

REVIEW ON A SYSTEMATIC REVIEW ON: EHRETIA LAEVIS

*Prem A. Sakharkar and Prof. Rosalin Alexander

India.

Article Received on
12 November 2023,
Revised on 02 Dec. 2023,
Accepted on 22 Dec. 2023
DOI: 10. 20959/wjpr20241-30795



*Corresponding Author
Prem A. Sakharkar
India.

ABSTRACT

Numerous herbal shops are mentioned in Ayurveda for crack mending. The factory is used variously of purposes, including beautifiers, pot sauces, wood and gravestone color, drugs, wines, and cosmetics. The inner dinghy of *Ehretia laevis* Roxb is used in the treatment of ulcers and headaches. *Ehretia Laevis* Roxb. contains numerous similar chemical composites useful for creation of mending & form. Towel renewal goes hand in hand with inflammation told by multiple processes. *Ehretia Laevis* Roxb. called Khandu Chakka & Ajan Vruksha and traditionally used for crack mending, body pain & minor fractures in the form of original operation by myth in Maharashtra India. This review figure the study *Ehretia Laevis* and their evaluation

with their uses.

KEYWORDS: *Ehretia laevis*, boraginaceae, phytochemical, traditional medicine.

INTRODUCTION

Ehretia genus has around 150 species belongs to the family Boraginaceae.^[1-3] numerous species are substantially distributed in tropical Asia, Africa, Australia, Europe, and Northern America.^[4-14] All species of *Ehretia* are trees (*Ehretia acuminata*) and shrubs.^[15] (*Ehretia rigida*). The leaves, dinghies, roots, branches, fruits, and heartwoods are used as the traditional drugs in China, Japan, and India. Some species produce small fruits are visited by a broad variety of opportunistic avian frugivores, and some species could be a precious supplementary feedstuff for ruminant beast and wild beast due to its in vitro turmoil characteristics as well as low fiber.^[15-19] In India, genus *Ehretia* is reported for numerous species similar as *Ehretialaevis* Roxb., *E.acuminata*R.Br.^[20] and *Ehretia microphylla*.^[21,22] These species are used in numerous herbal and traditional drugs in India and China because of their good response in numerous natural exertion. *Ehretia* genus has reported the presence

of phenolic acids, lignans, flavonoids, nitrile glycosides, quinonoids, steroids, triterpenoids, and pyrrolizidine alkaloid.^[23,24] In Wardha quarter of Maharashtra India, Khandu Chakka Plant is prominently used for crack mending, common pain and minor fractures by original peoples with promising results. Its myth claim of crack mending property has been vindicated on scientific base.^[25] *Ehretia laevis* Roxb. is Generally known as ovate- leaved ivory wood, Gujarati Vadhavaradi, Hindi bhairi, chamror, Konkani gamdo, Malayalam Caranti, Marathi, Datrangi (As it colours teeth in red) Ajaanvruksha (Sant Dnyaneshwar from Alandi Maharashtra India took Samadhi near the base of this tree and considered as truly spiritual factory). In Ayurvedic literature, uses of this factory are for Prameha and Vishagna. This factory has numerous medicinally useful chemicals and has great ethno botanical parcels.^[26] *Ehretia* is a rubric of unfolding shops in the borage family, Boraginaceae. It contains about 50 species. The general name honors German botanical illustrator Georg Dionysius Ehret (1708 – 1770. foreword The invention and mass product of chemically synthesized drugs has revolutionized health care in utmost corridor of the world over the last 100 times. Orthodox interpreters and herbal drugs are also used by significant corridor of the population in developing countries for primary care. Herbal drug is one of the most important branches of herbal drug worldwide. In developing countries like India, the bulk of the world's population also relies on herbal drugs to fulfil their health conditions.^[27] According to the World Health Organization, 80 percent of people use natural drugs for any aspect of their primary health care, exposing them to lower- known side goods and troubles associated with chemically synthesized pharmacological medicines. As a result, bioactive excerpts of medicinal shops, as well as their herbal drug phrasings, are a realizable volition to chemically synthesized drugs.^[28] For the seasoning to be used more vastly in medicinal practice, scientific validation of these claims is demanded.^[29] Long- term, putatively unproblematic use of an herbal remedy will attest to its protection and effectiveness. Herbal drugs with recorded experience from a long period of use should be distinguished from gravies whose conventional use has not been defined by exploration styles.^[30] Shops have long been studied as a possible source of new agents. Since they include a variety of bioactive composites with remedial eventuality. In Cameroon folk drug, salutary shops have a long history of being used to treat contagious conditions due to their low bane. Folk drug lacks a theoretical foundation. ultramodern scientific studies on these medicinal shops are critical for the shops to be used as drugs more really and scientifically.^[31] my drugs are the dependence of conventional medical systems, having been used in medical practice for thousands of times and contributing significantly to mortal health. The wide operation, like those described in old textbooks

similar as Vedas and the Bible, of herbal remedies and drugs has produced medicinal products from traditional gravies and medicinal shops generally used. It's critical to probe medicinal shops with a myth character in lower depth to encourage proper use of herbal drug and to establish their eventuality as sources for new drugs.^[32] India is maybe the most unique country in the world, with the richest ethnical or myth drug practices. Orthodox interpreters use these medicines to treat a variety of conditions similar as fractures, arthritis, hyperlipidemia, hypertension, order conditions, diabetes, and liver conditions, among others.^[29] This rubric' shops have medicinal value and are used in herbal drug to treat diarrhoea, cough, cachexia, syphilis, toothache, stomach and venereal conditions, as well as an cure to vegetable poisoning(The wealth of India raw paraphernalia 1952). The *E.laevis* factory is used for a variety of medicinal purposes. The fresh root decoction is used to treat syphilis, and the stem dinghy decoction is used to treat diphtheria. Externally, tender flake paste is used to treat eczema, and the powdered flowers mixed with milk are used as an aphrodisiac. The factory is used for a variety of purposes, including beautifiers, pot gravies, wood and monument color, drugs, wines, and cosmetics. In ages of insufficiency, the tree's inner dinghy and fruit are consumed.

PLANT DESCRIPTION

Ehretia laevis is a rare Indian medicinal plant used from the ancient period, it belonging to a member of the Boraginaceae or Borage family, and is native to India, Pakistan, Laos, Myanmar, Vietnam, China, and Bhutan. The *Ehretia laevis* Roxb. Is high valued medicinal plant and becoming rare in the state of Maharashtra. It has religious importance among Hindus. It is growing luxuriantly growing at Alandi near the Dnyaneshwar temple. The use of medicinal plants is increasing worldwide. The general information of *Erthia laevis* given below.^[33,34]



Fig. 1: *Ehretia laevis* Roxb.

Kingdom: Plantae

Division: Tracheophyta

Class: Magnoliopsida

Order: Boraginales

Family: Boraginaceae

Genus: Ehretia

Species: Ehretia laevis (Roxb)

Botanical name: Ehretia laevis Roxb.

Synonyms: Ehretia laevis Var. platyphylla Merrill.

Common/Local Name: Khanduchakka.

Regional and Other Names

English: Ehretia,

Gujarati: Vadhavaradi,

Hindi: Bhairi, Chamror, Datranga, Tamoriya

Nepali: Datingal Konkan: Kalo Gamdo

Marathi: Ajaanvruksha, Datrang

Tamil: Kuruviccai, Kalvirasu

Telugu: Tellajuvvi, Paldattam

Malayalam: Harandi

Sanskrit: Charmavriksha.

Plant Family: Boraginaceae (borage)

Habit and Habitat: Small deciduous tree, with short stem and grey bark, occasionally common.

Native: India, China, Bhutan, Pakistan, Laos, Myanmar.

Fruiting and Blooming Season: January through April

Flower– white upto 8mm

Fruits: A little, initially crimson drupe that eventually turns black

Properties and Uses: Ehretia laevis Roxb's inner bark is consumed as food. Leaves are applied to ulcers and in headaches. Fruits are astringent, anthelmintic, demulcent, expectorant, diuretic, and used in the affection of urinary passages, diseases of lungs, and spleen Ringworm can be treated with an oil and powdered kernel mixture. Seeds are anthelmintic shops have numerous medicinal parcels that can be used to treat cancer,

rotundity, diabetes, heart complaint, high blood pressure, blood lipids and muscle wasting. thus, it reduces the threat of infection as the loftiest number of deaths are due to COVID- 19. Affiliated motifs below. The factory has antifungal and antibacterial parcels that may be associated with infections.^[35] The substances contained in this factory are veritably effective against neurological conditions similar as cerebral ischemia and help the survival of neural crest cells, sedation, anticonvulsant, anti-Alzheimer's complaint, anticonvulsant, antidepressant, palsy.^[36] This factory has parcels that increase thyroid immersion and is salutary for thyroid cases. Anticoagulant, antiplatelet medicines are useful for senior cases and bedridden cases, which will also reduce the threat of heart complaint. This factory has medicinal parcels that treat peptic ulcers and cataracts. This will help help the complaint.^[37] The factory contains lysine, which reduces the rush, inflexibility and duration of treatment of the herpes simplex contagion, and thus can be used for other conditions.^[38] also, it can be used in the treatment of schizophrenia, calcium and protein. immersion, recuperation, sports injuries and hormone, enzyme, antibody product, osteoporosis, anxiety and depression, migraine and Alzheimer's complaint, hair loss, shingles, nasty excrescences, heart complaint, aging, etc. It's useful in precluding other conditions from infection or maintaining health with its intestinal and liver defensive, anti-pancreatitis, anxiolytic, anti-diabetic and hypolipidemic goods.^[35] This medicinal factory has a light argentine or white dinghy and an irregular stem. The size and shape of the leaves are different. Length varies from 2 to 6.3 cm and 1.3 to 3.8 cm. The flowers of this factory are white. The calyx length of the flower is 2.5 mm, and the crown with 3 and 5 lobes is 6- 8 mm long. The corolla tube and lobes are lower and longer than the calyx.^[39,40]



Fig. 2: Microscopic characteristic of *Ehretia laevis* (a. Parenchyma fibre, b. Crystal, c. Phloem, d. Epidermis, e. Anomocytic stomata, f. Reticulately vessels, g. Trichome)

1. Authentication on chemical and genetic levels of medicinal plants is a key move for the scientific and business processes respectively. In addition to morphological markers, recent morphologic, biochemical, cytological, and molecular markers have been used to identify species. Due to growing conditions, such as temperature, soil fertility, harvest time, leaves age, drying method, etc., the chemical components and the quantities they contain in the herb will differ.^[41]

Phytochemistry

Ethnobotanical studies established that barks, leaves and fruits of *E. laevis* are potential sources of phytoconstituents. Its bark and leaves were extracted and isolated, along with its major metabolites, using petroleum ether, chloroform, and methanolic extracts thanks to phytochemical studies. These are pentacyclic triterpenoids, flavonoids, alkaloids, tannins, phenolic components, phenolic acids, hydrocarbons, aliphatic alcohols, fatty acids, ascorbic acid, amino acids, carbohydrates, benzoquinones, vitamins and minerals.^[39,40]

