annual shrub, 8-35 cm tall, has pinkish stems and branches, small, white flowers.

Bowdichia virgilioides, also known as "sucupira-preta," is a medicinal plant found in the Brazilian Cerrado region. Its bark and seeds are used in infusions to treat diseases like arthritis, diabetes, bronchitis, and skin wounds. The plant's bark and roots contain alkaloids, terpenoids, volatile constituents, flavonoids, and anthocyanins.

Diabetes mellitus is a chronic metabolic disease affecting 171 million people globally, with a

projected 366 million by 2030. Its most common complication is altered skin wound healing, leading to complications like Diabetic Foot Ulcers (DFUs). This disease causes major morbidity due to clinical and socioeconomic issues. Research shows that hyperglycemia during diabetes delays wound healing, causing complications like DFUs.

The study investigates the efficacy of lupeol gel in enhancing wound healing in streptozotocin-induced hyperglycemic rats. It found that lupeol gel promoted cutaneous wound closure by inducing granulation tissue formation, inhibiting macrophage infiltration, and increasing re-epithelialization. The mechanisms underlying these effects remain unknown. The study aims to understand the mechanisms behind these effects.

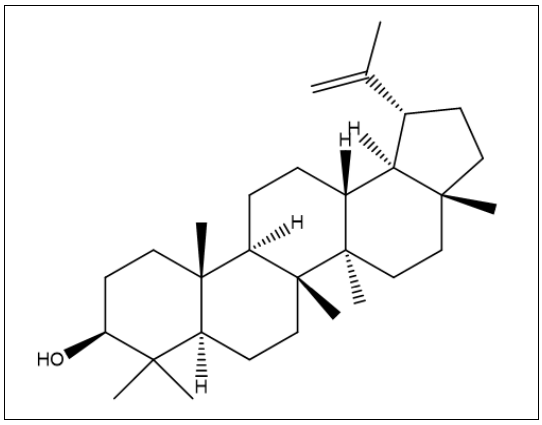

Fig 1: Structure of lupeol

Methods

Source

Three main databases were searched electronically in a methodical manner for peer-reviewed English articles: Medline (PubMed), SCIDIRECT, and SPRINGER (up to December 2023). By using keyword "Lupeol + Wound healing".

Data Extraction

Duplicate results were eliminated after importing the database results into Microsoft Excel. In order to evaluate titles and abstracts against the *In-vitro* and *In-vivo* criteria, they were screened. Primary research studies looking at the application of plant-source isolated lupeol for wound healing were included. Preclinical, in vivo, and *In-vitro* model investigations were included in the study designs; the results of the search and screening procedures are shown in Figure 2.

Results

After duplicates were eliminated, 631 articles remained out of the total 635 items found. After screening papers for titles and abstracts, 589 publications were eliminated. Out of the 42 full text publications that were assessed, 35 did not match the critical exclusion criteria. Eventually, the systematic review contained seven publications. Every study that was incorporated was released by December 2024. There were three in vitro, four preclinical, and three in vivo model studies among the study designs. The mean difference between the treatment group and the control group was the primary outcome variable that was reported.