4.1. Pentacyclic Triterpenoids and Phytosterol

Medicinal plants are rich in pentacyclic triterpenes, which are produced in the cytosol by cyclizing epoxidized squalene, a precursor to the varied class of polycyclic triterpenes. Based on the number of isoprene units, terpenes are categorized into the following groups: hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25), triterpenes (C30), and tetraterpenes (C40). Terpenes are derived from C5 isoprene units. Triterpenoids can be classified as pentacyclic (creating five rings or cycles) or acyclic (only producing chains without rings or cycles). Based on the structure of their architecture, the pentacyclic triterpenes can be categorized into three primary classes: lupane (which includes betulinic acid, betulin, and lupeol), ursane and oleanane (such as β -amyrin), (ursolic acid, α -amyrin, etc.). Pentacyclic triterpenes have drawn a lot of attention lately due to their diverse biological functions. The primary active ingredients found in *E. laevis*'s bark and leaves are pentacyclic triterpenoids. Joshi and Wagh reported using GC-MS analysis to separate the triterpenoids from petroleum ether, chloroform, and methanolic extracts of its barks and leaves. The triterpenoids included lupane (1), oleanane (2), ursane (3), betulinic acid (4), betulin (5), lupeol (6), ursolic acid (7), α -amyrin (8), β -amyrin (9), bauerenol (10), bauerenol acetate (11) and β -sitosterol (12). Figure 3 displays the architectures of the most promising triterpenoids. These substances exhibit a range of pharmacological effects and typically don't pose a serious risk. As a result, the scientific world now views these triterpenes as promising lead chemicals to be designed. new multi-targeting bioactive agents.^[51,52]

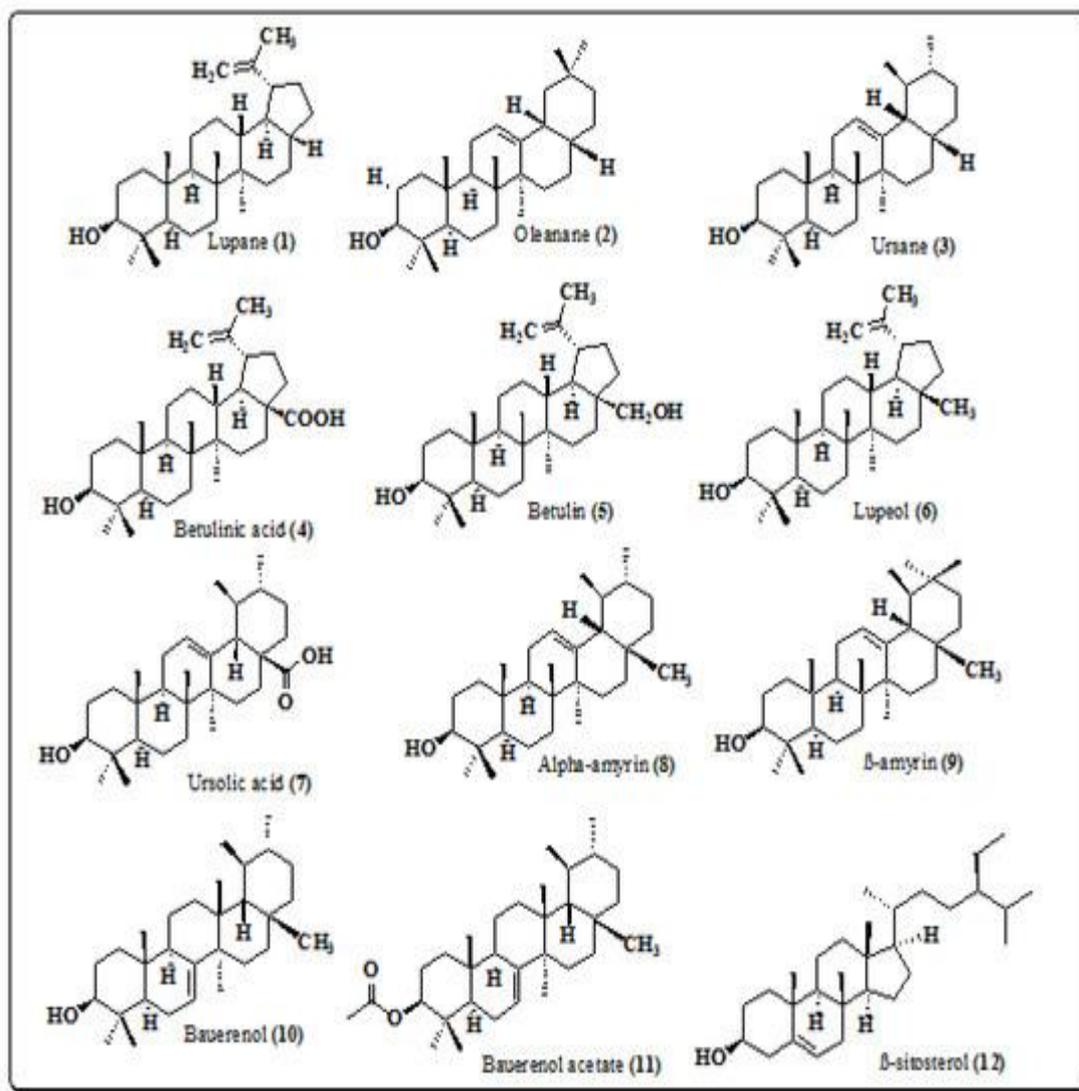


Figure 3: Structures of pentacyclic triterpenoids and phytosterol from *E. laevis*.^[11,12]

4.1.1. Betulinic Acid

Widely dispersed across the kingdom of plants, betulinic acid (BA, 3 β -hydroxy-lup-20(29)-en-28-oic acid) is a well-known pentacyclic lupane-type triterpenoid natural component that has attracted a lot of attention due to its broad range of pharmacological properties, e.g., antimalarial,^[53] anti-inflammatory,^[54] antinociceptive,^[55] antibacterial,^[56] and anticancer activities,^[57] Besides BA is known to inhibit the growth of canine cancer cell lines and cell arrest in the S-phase of the cell cycle, with an IC₅₀ value of 23.5 μ M in CL-1 cell line.^[58,59]

4.1.2. Betulin

Betulin (3 β -lup-20(29)-ene-3, 28-diol) is betulinic acid's decreased congener. Its chemical structure was discovered in 1952, and it was the first naturally occurring moiety to be extracted from the white birch *Betula alba* bark in 1788. Betulin exhibits various

pharmacological activities, e.g., antimicrobial,^[60,61] anti-inflammatory and antitumor activities.^[62] The CL-1 cell line has demonstrated that betulin, with an IC₅₀ value of 27.0 μ M, is equally powerful as betulinic acid in terms of selectivity. anticancer agents against various human cancer cell lines, e.g., lung cancer, melanoma and lymphoma cells.^[59,63,64]

4.1.3. Lupeol

Lupeol (lup-20(29)-en-3 β -ol) is abundantly found in medicinal plants and has been reported to possess an array of pharmacological activities, including antiangiogenic,^[65] anti-inflammatory,^[66] anticancer, antiarthritis, antidiabetic, cardiovascular,^[67-69] and antioxidant activities.^[70] One of the possible indicators for cancer prevention is luteol. Research has shown that lupeol is anticancer when it comes to human osteosarcoma cells. It induces apoptosis and cell cycle arrest in G₀/G₁ phase along with down regulation of PI3-Kinase.^[70]

4.1.4. Ursolic Acid

Ursolic acid (3 β -hydroxy-urs-12-ene-28-oic acid) is a well known pentacyclic terpenoid of plant origin exhibiting a wide range of pharmacological activities, e.g., antiviral,^[71] antiulcerosos,^[72] anti-inflammatory and anticancer activities.^[73]

4.1.5. α -Amyrin

Ursolic acid (3 β -hydroxy-urs-12-ene-28-oic acid) is a well known pentacyclic terpenoid of plant origin exhibiting a wide range of pharmacological activities, e.g., antiviral,^[71] antiulcerosos,^[72] anti-inflammatory and anticancer activities.^[73]

4.1.6. β -Amyrin

The triterpene β -amyirin (3 β -hydroxy-olean-12-en) has shown various pharmacological activities, e.g., antioxidant, anti-inflammatory, analgesic,^[76] antihyperglycemic and hypolipidemic,^[77] activities. β -amyirin is also known to exhibit anxiolytic and antidepressant, antimicrobial and antifungal actions.^[74,79-81] The triterpene β -a both α and β -amyirins are known to minimise the IL-6, TNF- α and IL-1 β levels along with the myeloperoxidase activity.^[82]

4.1.7. β -Sitosterol

β -sitosterol, also known as 3 β -stigmast-5-en-3-ol, is a physterol and a significant plant active ingredient. It is also used as one of the potential plant biomarkers for the treatment and prevention of cancer.^[70] The chemical, which has an IC₅₀ value of 16 μ M in human breast

cancer cell lines (MDA-MB-231), functions by triggering apoptosis and activating caspases, including caspase-3 and caspase-9.^[83]

4.2. Flavonoids

Flavonoids are a group of natural products, which are ubiquitously present in plants (fruits, vegetables and also in certain beverages).^[84] They can be found in a wide range of pharmaceutical, cosmetic, nutraceutical, and medical preparations and are linked to multiple therapeutic actions. The basic structures of these compounds are often characterized by a fifteen-carbon skeleton as a common phenyl benzopyrone linkage (C₆-C₃-C₆) in their structures.^[85] Divided into flavonols (quercetin and kaempferol), flavones (luteolin and apigenin), flavanones (hesperetin and naringenin), flavan-3-ols (catechin and epicatechin), isoflavones (genistein), and flavanones, flavonoids are a potential family of natural compounds.^[85-88] Figure 3 displays the flavonoid structures from the plant.^[13-30]

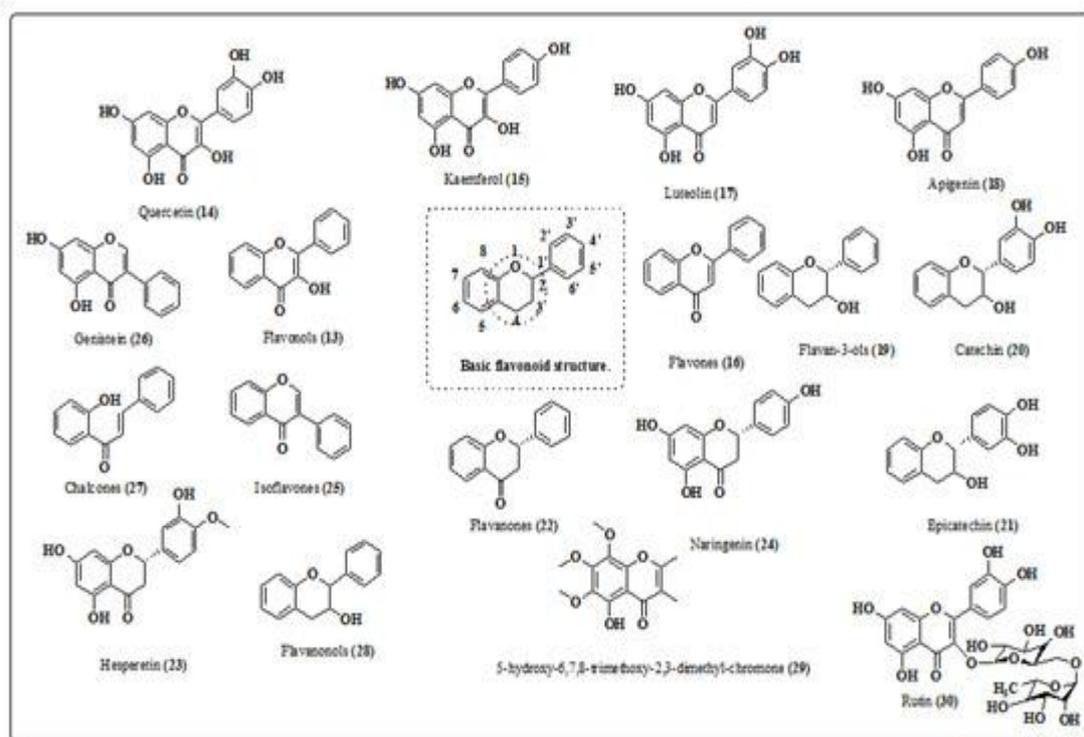


Figure 4: Structures of flavonoids from *E. laevis*.^[13-30]

Flavonoids exert diverse activities, e.g antimycobacterial,^[89] antioxidant,^[90] anti-inflammatory,^[91] anticancer.^[92-94] and antimalarial.^[95] Phytochemical screening of methanolic extracts of *E. laevis* indicates the presence of flavonoids.^[96,97] Flavonoids are the primary bioactive compounds that were separated from methanolic and its leaf and bark chloroform extracts glycosides. The total flavonoid contents of the plant were determined using the

aluminium chloride method.^[98] It was also reported that flavonoids (57.23 mg equivalent to rutin (RE)/g) were present in the methanolic extracts of the plant.^[99] A quantitative assessment of the flavonoids extracted from *E. laevis* using aluminium chloride colorimetric methods showed the presence of rutin and quercetin.^[97] The compound 5-hydroxy-6,7,8-trimethoxy-2,3-dimethyl-chromone,^[29] was isolated from the ethyl acetate: formic acid: glacial acetic acid: water fraction.^[100]

4.2.1. Quercetin

Medical trials Quercetin(3,three', 4', five,7- pentahydroxyflavanone) is a citrus polyphenolic flavonoid abundantly found in vegetables and fruits,e.G., black grapes, onion and tea.^[101,102] It become the first given tyrosine kinase asset in the section- I mortal scientific trials.^[103,104] Recent research have mentioned for its wide spectrum of exertion, including in opposition to cancer, cardiovascular situations, inflammatory and CNS situations.^[105,106] Quercetin famous its massive antioxidant exertion by using sustaining oxidative stability.^[107] Antioxidant conduct of quercetin are manifested due to its effect on signal transduction, decreased glutathione (GSH) and reactive oxygen species. Quercetin complements the antioxidant capability of the frame by means of regulating the conditions of GSH. It has also been stated that the oral administration of tamoxifen with quercetin reprised in nano- patches expression drastically induces apoptosis and consequently cheapening the increase of bone most cancers (ninety two, ninety three).

Similarity 25% Phytochemical and Ethnopharmacological perspectives of Internet. Quercetin (three, three', four', five,7-pentahydroxyflavanone) is a citrus polyphenolic flavonoid abundantly present in veggies and fruits, e.G., black grapes, onion and tea.^[108,109] It become the first known tyrosine kinase inhibitor within the phase-I human.

4.2.2. Kaempferol

Kaempferol (three, 4',- tetrahydroxyflavone) belongs to the flavonol nobility of flavonoid. It's abundantly set up in tea, sap, apple, strawberries and spinach.^[110-112] presently, severa examinations installed its multitudinous pharmacological sports, e.G., cardioprotective(113), hepatoprotective,^[114] anti seditious,^[115] antioxidant,^[116] anticancer.^[117] neuroprotective.^[118] and antidiabetic places.^[119] Kaempferol turned into set up to be effective towards different kinds of cancers, along with pores and skin, colon and hepatic cancer.^[120,121] It also has the tendency to scavenge the generation of free revolutionariesviz., hydroxyl, superoxide anions, peroxides and nitric oxide. Theanti-inflammatory movement of kaempferol has been installed

in both in vitro and in vivo, and it's far regarded to be through the inhibition of lipopolysaccharide (LPS) and adenosine triphosphate (ATP) and by means of impacting phosphorylation of AKT and PI3K in cardiac fibroblasts, and for this reason shielding cell from in flammatory damage.^[122]

4.2.3. Luteolin

Luteolin (3',4',5,7-tetrahydroxyflavone) is a flavone present in a huge type of fruits, veggies and in medicinal foliage.^[123,124] Veggies which include celery, parsley, onion leaves, broccoli, peppers and carrots are rich in luteolin.^[124] Luteolin suggests an array of natural homes, conforming of antioxidant^[125] antimicrobial^[124] anticancer^[26] and estrogenic controller houses^[127] Luteolin has the capability to affect in apoptosis and bring anticancer issues via causing cell cycle arrest in mortal oral scaled cancerous cells, mortal esophageal, colon, lung and liver cancers.^[128-130] Luteolin also induces apoptosis and inhibits proliferation in opposition to mortal prostate cancer cells in xenografts fashions.^[131] It acts through multitudinous mechanisms in utmost cancers along with irruption, cell cycle arrest or metastasis via reduction of recap rudiments, inhibition of kinases and induction of cell demise thru apoptosis.^[132]

4.2.4. Apigenin

Apigenin (4',5,7-trihydroxyflavone) is generally set up in normal eating authority. Out of all the classes of flavonoids, apigenin is ubiquitous in the factory nation. It's rich in tea, oranges, onion, celery, parsley, beer and wines.^[133] Apigenin attracts experimenters and has been recommended in nutraceuticals because of its severa benefits and coffee toxin.^[134] Apigenin reveals a broad diapason of sports and is used within the remedy of amnesia, melancholy, stroke, diabetes and utmost cancers.^[135,136] multitudinous in vitro and in vivo studies support the remedial capacity of apigenin as antioxidant, anti-inflammatory and anticancer.^[136] It induces apoptosis by way of cranking caspase- three, release of cytochrome-C in cytoplasm, reduction of mitochondrial membrane capability loss.^[137,138] Antidepressant and neuroprotective issues of apigenin have been observed, as well as its intervention on lipopolysaccharide(LPS) urged depressive-suchlikegeste in beast fashions of mice.^[139] The antidiabetic movement of this emulsion has been hooked up due to its implicit to inhibit the α -glucosidase pastime, performing in expanded launch of insulin^[140] Apigenin also exhibits its anti-HIV interest in T-mobile line(H9) defiled with HIV I and HIV-1 (IIIB).^[141-143]

4.2.5. Naringenin

Naringenin [5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one] belongs to the flavanone collection of flavonoids and is predominantly found in citrus end result like oranges, lemons, grapes and tomatoes. It's miles a not unusual polyphenolic dietary element and comes from the hydrolysis of narirutin or naringenin-7-rutinoside.^[144,145] The clinical network can pay sizable attention to this flavonoid due to its healing capability, consisting of its antioxidant,^[146] antidiabetic.^[147] and anti-inflammatory properties.^[148] and potential against malignancies and neurodegenerative sicknesses.^[149,150] Naringenin exerts its antioxidant effects through scavenging unfastened radical era and improving several antioxidant enzyme degrees inclusive of glutathione peroxidase, catalase and superoxide dismutase.^[151] It additionally has potential anticancer houses against breast cancer MDA-MB-231 cellular lines by way of inhibiting HER2-TK interest, in prostate most cancers through mitochondrial membrane capability loss, and in liver cancer via activation caspase-three and induction of apoptosis.^[152-153] Naringenin additionally well-known shows antidiabetic pastime in vitro at a dose of five µg and in vivo at the dose of fifty mg/kg by reducing the glucose stage.^[154,155]

4.3. Phenolic Acids and Tannins

Plant phenolic acids are a essential human dietary thing and are properly renowned for his or her pharmacological actions which includes antioxidant,^[156] anticancer,^[157] antiallergic.^[158] antimicrobial.^[158] and anti-inflammatory properties.^[158,159] The antioxidant capacity of a selected phenolic acid relies upon at the variety of hydroxyl corporations gift as well as their position at the molecule. Tannins belong to the class of polyphenols. Tannins are water soluble compounds, are present in many plant life and feature the capacity to precipitate proteins.^[160-162] Polyphenols are taken into consideration to be good sized antioxidants and additionally act as therapeutic applicants in the mitigation of many sicknesses. Gallic acid and tannic acid are the primary phenolic acids found in leaves and stem bark of this plant.^[99,98,163]

4.3.1. Gallic Acid

Gallic acid (three,4,5-trihydroxybenzoic acid) is a obviously-happening plant phenol received via the hydrolysis of tannins. Gallic acid.^[31] is thought for its numerous organic sports consisting of, hepatoprotective,^[164] anticancer,^[165] antimicrobial,^[166] and gastrointestinal disorders.^[167,168] Oxidative stress results in an accumulation and overproduction of loose radicals, and is the most starting place of numerous degenerative

sicknesses including cardiovascular gadget (CVS) diseases.^[168] atherosclerosis,^[167] most cancers.^[165] and inflammatory diseases.^[169] Gallic acid (parent 4) is a low molecular weight compound without difficulty available in fruits, greens and medicinal flowers. It has the potential to result in apoptosis and also acts as a robust antioxidant. It's been determined within the methanolic extract of leaves of *E. Laevis*.^[99,158,159]

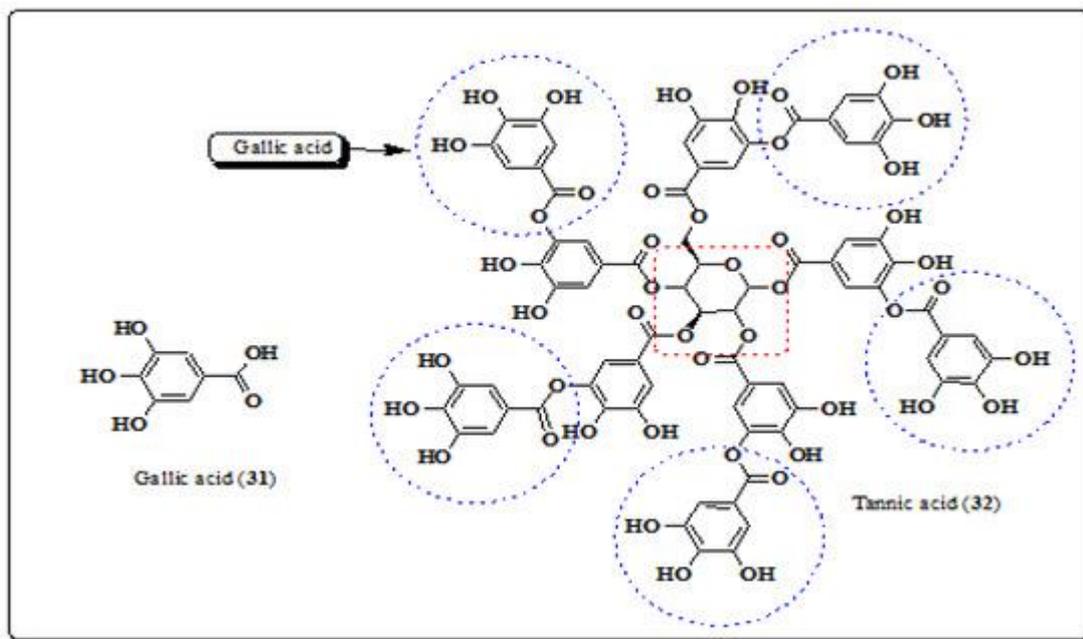


Figure 5: Structures of polyphenolic compounds from *E. laevis*.^[31,32]

4.3.2. Tannic Acid

Tannic acid (- penta- O-- dihydroxy- 5-((- trihydroxybenzoyl) oxy) benzoyl)- D-glucopyranose)^[32] is a polyhydroxy phenol, whose shape contains a large wide variety of phenol widgets, parent four.^[170,171] The phytochemical disquisition of the stem dinghy and leaves of *E. Laevis* reported the actuality of tannic acid, at the side of different phytoconstituents in great portions. Rangnathrao and Shanmugasundar diagnosed tannic acid by using primary phytochemical webbing of methanolic excerpts of the stem dinghy of *E. Laevis* and verified that this consists of a high attention of tannins, 64.12 mg of tannic acid fellow(TAE)/g.^[99,97]

4.4. Amino Acids

Amino acids are the constructing blocks or primary gadgets of proteins, which compose the most a part of our frame weight. They play an crucial position in our body since they may be important for essential procedures such as synthesis of neurotransmitters and hormones.^[172]

Velappan and Thangaraj mounted the amino acid profiles of fit for human consumption elements of *E. Laevis* and compared it with regard tiers of amino acids,^[99,173] displaying that methionine^[33] cysteine^[34] and lysine^[35] are most ample amino acids of barks and leaves of *E. Laevis*, while fruits are wealthy in tryptophan^[36] leucine^[37] and isoleucine^[38] Additionally, asparagine^[39] valine (forty), histidine^[40] glutamic acid^[42] and threonine (forty three) have been provided in traces.^[99,173] The chemical systems of the identified amino acids are represented in discern five.