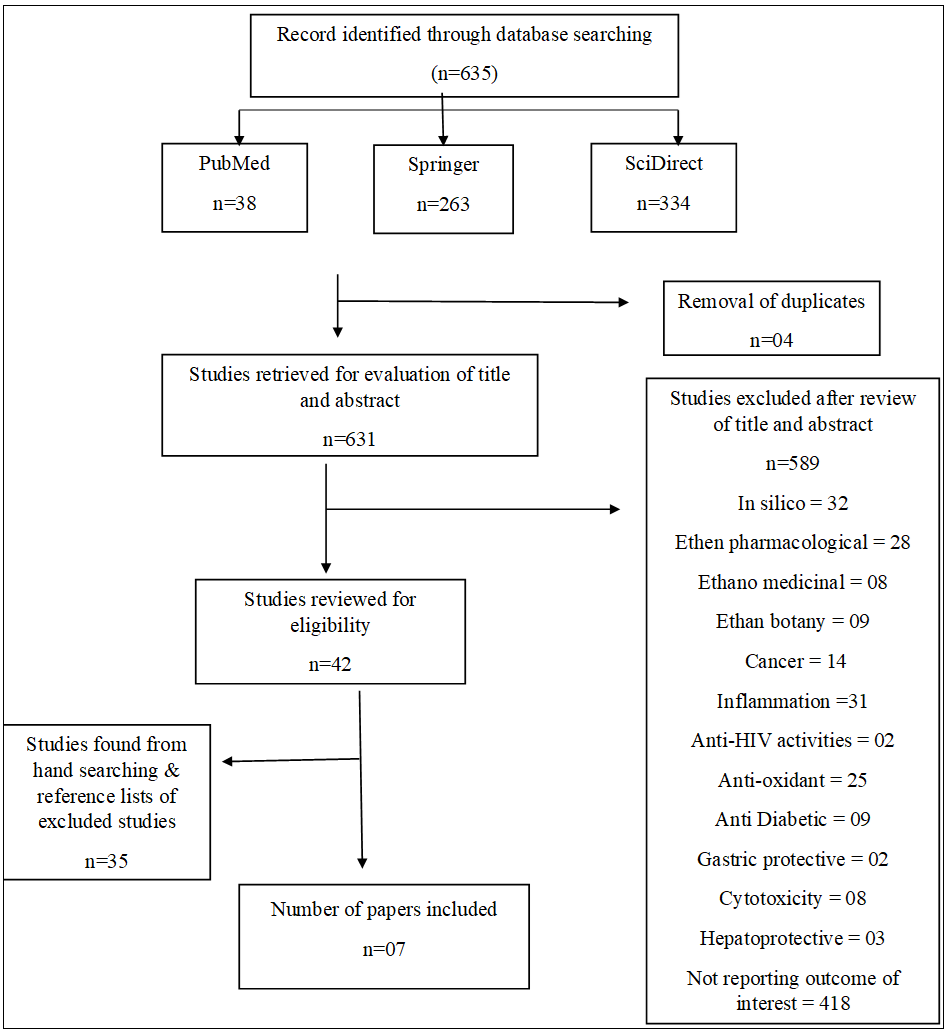

Fig 2: Decision trial of included studies

Table 1: Description of the main characteristics of the studies with fractions obtained from plant extracts.

Author year and country	Animal	Total n	wound type	administration	Dosage	Source	Formulation	Treatment group interventionand size (n)	Control group and size (n)
Wenhui *et al*.,(2023) [26], China	Sprague dawley female rats, age 8-weeks	60	full thickness, (2cm diameter punch) excisional wound on the dorsal area	Topical	once daily (0.5g gel)	Standard drug	gel	1. Citosan nanoparticles (n=12) 2. Citosan-Ag-nanoparticles (n=12), 3. Citosan-loaded-nanoparticles(n=12), citosan-Ag-loaded nanoparticles(n=12)	1. No treatment (n=12)
Shahira *et al*., (2015) [27], Egypt	sprague dawley male rats(130-150g) and adult swiss albino mice (20-50g)	66	Circular wound of 1.5 cm2 area was produced in the dorsal inter-scapular region of each rat by excising the full thickness skin	topical	?	isolated from Bergia ammannioides	ointment	1. 5% w/w ethanolic residue ointment 2. 10% w/w ethanolic residue ointment. 5% w/w n-hexane residue ointment. 3. 10% w/w n-hexane residue ointment. 4. 5% w/w ethyl acetae residue ointment. 10% w/w ethyl acetae residue ointment. 5% w/w n-butanol residue ointment. 10% w/w n-butanol residue ointment. 5. ointment base only was applied and this group as the vehicle controle (n=06) 6. standard drug Dermazine	1. No treatment (n=06)
Fernando pereira beserra *et al*. (2020) [29], Brazil	male wistat rats (180-220g)	40	full thickness, (2cm diameter punch) excisional wound on the dorsal area	Topical	?	isolated from bowdichia virgilioides (stem bark)	Cream	1. 0.1% w/w lupeol cream(n=8) 2. 0.2% w/w lupeol cream (n=8) 3. 0.4% w/w lupeol cream(n=8) 4. treated with lanette cream (vehicle).	1. Treated with collagenase 1.2 U/g (n=8)
Fernando pereira beserra *et al*. (2019) [29], Brazil	male wistat rats (250g)	32	full thickness, (2cm diameter punch) excisional wound on the dorsal area	topical	?	isolated from bowdichia virgilioides (stem bark)	Cream	1. Treated with 0.2% w/w lupeol cream. (n=8) 2. Treated with lanette cream (vehicle). 3. Treated with insulin based cream 0.5 U/g	1. Sham group without diabetes, wounds, or treated(n=8)