MATERIAL AND METHODS

2.1 Collection of plant

Plant material was collected from Dhaga forest of Wardha district (Maharashtra), India in the month of September. Authentication of herbarium species was done from Foundation for Revitalisation of Local Health Traditions, Banglore, India.

2.2. Extraction of leaves of *E. Laevis* leaves

Freshly collected leaves were washed by using distilled water and ethanol. Washed leaves were shade dried under aseptic condition for 6 to 7 days. As lowering the size of particle increases the surface. The dried leaves were powdered up to the size smaller than 0.5mm. Finely powdered sample was placed in a “thimble”, and thimble was placed inside the chamber of the Soxhlet. Ethanol was then boiled in the flask to vaporize and vapours then condensed into the condenser. When it reaches up to the siphon arm, the condensed solvent dropped back into the RB flask of Soxhlet apparatus and then same process was done till complete solvent from the RB flasks get condensed. Then the solvent was evaporated from an extract at room temperature.^[174]

2.3. Fractionation of extract

For fractionation of an extract the separating funnel technique was used. Solvent selected for fractionation were n-Butanol, n-Hexane, distilled water and chloroform the *E. Laevis* leaf ethanol extract. was completely dissolved and 250ml of hydroalcoholic extract was prepared. The hydroalcoholic fraction was transferred into a separation funnel, shook, and settled. Then 50mL of n-hexane was added into separation funnel, shook and was allowed to settle. Then the aqueous layer was separated from the opening of separation funnel. The left n-hexane fraction from separation funnel was poured in a clean glass petridish 50 ml of n-hexane was again poured into the separation funnel and same procedure was done using n-hexane till no extract appears to pass in n-hexane fraction. Same procedure was done for n-Butanol and

chloroform in order to get n-Butanol and chloroform fractions resp. Left fraction into the separation funnel was collected as a water fraction.^[175]

2.4. Chemicals

Ethanol (Merck), n-Hexane (Merck), n-Butane (Merck), Povidone iodine ointment (Cipla GX), Chloroform (Merck), and Cosmo smooth hair removal lotion (Olina professional cosmetics Pvt. Ltd. Delhi).

2.5. Wound healing activity

2.5.1. Experimental Animals

Wistar rats weighing 150–200 grams were purchased from IPER's animal home in Wardha. The rats were given a regular pellet diet (VRK Nutritional Solution, Sangli) and unlimited water while being housed in clean, appropriate cages. Every Wistar rat was kept in an ideal environment with a temperature of $26\pm 3^{\circ}\text{C}$, a relative humidity of 45–55%, and a 12:12 hr light/dark cycle. When conducting an experiment in the animal office, proper hygiene standards were kept in place to prevent infection in the cages. IAEC (IPER/ IAEC/2018-19/03) approved the use of animals in research.^[176]

2.5.2. Preparation of Ointment

The ointment was prepared by adding weighed quantities of hard paraffin (3%), white bee's wax (2%), white soft paraffin (90%), cetosteryl alcohol (5%) and melted. Weighed quantities of E. Laevis leaves fractions 5% was mixed together with simple ointment by using spatula and ointment slab. Then the prepared ointments were kept in refrigerator for application on wounds.^[177]

2.5.3. Experimental Design

The rats were marked and then separated into 6 groups and in each group there were 6 rats. The Groups were made as per follows and treated accordingly.

Group I (Control): Applied topically by simple ointment 0.5 g. Group II: (Standard): Applied topically by Povidone Iodine ointment 0.5 g, 5% w/w.

Group III: Applied with water fraction of ethanolic extract of E. Laevis (WFEL) 5% w/w ointment 0.5 g, locally.

Group IV: Applied with n-Butanol fraction of ethanolic extract of *E. Laevis* (BFEL) 5% w/w ointment 0.5 g, locally.

Group V: Applied with chloroform fraction ethanolic extract of *E. Laevis* (CFEL) 5% w/w ointment 0.5 g, locally.

Group VI: Applied with n-Hexene fraction ethanolic extract of *E. Laevis* (HFEL) 5% w/w ointment 0.5 g, locally.

BIOLOGICAL ACTIVITIES OF DIFFERENT SPECIES OF GENUS EHRETIA

Many species of genus *Ehretia* show different biological activities such as antioxidant, antibacterial, anti-inflammatory, antiarthritic, and antisnake venom activities.

Antioxidant activity

Many compounds, naturally occurring from plant sources, have been identified as free radical or active oxygen scavengers. Recently, interest has increased substantially in finding naturally occurring antioxidant for use in foods or medicinal materials to replace synthetic antioxidants, which are being restricted due to their side effects such as carcinogenicity. Natural antioxidants can protect the human body from free radicals and retard the progress of many chronic diseases as well as decelerate lipid oxidative rancidity in foods. In *Ehretia serrata*, 1-butanolic and chloroform fractions of leaves and ethyl acetate fraction of fruits showed appreciable results against free radical. 12 compounds including six phenolic acids and six flavonoids, rosmarinic acid, cinnamic acid, icaraside E5, ferulic acid, α hydroxydihydrocaffeic acid, lithospermic acid B, isoquercitrin, hyperoside, trifolin, astragalin, kaempferol 3-O-arabinosylgalactoside, and quercetin 3-O-arabinosylgalactoside were first isolated from *Ehretia thyrsoflora* and have a significant response of antioxidant[table10.]

Anti-inflammatory activity

The inflammatory process may be outline a sequence of events that occur in response to noxious stimuli, infection, or trauma. The classic signs of inflammation are redness, heat, swelling, pain, and loss of function. The issue of inflammation that underlines these manifestations are induced and regulated by a large number of chemical mediators including eicosanoids, kinins, complement proteins, histamine, and monokines (Table 11).

Antiallergic activity

Allergic disorders such as rhinitis, sinusitis, atopic dermatitis, asthma, pollenosis, and food allergy are the most common cause of human disease. There are a number of pharmacological agents available for the treatment of allergic conditions such as asthma and allergy rhinitis, and we also focus antiallergic activity as an essential step to the development of effective antiallergic agent. Some species of *Ehretia* genus have compounds such as dimeric prenylbenzoquinones, nitrile glucosides, and rosmarinic acid show antiallergic effect.

Anti-bacterial activity All extracts of *E. laevis* leaves (methanol, chloroform, and aqueous solvent) have revealed excellent antibacterial activity. When compared to methanol, chloroform, and aqueous methanolic extract showed the high antibacterial activity on Gram-positive and Gram-negative bacteria, and aqueous extracts show the high antibacterial activity on Gram-negative than Gram-positive. Some other species also show positive respond against antibacterial activity (Table 13).

Antitubercular activity

In human being, tuberculosis is a contagious infectious disease primarily caused by *Mycobacterium tuberculosis*. There are regimens for treating tuberculosis, however they are not optimal. Development of efficient strategies for the treatment of human tuberculosis has posed a challenge, considering the increase in infections associated with the human immunodeficiency virus and immunocompromised patients. Phytoconstituents have been used in traditional treatment of many diseases; however, careful investigation of these constituents has not been undertaken with respect to treatments of tuberculosis. Two compounds ehretiolide and prenylhydroquinone have extracted from root of *Ehretia longiflora* are responsible for antitubercular activity (Table14).

Anti-snake venom activity

Snakebite is an important cause of morbidity and mortality and is one of the major health problems in India and other Asian countries. *Ehretia buxifolia* claimed to be useful in treating snake poison. The present study evaluated the potential antivenom effect *Ehretia* genus. A compound ehretianone has isolated from MeOH extract from *E. buxifolia* is responsible for anti-snake venom activity (Table 15).

Antiarthritic activity

Arthritis is an inflammatory disorder involving damage of joints. There are over a hundred different forms of arthritis, of which rheumatoid arthritis, osteoarthritis, and psoriatic arthritis are the most common. The treatment of any systemic disorder with allopathic drugs causes moderate-to-severe adverse effect that could cause death. Hence, alternative systems of medicine are being explored to treat diseases. *E. laevis* treatment supports antiarthritic activity. Of the three parts such as stem, leaf, and bark and fruit employed, the leaf extract was the most effective. This antiarthritic response may be due to the presence of active constituents such as hexadecanoic acid (palmitic acid), oleanenic acid, and other fixed oils

Antitrypanosomal and antiprotozoal activity

Sleeping sickness, leishmaniasis, Chagas disease, and malaria are infectious diseases caused by unicellular eukaryotic parasites “protozoans.” The available drugs for the treatment of trypanosomiasis and protozoans are old, expensive, and less efficient, linked to serious side effects, and dealing with the issue of medication resistance. This situation underlines the urgent need for the development of new safe, cheap, and effective drugs for the treatment of parasitic disease. The search for new antitrypanosomal and antiprotozoal agents in this study is based on ethnomedicine. *E. amoena* show weak antitrypanosomal potential with ethanol extract of leaves, bark, and root. *E. acuminata* show antiprotozoal activity with methanol extract of leaves (Table 17).

Antidiabetic activity

Diabetes mellitus, one of the fastest-growing health problems, is concerned about the use of antihyperglycemic drugs because of undesirable pathological conditions, for example, the adverse effect of metformin is gastrointestinal discomfort, pioglitazone with bladder cancer and heart failure, and sulfonylureas with hypoglycemia and weight gain. There are the ethnobotanical studies of medicinal plants used in the treatment of diabetes mellitus in many countries. A lot of genus have already reported for effective response of antidiabetic potential, but a few species of genus *Ehretia* are reported for antidiabetic activity yet. A species of *E. laevis* shows antidiabetic potential using multiwalled carbon nanotubes paste electrode in electrochemical measurement.

Cardiotonic activity

Carmona retusa (*E. microphylla*) has a high potential in fighting the growth and multiplication of cancer cells. However, there are no scientific data on the use of this plant on cardiotonic

activity. Hence, this study was carried out to evaluate the effect of aqueous extract of various aerial parts of *C. retusa* on isolated frog's heart. The activity of the aqueous extract was found to be effective.