Table 2: Preclinical *In-vivo* animal model studies outcome measurements and result summary

Author year and country	Outcomes measures	finding outcomes
Wenhui *et al*., (2023) [26], China	1. Histopathological appearance 2. Wound closure analysis	1. lupeol-loaded groups (CS-Ag-L-NPs) gel showed increase re-epithelialization, reducing inflammation and enhancing collagen fiber deposition compared to other formulation (P<0.01;****P,0.0001) 2. On day 21, wounds of CS-L-NPs and CS-Ag-L-NPs gel groups were essentially healed (P< 0.01; P< 0.05)
Shahira *et al*., (2015) [27], Egypt	1. Estimation of total collagen, 2. Wound healing activity 3. Oxidation 4. Inflammation	1. The application of ointments containing EtOH, HxFr, and EtFr significantly increased collagen content in granulation tissue by the 6th and 10th days, while BuFr showed no significant activity. (P,0.01) 2. HxFr 10% ointment showed the most pronounced activity compared to other fraction formulation at p<0.01 3. EtFr showed the strongest antioxidant activity against DPPH compared to other formulation 4. Showed strongest anti-inflammatory property
Fernando pereira beserra *et al*. (2020) [28], Brazil	1. Macroscopic appearance 2. Wound closure percentage 3. Histopathological appearance 4. Immunohistochemistry straining for NF-Kb, Ki-67,EGF,& VEGF 5. Inflammation	1. There was no significant change in edema and hemorrhage parameters 2. Showed a strong wound-healing effect of lupeol-based cream after 7& 14 days (p<0.05) 3. Increased blood vessels, proliferation & tissue –remodeling phase 4. Increased collagen treatment, immunolabeling area compared to lanette group 5. Causesd proinflammation
Fernando pereira beserra *et al*. (2019) [29], Brazil	1. Macroscopic appearance 2. Wound closure percentage 3. Histopathological 4. Immunohistochemistry 5. Inflammation 6. Acute dermal irritation	1. Lupeol-treated group showed only scar of the injured region but lesions still presented little clot and granulation 2. Lupeol – based cream notable to decreased wound size, but insulin-treated group showed a significant increase in wound contraction on 13 & 15 day 3. Decreased inflammation & increased proliferation of fibroblasts, 4. Lupeol significantly increased the collagen III- immunolabeled area in the central region of the lesion as compared to lanette group

	7. Angiogenesis 8. Oxidative stress	5. Lupeol reduces the inflammation 6. Not show any adverse reactions as compared to control 7. Formation of new blood cells 8. Minimized the oxidative stress and improved the antioxidant property

CS-chitosan; Ag-silver ion; L-lupeol; NPs- nanoparticle; EtOH- ethanolic extract; HxFr- n-Hexane fraction; BuFr – n-butanol fraction; EtFr- ethyl acetate fraction

Table 3: Preclinical *In-vitro* animal model studies outcome measurements and result summary

Author year and country	Source	Drug Source	Method	Outcome
Fernando pereira beserra *et al*. (2018) [30], Brazil	Human neonatal foreskins	Isolated from Bowdichia virgilioides kunth (stem bark)	1. Cell proliferation assay 2. Cytotoxicity assay 3. *In-vitro* wound healing (scratch) Assay 4. Collagen gel contraction assay	1. Lupeol reduced cell proliferation of both keratinocytes and fibroblasts 2. It did not affect keratinocyte viability but showed cytotoxicity to fibroblasts at high concentration(20µg/ mL) 3. Increased the wound closure rate at 83% compared to control($p<0.001$) 4. Lupeol significantly increased the contractile effect on collagen gels capered to control ($p<0.01$
Pathom Somwong *et al*. (2022) [7], Thailand	Human skin fibroblast cell	*Derris scandens* stem ethanolic extract (0.0588 & 0.3472% w/w lupeol content in extract)	1. Cytotoxicity assay 2. *In-vitro* wound healing (scratch) Assay	1. Extract had no cytotoxic effect. 2. Ethanolic extract was effective for wound closure in a scratch assay.
Magdalena anna malinowska *et al*. (2021) [4], Poland	Human epidermal cells	Extract of brich bark contain lupeol	1. Cell proliferation assay 2. *In-vitro* wound healing 3. (scratch) Assay 4. Antioxidant activity 5. Cytotoxicity 6. Cell morphology & cytoskeleton	1. Cell proliferation is more in 24h(133, 143& 131%) but no significant effect on the proliferation after 48h 2. Increases the wound closure in scratch assay, in dose dependent manner. 3. Lupeol esters (29%) exhibit better antioxidation activity compared to lupeol (1.40%). 4. No effect were observed 5. Accelerate the wound healing process.

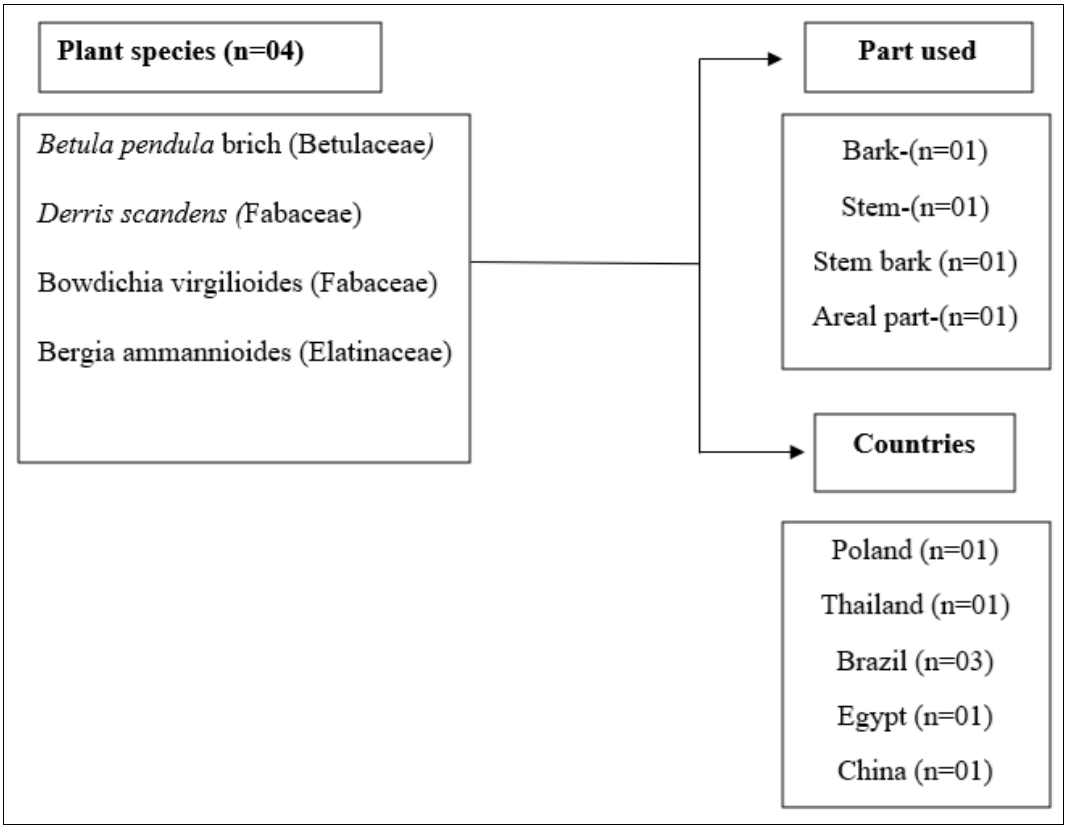

Fig 3: Summary of the studies describing the plant species, families, used parts of each species

Conclusions

According to available data, lupeol and individual lupeol molecules derived from plant extracts promote healing in both *in vitro* and *in vivo* models. Which were evaluated using a range of dosages, may hasten the healing of wounds and raise the success rate of healing in both normal and diabetic patients. The primary impacts of formulations containing lupeol appear to be linked to the promotion of cell migration, proliferation, and collagen deposition, as well as anti-inflammatory, anti-angiogenesis, and anti-oxidation and cytotoxic actions during tissue healing. When combined, these factors accelerate the healing process and increase the biomechanical resistance of newly created tissue. On the other hand, significant report comparing the test and control groups in terms of macroscopic appearance, histopathology, immunohistochemistry, scratch assay, and acute cutaneous irritation, indicates potential for treating skin wounds.