Macroscopy of plant

This plant has an irregular trunk with a light grey or whitish bark. Leaves are variable in size and shape. They vary from 2 cm to 6.3 cm in length and 1.3 cm to 3.8 cm in width. Flowers are white in color. These blooms have a 2.5 mm long, three-lobed calyx and a 6 to 8 mm long, five-lobed corolla. The tube and lobes of corolla are longer than the calyx. Fruits also known as drupe. They are depressed and globes, generally 6 mm in diameter. As they mature, they turn orange-red (Fig1.abc) Macroscopy of leaf powder Fine powder of leaf having light green colour, astringent and bitter in taste with specific odour. (Table 1)

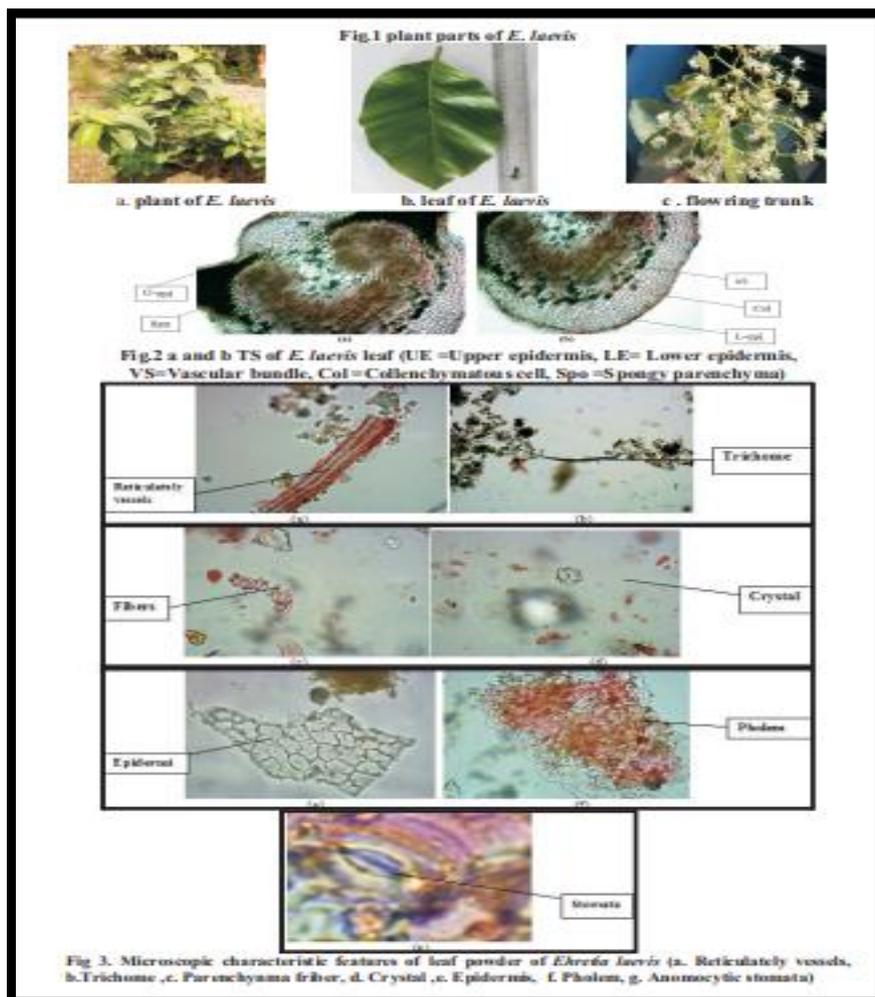
Microscopy

Transverse section of *Ehretia laevis* leaf

Leaf shows dorsiventral structure; the epidermis covered by thin cuticle present on both the surfaces; a single layer of palisade parenchyma underneath the upper epidermis occupying more than half the portion of the mesophyll tissue; spongy parenchyma 2-3 layers; Mid-rib consists of upper epidermis, single layer of parenchymatous hypodermis and collateral vascular bundle surrounded by 3-6 layers of collenchymatous cells; calcium oxalate rosette crystals present in mesophyll and collenchymatous cells; unicellular trichomes are present on both surface (Fig. 2).

Powder Study of the *E.laevis*

Powder of the herb is fine, greyish-green, slightly bitter and having indistinct odor. Under microscopic observation it shows presence of the reticulately thickened vessels (Fig.3a); unicellular uniseriate trichome (Fig.3b); parenchyma fiber, (Fig.3c); crystals of calcium oxalate (Fig.3d); epidermis (Fig.3e); phloem tissue (Fig.3f); and anomocytic.(Fig.3g) tomato. The analysis was carried out by using standard procedures [10]. It revealed the presence of Phenolic compounds, alkaloid and saponins etc (Table 2) (Fig.4) The observation and result of the present paper deals with the study of T.S. of leaf, Powder analysis and preliminary phytochemical investigation are as follows.



Uses

Ehretia laevis Roxb. Numerous compounds found in plants are beneficial for a variety of conditions, including wound healing, fractures, UTIs, aphrodisiacs, headaches, antihelminthics, diuretics, demulcents, expectorants, RTIs, fever, fungal infections, hepatoprotective, cytotoxic, insecticidal, anti-inflammatory, anti-apoptotic, anti-carcinogenic, weight gain, diabetes, muscle atrophy, immunity booster, lower serum lipid levels, neural crest cell survival, sedation, anti-Alzheimer, antinociceptive, thyroid uptake promotion,, anticoagulant, antiplatelet aggregatory, peptic ulcer, antiasthmatic, antiosteoporotic & antiosteopenic, anticataract & ophthalmic effect, decongestant, skin protective, nephroprotective, anti fatigue effect, protection of human sperm, protection of testicular tissue atopic dermatitis, anti-fatigue, neuroprotective, retinoprotective, lung tissue protection, heart protection, prevention of splenocyte apoptosis, alleviate stress and enhance sleep, hepatic encephalopathy, anti-secretory, larvicidal, antimalarial, antiretroviral, cosmetics product neurotransmitter, myelin sheath maintenance, gastric acid secretion & regulation,

metal ions chelator, anemia, psychiatric disorders, collagen formation, reduce the recurrence, severity, healing period of herpes simplex virus infections, calcium absorption, muscle protein, post surgery recovery, sports injuries, hormones, aging, used in psychotropic drugs.^[5]

Marketing Strategies: to effectively market the systematic review on *Ehretia Laevis*, consider the following strategies.

1. Targeted online Advertising

Utilize search engine marketing and social media advertising to reach scientists, researchers, and professionals in the field of botany or plant biology. Create targeted ads highlighting the key findings and potential applications of the study.

2. Email Marketing

Develop an email marketing campaign targeting botany departments, research institutions, and botanical gardens. Craft a compelling email subject line and provide a concise summary of the study's findings, emphasizing its relevance to their work or collections.

3. Collaborations with botanical associations

Partner with relevant botanical associations or societies specializing in plant biology or conservation. Offer to present the study findings at their conferences or webinars, or provide them with exclusive access to the full report. This collaboration can help increase exposure and credibility for the study.

4. Thought Leadership Content

Publish thought leadership articles or blog posts on reputable botanical websites or journals. These articles should discuss the study's findings, implications, and potential benefits for the field of botany. Include links to the full study or a landing page where interested readers can access more information.

5. Social Media Engagement

Establish a strong presence on platforms like Twitter, LinkedIn, or Facebook, targeting scientists, researchers, and botanical communities. Regularly share updates about the study, engage with followers by answering questions or participating in relevant discussions, and encourage sharing among peers.

6. Press Releases

Draft and distribute press releases to scientific news outlets and industry-specific publications. Highlight the key findings of the study, its potential impact on plant biology or conservation efforts, and any unique aspects that differentiate it from previous research. Include contact information for media inquiries or interviews.

7. Webinars or Online Presentations

Organize webinars or online presentations to share the study's findings with a wider audience. Invite scientists, researchers, and experts in the field to attend or speak at these events. Record the sessions and make them available for on-demand viewing to extend the reach and impact.

8. Collaborate with Influencers

Identify influential scientists or researchers within the field of botany who have a significant following on social media or other platforms. Reach out to them to discuss the study's findings and potential collaborations, such as guest blog posts, interviews, or social media shout-outs.

9. Academic Journals and Publications

Submit the systematic review to relevant academic journals or publications specializing in plant biology, conservation, or ecology. Ensure that the study adheres to their submission guidelines and highlight any unique aspects or contributions it makes to the existing literature.

10. Engage with Botanical Communities

Participate in online forums, discussion boards, or social media groups where scientists and researchers actively engage. Share insights from the study, answer questions, and engage in meaningful discussions to establish yourself as a trusted source of information.

Tailor your marketing strategies based on your target audience and their preferred communication channels. Monitoring and analyzing the effectiveness of each strategy will help refine your approach and maximize impact.

CONCLUSION

In conclusion, this systematic review has delved into the multifaceted dimensions of *Ehretia laevis*, shedding light on its diverse pharmacological properties, ecological significance, and

potential therapeutic applications. Through an exhaustive examination of the existing literature, we have synthesized a comprehensive overview of the various biological activities exhibited by this plant species, ranging from anti-inflammatory and antioxidant properties to its role in traditional medicine. The findings presented in this review underscore the importance of continued research on *Ehretia laevis*, as it holds promise as a valuable resource in drug development and environmental conservation efforts. The documented therapeutic potentials, coupled with its ecological adaptability, emphasize the need for further investigations to unlock its full potential. As we navigate the complex landscape of natural products and their applications, *Ehretia laevis* emerges as a compelling subject for future studies, offering a wealth of opportunities for both scientific exploration and practical applications.

REFERENCES

1. Gottschling M, Hilger HH. Characterisation of a novel fruit type found in *Ehretia* (*Ehretiaceae*, *Boraginales*). *Blumea*, 2004a; 49: 145-53.
2. Sahay SK. On the Pollen Morphology of *Ehretiaceae* with Reference to Taxonomy. *IV Int. Palynol. Conf*, 1979; 471-9.
3. Rabaey D, Lens F, Smets E, Jansen S. The phylogenetic significance of vestured pits in *Boraginaceae*. *Int Assoc Plant Taxonomy*, 2010; 59: 510-6.
4. Sultana A, Hussain MS, Rathore DK. Diversity of tree vegetation of Rajasthan, India. *Trop Ecol*, 2014; 55: 403-10.
5. Mandal G, Joshi SP. Analysis of vegetation dynamics and phytodiversity from three dry deciduous forests of Doon Valley, Western Himalaya, India. *J Asia Pac Biodivers*, 2014a; 7: 292-304.
6. Gottschling M, Hilger HH. The systematic position of *Ehretia cortesia* nom. nov. (- *Cortesia cuneifolia*: *Ehretiaceae*, *Boraginales*) inferred from molecular and morphological data. *Int Assoc Plant Taxonomy*, 2004b; 53: 919-23.
7. Hester AJ, Scogings PF, Trollope WS. Long-term impacts of goat browsing on bush-clump dynamics in a semi-arid subtropical savanna. *Plant Ecol*, 2006; 183: 277-90.
8. Miller JS. Classification of *Boraginaceae* subfam. *Ehretioideae*: Resurrection of the genus *Hilsenbergia* Tausch ex Meisn. *World*, 2003; 25: 151-89.
9. Forster PI. *Ehretia grahamii* (*Boraginaceae*): Notes on distribution, habitat, variation and conservation status. *Queensland Herbarium*, 1995; 4: 451-2.