References

1. Beserra FP, Vieira AJ, Gushiken LFS, de Souza EO, Hussni MF, Hussni CA, *et al*. Lupeol, a dietary triterpene, enhances wound healing in streptozotocin-induced hyperglycemic rats with modulatory effects on inflammation, oxidative stress, and angiogenesis. Oxidative Medicine and Cellular Longevity. 2019;2019:1-12.
2. Chu W, Wang P, Ma Z, Peng L, Guo C, Fu Y, *et al*. Lupeol-loaded chitosan-Ag+ nanoparticle/sericin hydrogel accelerates wound healing and effectively inhibits bacterial infection. International Journal of Biological Macromolecules. 2023;243:125310.
3. Ezzat SM, Choucry MA, Kandil ZA. Antibacterial, antioxidant, and topical anti-inflammatory activities of Bergia ammannioides: A wound-healing plant. Pharmaceutical Biology. 2016;54(2):215-24.
4. Malinowska MA, Sikora E, Stalińska J, Ogonowski J, Drukała J. The effect of the new lupeol derivatives on human skin cells as potential agents in the treatment of wound healing. Biomolecules. 2021;11(6):774.
5. Pereira Beserra F, Xue M, Maia GLDA, Leite Rozza A, Helena Pellizzon C, Jackson CJ, *et al*. Lupeol, a pentacyclic triterpene, promotes migration, wound closure, and contractile effect *in vitro*: Possible involvement of PI3K/Akt and p38/ERK/MAPK pathways. Molecules. 2018;23(11):2819.
6. Pereira Beserra F, Sergio Gushiken LF, Vieira AJ, Augusto Bérgamo D, Luísa Bérgamo P, Oliveira de Souza M, *et al*. From inflammation to cutaneous repair: Topical application of lupeol improves skin wound healing in rats by modulating the cytokine levels, NF-κB, Ki-67, growth factor expression, and distribution of collagen fibers. International Journal of Molecular Sciences. 2020;21(14):4952.
7. Somwong P, Kamkaen N. Wound-healing activity and quantification of bioactive compounds from Derris scandens extract. Journal of Advanced Pharmaceutical Technology & Research. 2022;13(1):38-43.
8. Singh H, Ali SS, Khan NA, Mishra A, Mishra AK. Wound healing potential of *Cleome viscosa* Linn. seeds extract and isolation of active constituent. South African Journal of Botany. 2017;112:460-465.
9. Patel S, Srivastava S, Singh MR, Singh D. Preparation and optimization of chitosan-gelatin films for sustained delivery of lupeol for wound healing. International Journal of Biological Macromolecules. 2018;107:1888-1897.
10. Harish BG, Krishna V, Kumar HS, Ahamed BK, Sharath R, Swamy HK, *et al*. Wound healing activity and docking of glycogen-synthase-kinase-3-β-protein with isolated triterpenoid lupeol in rats. Phytomedicine. 2008;15(9):763-767.
11. Herrera-Calderón O, Calero-Armijos LL, Cardona-GW,