10. Gottschling M, Hilger HH. First fossil record of transfer cells in angiosperms. *Am J Bot*, 2003; 90: 957-9.
11. Gurke M. Die Natürlichen Pflanzenfamilien. Vol. 4. Germany: W. Engelmann, Leipzig, 1893; 59-96.
12. Pimienta-Barrios E, Robles-Murguía C, Martínez-Chavez CC. Ecophysiological responses of native and exotic young trees to drought and rainfall. *Rev Fitotecnia Mex*, 2012; 35: 15-20.
13. Retief E, Van Wyk AE. The genus *Ehretia* (Boraginaceae: Ehretioideae) In Southern Africa. *Bothalia*, 2001; 31: 9-23.
14. Shu HK. *Ehretia P. browne*, *Civ. nat. Hist. Jamaica* 168. 1756. *Flora of China*, 1995; 16: 333-6.
15. Miller JS. A revision of the new world species of *Ehretia* (Boraginaceae). *Ann Mo Bot Gard*, 1989; 76: 1050-76.
16. Scott PE, Martin RF. Avian consumers of *Bursera*, *Ficus*, and *Ehretia* fruits in Yucatán. *Biotropica*, 1984; 16: 319-23.
17. Joshi R, Singh R. Feeding behaviour of wild Asian elephants (*elephas maximus*) in the Rajaji National Park. *J Am Sci.*, 2008; 4: 34-48.
18. Bakshi MP, Wadhwa M. Evaluation of forest tree leaves of semi-hilly arid region as livestock feed. *Asian Aust J Anim Sci.*, 2004; 17: 777-83.
19. Tefera S, Mlambo V, Dlamini BJ, Dlamini AM, Korlagama KD, Mould FL. Chemical composition and in vitro ruminal fermentation of common tree forages in the semi-arid rangelands of Swaziland. *Anim Feed Sci Technol*, 2008; 142: 99-110.
20. Bandyopadhyay S, Kr MS. Wild edible plant of Koch Bihar District, West Bengal. *Natl Prod Radiance*, 2009; 8: 64-72.
21. Mandal G, Joshi SP. Quantitative vegetation dynamics and invasion success of *lantana camara* from the tropical forests of doon valley. *Int J Conserv Sci.*, 2014b; 5: 511-26.
22. Rao BH, Rao PSP. Embryology of three species of *Ehretia*. *Proc Indian Acad Sci (Plant Sci.)*, 1984; 93: 57-65.
23. Li L, Li MH, Xu LJ, Guo N, Wu-Lan T, Shi R, et al. Distribution of seven polyphenols in several medicinal plants of Boraginaceae in China. *J Med Plants Res*, 2010; 4: 1216-21.
24. Jeruto P, Mutai C, C. L, O. G. Phytochemical constituents of some medicinal plants. *JAnim Plant Sci.*, 2011; 9: 1201-10.

25. Thakre Rushikesh, et al unexplored wound healing property of *Ehretia laevis* roxb. (khandu chakka) plant Int. J. Res. Ayurveda Pharm., Sep/Oct 2016; 7(Supply 4).
26. Thakre Rushikesh, et al ethano botanical properties of unexplored plant khandu chakka (*Ehretia laevis* roxb.) international journal of ayurveda and pharma research, 2016; 4(7): 68-73.
27. Wachtel-Galor S, Benzie IFF. Herbal Medicine: An Introduction to Its History, Usage, Regulation, Current Trends, and Research Needs. In: Benzie IFF, WachtelGalor S, editors. Herbal Medicine: Biomolecular and Clinical Aspects. 2nd edition. Boca Raton (FL): CRC Press/Taylor & Francis, 2011.
28. WHO Traditional medicine. World Health Organization, 2008. (Accessed on 11 September 2015).
29. Mori Hardhikumar. Jamanadas-Anti hyperlipidemic Activity of Kukkutnakhi (*Aspidum acutarium* SW - Dryopteridace). A folklore Herb. D-G, IPGT & RA, Jamnagar, Gujarat, 2014; 1.
30. Guidelines for the assessment of herbal medicine program on traditional medicine Geneva World Health Organization, document (WHO/TRM/91, 4), 1991.
31. Md. Mahabub Nawaz AH et al. An ethnobotanical survey of Rajshahi district in Rajshahi division, Bangladesh, Am. Eurasian J Sustain. Agric, 2009; 3(2): 143-150.
32. Joshi SG. Biotechnological strategies for the conservation of medicinal and ornamental Medicinal Plants, Oxford and IBH Publishing Co. Pvt. Ltd. New Delhi, 2000; 102.
33. Thakre R, Harne K. Comparative Antimicrobial Study of Polar and Non-Polar Extracts of *Ehretia laevis* Roxb. (Khandu Chakka) Plant. Aayushi International Interdisciplinary Research Journal (AIIRJ), 2019; 10(6): 7-9.
34. Shukla A, Kaur A. A systematic review of traditional uses bioactive phytoconstituents of genus *Ehretia*. Asian Journal of Pcal and Clinical Research, 2018; 11(6): 88-100.
35. Rushikesh Thakre et al. Role of Ajan Vruksha/Khandu Chakka Plant (*Ehretia laevis* Roxb.) in Covid-19 Pandemic Int. J Res. Pharm. Sci., 2020; 11(SPL)(1): 224- 233.
36. Rushikesh T, Bhutada S, Chouragade B, Khobragade P, Ketaki H. Evaluating the systematic position of *Ehretia asperula* Zoll. & Moritzi based on ITS1, matK and trnL-trnF DNA sequences. International Journal of Research in Ayurveda and Pharmacy, 2012; 36(2): 93– 102.
37. Rushikesh T, Bhutada S, Chouragade B, Khobragde P, Ketaki H. Ethano Botanical Properties of Unexplored Plant Khandu Chakka (*Ehretia laevis* Roxb.). International Journal of Ayurveda and Pharma Research, 2016; 4(7): 68–73.

38. Sivasankari V, Revathi P, Parimelazhagan T. Evaluation of In Vitro Antioxidant Activity in Edible Fruits of *Ehretia laevis* Roxb. *Int J Pharm Bio Sci.*, 2013; 4: 847-57.
39. Ahmad UV, Abbasi MA, Hussain H, Akhtar MN, Farooq U, Fatima N et al. Phenolic glycosides from *Symplocos racemosa*: natural inhibitors of phosphodiesterase –I. *Phytochemistry*, 2003; 63(2): 217- 220.
40. Goodarzi M, Russel PJ, Heyden YV. Similarity analyses of chromatographic herbal fingerprints: A review. *Analytical Chemical Acta*, 2013; 804: 16-28.
41. Tarke Santosh Rangnathrao, Dr. P Shanmugasundaram. Preliminary phytochemical screening and HPTLC method for qualitative determination of phytochemical compounds in extract of *Ehretia laevis* Roxb *Journal of Pharmacognosy and Phytochemistry*, 2018; 7(6): 867- 874.
42. Torane, R.C.; Ruikar, A.D.; Chandrachood, P.S.; Deshpande, N.R. Study of amino acids and carbohydrates from the leaves of *Ehretia Laevis*. *Asian J. Chem*, 2009; 21: 1636–1638.
43. Li, L.; Yong, P.; Xia, Y.; Li-Jia, X.; Ta-Na, W.; Yong, L.; Ren-Bing, S.; Pei-Gen, X. Chemical constituents and biological activities of plants from the genus *Ehretia* Linn. *Chin. Herb. Med.*, 2010; 2: 106–111.
44. Velappan, S.; Thangaraj, P. Phytochemical constituents and antiarthritic activity of *Ehretia laevis* Roxb. *J. Food Biochem*, 2014; 38: 433–443. [CrossRef]
45. Joshi, U.P.; Wagh, R.D. GC-MS analysis of phytochemical compounds present in the bark extracts of *Ehretia laevis* Roxb. *Int. J. Res. Dev. Pharm. Life Sci.*, 2018; 7: 3150–3154. [CrossRef]
46. Torane, R.C.; Kamble, G.S.; Chandrachood, P.S.; Deshpande, N.R. Preliminary phytochemical screening and nutritional analysis of leaves of *Ehretia laevis*. *J. Pharm. Res.*, 2010; 3: 1384–1385.
47. Dan, S.; Dan, S.S. Triterpenoids of the bark of *Ehretia laevis*. *Fitoterapia*, 1982; 53: 51–52.
48. Thapliyal, P.C.; Yadav, S.K. A new naphthoquinone from aerial parts of *Ehretia laevis*. *J. Inst. Chem*, 2003; 75: 13–15.
49. Ali, M. *Textbook of Pharmacognosy*, 2nd ed.; CBS Publishers: Daryaganj, New Delhi, India, 2007; 490–504.
50. Torane, R.C.; Kamble, G.S.; Kale, A.A.; Gadkari, T.V.; Deshpande, N.R. Quantification of dioctyl phthalate from *Ehretia laevis* Roxb by HPTLC. *J. Chem. Pharm. Res.*, 2011; 3: 48–51.

51. Joshi, U.P.; Wagh, R.D. GC-MS analysis of phytochemical compounds present in the bark extracts of *Ehretia laevis* Roxb. *Int. J. Res. Dev. Pharm. Life Sci.*, 2018; 7: 3150–3154. [CrossRef]
52. Dan, S.; Dan, S.S. Triterpenoids of the bark of *Ehretia laevis*. *Fitoterapia*, 1982; 53: 51–52.
53. Bringmann, G.; Saeb, W.; Assi, L.A.; Francois, G.; Narayanan, A.S.S.; Peters, K.; Peters, E.M. Betulinic acid: Isolation from *Triphyophyllum peltatum* and *Ancistrocladus heyneanus*, antimalarial activity, and crystal structure of the benzyl ester. *Planta Med.*, 1997; 63: 255–257. [CrossRef]
54. Huguet, A.I.; Recio, M.D.C.; Manez, S.; Giner, R.M.; Rios, J.L. Effect of triterpenoids on the inflammation induced by protein kinase C activators, neuronally acting irritants and other agents. *Eur. J. Pharmacol*, 2000; 410: 69–81. [CrossRef]
55. Kinoshita, K.; Akiba, M.; Saitoh, M.; Ye, Y.; Koyama, K.; Takahashi, K.; Kondo, N.; Yuasa, H. Antinociceptive effect of triterpenes from *Cacti*. *Pharm. Biol.*, 1998; 36: 50–57. [CrossRef]
56. Chandramu, C.; Manohar, R.D.; Krupadanam, D.G.; Dashavantha, R.V. Isolation, characterization and biological activity of betulinic acid and ursolic acid from *Vitex negundo* L. *Phytother. Res.*, 2003; 17: 129–134. [CrossRef] [PubMed]
57. Fulda, S.; Debatin, K.M. Betulinic acid induces apoptosis through a direct effect on mitochondria in neuroectodermal tumors. *Med. Pediatr. Oncol*, 2000; 35: 616–618. [CrossRef]
58. Zuco, V.; Supino, R.; Righetti, S.C.; Cleris, L.; Marchesi, E.; Gambacorti-Passerini, C.; Formelli, F. Selective cytotoxicity of betulinic acid on tumor cell lines, but not on normal cells. *Cancer Lett.*, 2002; 175: 17–25. [CrossRef]
59. Zhao, J.; Li, R.; Pawlak, A.; Henklewska, M.; Sysak, A.; Wen, L.; Yi, J.; Obminska-Mrukowicz, B. Antitumor activity of betulinic acid and betulin in canine cancer cell lines. *In Vivo*, 2018; 32: 1081–1088. [CrossRef]
60. Krasutsky, P.A. Birch bark research and development. *Nat. Prod. Rep.*, 2006; 23: 919–942. [CrossRef] [PubMed]
61. Krol, S.K.; Kielbus, M.; Rivero-Müller, A.; Stepulak, A. Comprehensive review on betulin as a potent anticancer agent. *Natural bioactive in cancer treatment and prevention. BioMed Res. Int.*, 2015; 2015: 584189. [CrossRef] [PubMed]

62. Pavlova, N.I.; Savinova, O.V.; Nikolaeva, S.N.; Boreko, E.I.; Flekhter, O.B. Antiviral activity of betulin, betulinic and betulonic acids against some enveloped and non-enveloped viruses. *Fitoterapia*, 2003; 74: 489–492. [CrossRef]
63. Bernard, P.; Scior, T.; Didier, B.; Hibert, M.; Berthon, J. Ethnopharmacology and bioinformatic combination for lead discovery: Application to phospholipase A2 inhibitors. *Phytochemistry*, 2001; 58: 865–874. [CrossRef]
64. Simone, F. Betulinic acid for cancer treatment and prevention. *Int. J. Mol. Sci.*, 2008; 9: 1096–1107.
65. Dzubak, P.; Hajduch, M.; Vydra, D.; Hustova, A.; Kvasnica, M.; Biedermann, D.; Ova, L.M.; Urban, M.; Sarek, J. Pharmacological activities of natural triterpenoids and their therapeutic implications. *Nat. Prod. Res.*, 2006; 23: 394–411.
66. Geetha, T.; Varalakshmi, P. Anti-inflammatory activity of lupeol and lupeol linoleate in rats. *J. Ethnopharmacol*, 2001; 76: 77–80. [CrossRef]
67. Tsai, F.S.; Lin, L.W.; Wu, C.R. Lupeol and its role in chronic diseases. *Adv. Exp. Med. Biol.*, 2016; 929: 145–175.
68. Fernandez, M.A.; de las Heras, B.; Garcia, M.D.; Saenz, M.T.; Villar, A. New insights into the mechanism of action of the anti-inflammatory triterpene lupeol. *J. Pharm. Pharmacol*, 2001; 53: 1533–1539. [CrossRef]
69. Sudhahar, V.; Kumar, S.A.; Sudharsanm, P.T.; Varalakshmi, P. Protective effect of Lupeol and its ester on cardiac abnormalities in experimental hypercholesterolemia. *Vascul. Pharmacol*, 2007; 46: 412–418. [CrossRef]
70. Alam, P.; Al-Yousef, H.M.; Siddiqui, N.A.; Alhowiriny, T.A.; Alqasoumi, S.I.; Amina, M.; Hassan, W.H.B.; Abdelaziz, S.; Abdalla, R.H. Anticancer activity and concurrent analysis of ursolic acid, β -sitosterol and lupeol in three different species of Hibiscus species by validated HPTLC method. *Saudi Pharm. J.*, 2018; 26: 1060–1067. [CrossRef]
71. Bag, P.; Chattopadhyay, D.; Mukherjee, H.; Ojha, D.; Mandal, N.; Sarkar, M.C.; Chatterjee, T.; Das, G.; Chakraborti, S. Anti-herpes virus activities of bioactive fraction and isolated pure constituents of *Mallotus peltatus* an ethnomedicine from Andaman Islands. *Viol. J.*, 2012; 9: 98–109. [CrossRef]
72. Gupta, M.B.; Nath, R.; Gupta, G.P.; Bhargava, K.P. Antiulcer activity of some plant triterpenoids. *Indian J. Med. Res.*, 1981; 73: 649–652. [PubMed]
73. Hirota, M.; Mori, T.; Yoshida, M.; Iriye, R. Antitumor-promoting and anti-inflammatory activities of triterpenoids and sterols from plants and fungi. *Agric. Biol. Chem*, 1990; 54: 1073–1075.

74. Aragao, G.F.; Carneiro, L.M.V.; Junior, A.P.F.; Vieira, L.C.; Bandeira, P.N.; Lemos, T.L.G.; Viana, G.S. A possible mechanism for anxiolytic and antidepressant effects of alpha- and beta-amyrin from *Protium heptaphyllum* (Aubl.). *Pharmacol. Biochem. Behav.*, 2006; 85: 827–834. [CrossRef] [PubMed]
75. Johann, S.; Soldi, C.; Lyon, J.P.; Pizzolath, M.G.; Resende, M.A. Antifungal activity of the amyrin derivatives and in vitro inhibition of *Candida albicans* adhesion to human epithelial cells. *Lett. Appl. Microbiol.*, 2007; 45: 148–153. [CrossRef]
76. Okoye, N.N.; Ajaghaku, D.L.; Okeke, H.N.; Ilodigwe, E.E.; Nworu, C.S.; Okoye, F.B.C. β -amyrin and α -amyrin acetate isolated from the stem bark of *Alstonia boonei* display profound anti-inflammatory activity. *Pharm. Biol.*, 2014; 52: 1478–1486. [CrossRef] [PubMed]
77. Santos, F.A.; Frota, J.T.; Arruda, B.R.; de Melo, T.S.; da Silva, A.A.; de Castro Brito, G.A.; Chaves, M.H.; Rao, V.S. Antihyperglycemic and hypolipidemic effects of α , β -amyrin, a triterpenoid mixture from *Protium heptaphyllum* in mice. *Lipids Health Dis.*, 2012; 11: 98–106. [CrossRef] [PubMed]
78. Kathryn, A.B.; da Silva, S.; Paszcuk, A.F.; Passos, G.F.; Silva, S.E.; Bento, A.F.; Meotti, F.C.; Calixto, J.B. Activation of cannabinoid receptors by the pentacyclic triterpene α , β -amyrin inhibits inflammatory and neuropathic persistent pain in mice. *Pain*, 2011; 152: 1872–1887.
79. Melo, C.M.; Carvalho, K.M.M.B.; Neves, J.C.S.; Morais, T.C.; Rao, V.S.; Santos, F.A.; Brito, G.A.B.; Chaves, M.H. α , β -amyrin, a natural triterpenoid ameliorates L-arginine induced acute pancreatitis in rats. *World J. Gastroenterol.*, 2010; 16: 4272–4280. [CrossRef] [PubMed]
80. Batovska, D.I.; Todorova, I.T.; Nedelcheva, D.V.; Parushev, S.P.; Atanassov, A.J.; Hvarleva, T.D.; Djakova, G.J.; Bankova, V.S. Preliminary study on biomarkers for the fungal resistance in *Vitis vinifera* leaves. *J. Plant. Physiol.*, 2008; 165: 791–795. [CrossRef] [PubMed]
81. Jabeen, K.; Javaid, A.; Ahmad, E.; Athar, M. Antifungal compounds from *Melia azederach* leaves for management of *Ascochyta rabiei*, the cause of chickpea blight. *Nat. Prod. Res.*, 2011; 25: 264–276. [CrossRef] [PubMed]
82. Vitor, C.E.; Figueiredo, C.P.; Hara, D.B.; Bento, A.F.; Mazzuco, T.L.; Calixto, J.B. Therapeutic action and underlying mechanisms of a combination of two pentacyclic triterpenes alpha- and beta-amyrin, in a mouse model of colitis. *Br. J. Pharmacol.*, 2009; 157: 1034–1044. [CrossRef] [PubMed]

83. Awad, A.B.; Roy, R.; Fink, C.S. β -sitosterol, a plant sterol, induces apoptosis and activates key caspases in MDA-MB-231 human breast cancer cells. *Oncol. Rep.*, 2003; 10: 497–500. [CrossRef]
84. Kumar, D.; Nepali, K.; Bedi, P.M.S.; Kumar, S.; Malik, F.; Jain, S. 4,6-diaryl Pyrimidones as Constrained Chalcone Analogues: Design, Synthesis and Evaluation as Antiproliferative Agents. *Anticancer Agents Med. Chem.*, 2015; 15: 793–803. [CrossRef]
85. Kumar, D.; Singh, O.; Nepali, K.; Bedi, P.M.S.; Qayum, A.; Singh, S.; Jain, S.K. Naphthoflavones as anti-proliferative agents: Design, synthesis and biological evaluation. *Anticancer Agents Med. Chem.*, 2016; 16: 881–890. [CrossRef]
86. Thakre, R.; Bhutada, S.; Chouragade, B.; Khobragde, P.; Harne, K. Ethnobotanical properties of unexplored plant Khandu chakka (*Ehretia laevis* Roxb.). *Int. J. Ayurveda Pharma. Res.*, 2016; 4: 68–73.
87. Shukla, A.; Kaur, A. A systematic review of traditional uses bioactive phytoconstituents of genus *Ehretia*. *Asian J. Pharm. Clin. Res.*, 2018; 11: 88–100. [CrossRef]
88. Kumar, D.; Sharma, P.; Nepali, K.; Mahajan, G.; Mintoo, M.J.; Singh, A.; Singh, G.D.; Mondhe, D.M.; Singh, G.; Jain, S.K.; et al. Antitumour, acute toxicity and molecular modelling studies of 4-(pyridine-4-yl)-6-(thiophen-2-yl)pyrimidin-2(1H)-one against Ehrlich ascites Carcinoma and sarcoma-180. *Heliyon*, 2018; 4: 61. [CrossRef]
89. Kumar, D.; Malik, F.; Bedi, P.M.S.; Jain, S. 2,4-Diarylpyrano[3,2-c]chromen-5(4H)-ones as Antiproliferative Agents: Design, Synthesis and Biological Evaluation. *Chem. Pharm. Bull.*, 2016; 64: 399–409. [CrossRef]
90. Kumar, D.; Jain, S.K. A Comprehensive Review of N-Heterocycles as Cytotoxic Agents. *Curr. Med. Chem.*, 2016; 23: 4338–4394. [CrossRef]
91. Sharma, P.; Sharma, R.; Rao, H.S.; Kumar, D. Phytochemistry and Medicinal Attributes of *A. Scholaris*: A Review. *Int. J. Pharm. Sci. Res.*, 2015; 6: 505–513.
92. Kumar, D.; Sharma, P.; Singh, H.; Nepali, K.; Gupta, G.K.; Jain, S.K.; Ntie-Kang, F. The value of pyrans as anticancer scaffolds in medicinal chemistry. *RSC Adv.*, 2017; 7: 36977–36999. [CrossRef]
93. Kaur, T.; Sharma, P.; Gupta, G.; Ntie-Kang, F.; Kumar, D. Treatment of Tuberculosis by Natural Drugs: A Review. *Plant. Arch.*, 2019; 19: 2168–2176.
94. Kumar, D.; Singh, G.; Sharma, P.; Qayum, A.; Mahajan, G.; Mintoo, M.J.; Singh, S.K.; Mondhe, D.M.; Bedi, P.M.S.; Jain, S.K.; et al. 4-aryl/heteroaryl-4H-fused pyrans as Anti-proliferative Agents: Design, Synthesis and Biological Evaluation. *Anticancer Agents Med. Chem.*, 2018; 18: 57–73. [CrossRef] [PubMed]