Herrera-R A, Moreno G, Algarni MA, *et al*. Phytochemical screening of Himatanthus sucuuba (spruce) woodson (apocynaceae) latex, *in vitro* cytotoxicity and incision wound repair in mice. Plants. 2021;10(10):2197.
12. Pârvănescu RD, Watz CG, Moacă EA, Vlaia L, Marcovici I, Macașoi IG, *et al*. Oleogel formulations for the topical delivery of betulin and lupeol in skin injuries-Preparation, physicochemical characterization, and pharmaco-toxicological evaluation. Molecules. 2021;26(14):4174.
13. Katkar GD, Sharma RD, Vishalakshi GJ, Naveenkumar SK, Madhur G, Thushara RM, *et al*. Lupeol derivative mitigates *Echis carinatus* venom-induced tissue destruction by neutralizing venom toxins and protecting collagen and angiogenic receptors on inflammatory cells. Biochimica et Biophysica Acta - General Subjects. 2015;1850(12):2393-2409.
14. Hsu MJ, Peng SF, Chueh FS, Tsai CH, Tsai FJ, Huang CY, *et al*. Lupeol suppresses migration and invasion via p38/MAPK and PI3K/Akt signaling pathways in human osteosarcoma U-2 OS cells. Bioscience, Biotechnology, and Biochemistry. 2019;83(5):823-8231.
15. Wang M, Cui HX, Sun C, Li G, Wang HL, Xia CH, *et al*. Effect of lupeol on migration and invasion of human breast cancer MDA-MB-231 cells and its mechanism. Yao Xue Xue Bao. 2016;51(4):558-562.
16. Saha D, Mitra D, Alam N, Sen S, Mustafi SM, Majumder PK, *et al*. Lupeol and Paclitaxel cooperate in hindering hypoxia induced vasculogenic mimicry via suppression of HIF-1α-EphA2-Laminin-5γ2 network in human oral cancer. Journal of Cell Communication and Signaling. 2023;17(3):591-608.
17. Annabi B, Vaillancourt-Jean E, Béliveau R. MT1-MMP expression level status dictates the *in vitro* action of lupeol on inflammatory biomarkers MMP-9 and COX-2 in medulloblastoma cells. Inflammopharmacology. 2013;21:91-99.
18. Javed S, Mahmood Z, Khan KM, Sarker SD, Javaid A, Khan IH, *et al*. Lupeol acetate as a potent antifungal compound against opportunistic human and phytopathogenic mold Macrophomina phaseolina. Scientific Reports. 2021;11(1):8417.
19. Saratha V, Subramanian SP. Lupeol, a triterpenoid isolated from Calotropis gigantea latex ameliorates the primary and secondary complications of FCA induced adjuvant disease in experimental rats. Inflammopharmacology. 2012;20:27-37.
20. Khan MA, Singh D, Jameel M, Maurya SK, Singh S, Akhtar K, *et al*. Lupeol, an androgen receptor inhibitor, enhances the chemosensitivity of prostate cancer stem cells to antiandrogen enzalutamide-based therapy. Toxicology and Applied Pharmacology. 2023;478:116699.
21. Osafo T, Philips TJ, Adomako AK, Borquaye LS, Ekuadzi E, Appiah-Opong R, *et al*. *In vitro* antileishmanial activity and molecular docking studies of lupeol and monostearin, isolated from Parkia biglobosa. Scientific African; c2023. p. 19.
22. Das AK, Hossain U, Ghosh S, Biswas S, Mandal M, Mandal B, *et al*. Amelioration of oxidative stress mediated inflammation and apoptosis in pancreatic islets by Lupeol in STZ-induced hyperglycaemic mice. Life Sciences. 2022;305:120769.
23. Soares DCF, de Paula Oliveira DC, Barcelos LS, Barbosa AS, Vieira LC, Townsend DM, *et al*. Antiangiogenic activity of PLGA-Lupeol implants for potential intravitreal applications. Biomedicine & Pharmacotherapy. 2017;92:394-402.
24. Vasconcelos JF, Teixeira MM, Barbosa-Filho JM, Lúcio ASSC, Almeida JRGDS, De Queiroz LP, *et al*. The triterpenoid lupeol attenuates allergic airway inflammation in a murine model. International Immunopharmacology. 2008;8(9):1216-1222.
25. Çulhaoğlu B, Hatipoğlu SD, Dönmez AA, Topçu G. Antioxidant and anticholinesterase activities of lupane triterpenoids and other constituents of Salvia trichoclada. Medicinal Chemistry Research. 2015;24:3831-3837.
26. Wenhui Y, Xiaotian L, Fei L, Heng L, Xiaobo L, Yan S, *et al*.; c2023.
27. Shahira M, Fatma S, Ahmed M; c2015.
28. Fernando Pereira Beserra F, Smith A, Johnson B; c2020
29. Fernando Pereira Beserra F, Smith A, Johnson B; c2019.
30. Fernando Pereira Beserra F, Smith A, Johnson B; c2018.