95. Bekono, B.D.; Ntie-Kang, F.; Onguene, P.A.; Lifongo, L.L.; Sippl, W.; Fester, K.; Owono, L.C.O. The potential of antimalarial compounds derived from African medicinal plants: A review of pharmacological evaluations from 2013 to 2019. *Malar. J.*, 2020; 9: 1–35. 84.
96. Zhishen, J.; Cheng, T; Joshi, U.P.; Wagh, R.D. GC-MS analysis of phytochemical compounds present in the bark extracts of *Ehretia laevis* Roxb. *Int. J. Res. Dev. Pharm. Life Sci.*, 2018; 7: 3150–3154. [CrossRef]
97. Rangnathrao, T.S.; Shanmugasundar, P. Preliminary phytochemical screening and HPTLC method for qualitative determination of phytochemical compounds in extract of *Ehretia laevis* Roxb. *J. Pharmacogn. Phytochem*, 2018; 7: 867–874.
98. Zhishen, J.; Cheng, T.; Jianming, W. The determination of flavonoid contents on mulberry and their scavenging effects on superoxide radical. *Food Chem*, 1999; 64: 555–559. [CrossRef]
99. Velappan, S.; Thangaraj, P. Phytochemical constituents and antiarthritic activity of *Ehretia laevis* Roxb. *J. Food Biochem*, 2014; 38: 433–443. [CrossRef]
100. 100. Joshi, S.G. *Medicinal Plants*; Oxford and IBH Publishing Co. Private Ltd.: New Delhi, India, 2000; 102.
101. Hakkinen, S.H.; Karenlampi, S.O.; Heinonen, I.M.; Mykkanen, H.M.; Torronen, A.R. Content of the flavonols quercetin, myricetin, and kaempferol in 25 edible berries. *J. Agric. Food Chem*, 1999; 47: 2274–2279. [CrossRef]
102. Stewart, A.J.; Bozonnet, S.; Mullen, W.; Jenkins, G.I.; Lean, M.E.; Crozier, A. Occurrence of flavonols in tomatoes and tomato-based products. *J. Agric. Food Chem*, 2000; 48: 2663–2669. [CrossRef] [PubMed]
103. Ferry, D.R.; Smith, A.; Malkhandi, J. Phase I clinical trial of the flavonoid quercetin: Pharmacokinetics and evidence for in vivo tyrosine kinase inhibition. *Clin. Cancer Res.*, 1996; 2: 659–668.
104. Davis, W.L.; Matthew, S.B. Antioxidants and cancer III: Quercetin. *Altern. Med. Rev.*, 2000; 5: 196–208.
105. Zerín, T.; Kim, Y.S.; Hong, S.Y.; Song, H.Y. Quercetin reduces oxidative damage induced by paraquat via modulating expression of antioxidant genes in A549 cells. *J. Appl. Toxicol*, 2013; 33: 1460–1467. [CrossRef]
106. Lesjak, M.; Beara, I.; Simin, N.; Pintac, D.; Majkic, T.; Bekvalac, K.; Orcic, D.; Mimica-Dukic, N. Antioxidant and anti-inflammatory activities of quercetin and its derivatives. *J. Funct. Foods*, 2018; 40: 68–75. [CrossRef]

107. Boots, A.W.; Haenen, G.; Bast, A. A health effect of quercetin: From antioxidant to nutraceutical. *Eur. J. Pharmacol*, 2008; 585: 325–337. [CrossRef] [PubMed]
108. Xu, D.; Hu, M.J.; Wang, Y.Q.; Cui, Y.L. Antioxidant activities of quercetin and its complexes for medicinal application. *Molecules*, 2019; 24: 1123. [CrossRef]
109. Jain, A.K.; Thanki, K.; Jain, S. Co-encapsulation of tamoxifen and quercetin in polymeric nanoparticles: Implications on oral bioavailability, antitumor efficacy, and drug induced toxicity. *Mol. Pharm*, 2013; 10: 3459–3474. [CrossRef]
110. Miean, K.H.; Mohamed, S. Flavonoid (myricetin, quercetin, kaempferol, luteolin and apigenin) content of edible tropical plants. *J. Agric. Food Chem*, 2001; 49: 3106–3112. [CrossRef] [PubMed]
111. Somers, S.M.; Johannot, L. Dietary flavonoid source in Australian adults. *Nutr. Cancer*, 2008; 60: 442–449. [CrossRef] [PubMed]
112. Chen, A.Y.; Chen, Y.C. A review of dietary flavonoid, Kaempferol on human health and cancer prevention. *Food Chem*, 2013; 138: 2099–2107. [CrossRef]
113. Suchal, K.; Malik, S.; Khan, S.I.; Malhotra, R.K.; Goyal, S.N.; Bhatia, J.; Ojha, S.; Arya, D.S. Molecular pathways involved in the amelioration of myocardial injury in diabetic rats by kaempferol. *Int. J. Mol. Sci.*, 2017; 18: 1001. [CrossRef] [PubMed]
114. Zhao, J.; Zhang, S.; You, S.; Liu, T.; Xu, F.; Ji, T.; Gu, Z. Hepatoprotective effects of nicotiflorin from *Nymphaea candida* against concanavalin α -induced and D-galactosamine-induced liver injury in mice. *Int. J. Mol. Sci.*, 2017; 18: 587. [CrossRef] [PubMed]
115. Nascimento, A.M.; Maria-Ferreira, D.; Lin, F.T.D.; Kimura, A.; de Santana-Filho, A.P.; de P. Werner, M.F.; Iacomini, M.; Sasaki, G.L.; Cipriani, T.R.; de Souza, L.M. Phytochemical analysis and anti-inflammatory evaluation of compounds from an aqueous extract of *Croton cajucara* benth. *J. Pharm. Biomed. Anal*, 2017; 145: 821–830. [CrossRef] [PubMed].
116. Arif, H.; Sohail, A.; Farhan, M.; Rehman, A.A.; Ahmad, A.; Hadi, S.M. Flavonoids induced redox cycling of copper ions leads to generation of reactive oxygen species: A potential role in cancer chemoprevention. *Int. J. Biol. Macromol*, 2018; 106: 569–578. [CrossRef]
117. Wang, L.; Tu, Y.C.; Lian, T.W.; Hung, J.T.; Yen, J.H.; Wu, M.J. Distinctive antioxidant and anti-inflammatory effects of flavonols. *J. Agric. Food Chem*, 2006; 54: 9798–9804. [CrossRef]

118. Wu, Y.; Sun, J.; George, J.; Ye, H.; Cui, Z.; Li, Z. Study of neuroprotective function of Ginkgo biloba extract derived-flavonoid monomers using a three-dimensional stem cell-derived neural model. *Biotechnol. Prog.*, 2016; 32: 735–744. [CrossRef]
119. Li, F.; Zhang, B.; Chen, G.; Fu, X. The novel contributors of antidiabetic potential in mulberry polyphenols revealed by UHPLCHR-ESI-TOF-MS/MS. *Food Res. Int.*, 2017; 100: 873–884. [CrossRef]
120. Calderon-Montano, J.M.; Burgos-Moron, E.; Perez-Guerrero, C.; Lopez-Lazaro, M. A review on the dietary flavonoid kaempferol. *Mini Rev. Med. Chem.*, 2011; 11: 298. [CrossRef] [PubMed]
121. Pei, J.; Chen, A.; Zhao, L.; Cao, F.; Ding, G.; Xiao, W. One pot synthesis of hyperoside by a three-enzyme cascade using a UDP galactose regeneration system. *J. Agric. Food Chem.*, 2017; 65: 6042–6048. [CrossRef]
122. Tang, X.L.; Liu, J.X.; Dong, W.; Li, P.; Li, L.; Hou, J.C.; Zheng, Y.Q.; Lin, C.R.; Ren, J.G. Protective effect of kaempferol on LPS plus ATP induced inflammatory response in cardiac fibroblasts. *Inflammation*, 2015; 38: 94–101. [CrossRef]
123. Harborne, J.B.; Williams, C.A. Advances in flavonoid research since 1992. *Phytochemistry*, 2000; 55: 481–504. [CrossRef]
124. Batra, P.; Sharma, A.K. Anticancer potential of flavonoids: Recent trends and future perspectives. *3 Biotech*, 2013; 3: 439–459. [CrossRef]
125. Knekt, P.; Jarvinen, R.; Seppanen, R.; Hellevar, M.; Teppo, L.; Pukkala, E.; Aromaa, A. Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. *Am. J. Epidemiol.*, 1997; 146: 223–230. [CrossRef]
126. Birt, D.F.; Hendrich, S.; Wang, W. Dietary agents in cancer prevention: Flavonoids and isoflavonoids. *Pharmacol. Ther.*, 2001; 90: 157–177. [CrossRef]
127. Neuhouser, M.L. Dietary flavonoids and cancer risk: Evidence from human population studies. *Nutr. Cancer*, 2004; 50: 1–7. [CrossRef] [PubMed]
128. Yang, S.F.; Yang, W.E.; Chang, H.R.; Chu, S.C.; Hsieh, Y.S. Luteolin induces apoptosis in oral squamous cancer cells. *J. Dent. Res.*, 2008; 87: 401–406. [CrossRef]
129. Ju, W.; Wang, X.; Shi, H.; Chen, W.; Belinsky, S.A.; Lin, Y. A critical role of luteolin induced reactive oxygen species in blockage of tumor necrosis factor activated nuclear factor kappa B pathway and sensitization of apoptosis in lung cancer cells. *Mol. Pharmacol.*, 2007; 71: 1381–1388. [CrossRef] [PubMed]

130. Zhang, Q.; Zhao, X.H.; Wang, Z.J. Flavones and flavonols exert cytotoxic effects on a human oesophageal adenocarcinoma cell line (OE33) by causing G2/M arrest and inducing apoptosis. *Food Chem. Toxicol.*, 2008; 46: 2042–2053. [CrossRef]
131. Chiu, F.L.; Lin, J.K. Down regulation of androgen receptor expression by luteolin causes inhibition of cell proliferation and induction of apoptosis in human prostate cancer cells and xenografts. *Prostate*, 2008; 68: 61–71. [CrossRef]
132. Lin, Y.; Shi, R.; Wang, X.; Shen, H.M. Luteolin, a flavonoid with potentials for cancer prevention and therapy. *Curr. Cancer Drug Targets*, 2008; 8: 634–646. [CrossRef]
133. Harborne, J.B.; Baxter, H. *The Handbook of Natural Flavonoids*; John Wiley and Sons: Chichester, UK, 1999; 1: 12.
134. Hostetler, G.L.; Ralston, R.A.; Schwartz, S.J. Flavones: Food sources, bioavailability, metabolism, and bioactivity. *Adv. Nutr.*, 2017; 8: 423–435. [CrossRef]
135. Falcone-Ferreira, M.L.; Rius, S.P.; Casati, P. Flavonoids: Biosynthesis, biological functions, and biotechnological applications. *Front. Plant. Sci.*, 2012; 3: 222. [CrossRef]
136. Kabera, J.N.; Semana, E.; Mussa, A.R.; He, X. Plant secondary metabolites: Biosynthesis, classification, function and pharmacological properties. *J. Pharm. Pharmacol.*, 2014; 2: 377–392.
137. Seo, H.S.; Ku, J.M.; Choi, H.S.; Woo, J.K.; Jang, B.H.; Shin, Y.C.; Ko, S.G. Induction of caspase-dependent apoptosis by apigenin by inhibiting STAT3 signalling in HER2-overexpressing MDA-MB-453 breast cancer cells. *Anticancer Res.*, 2014; 34: 2869–2882.
138. Salehi, B.; Venditti, A.; Sharifi-Rad, M.; Kregiel, D.; Sharifi-Rad, J.; Durazzo, A.; Lucarini, M.; Santini, A.; Souto, E.B.; Novellino, E.; et al. The therapeutic potential of apigenin. *Int. J. Mol. Sci.*, 2019; 20: 1305. [CrossRef] [PubMed]
139. Li, R.; Zhao, D.; Qu, R.; Fu, Q.; Ma, S. The effects of apigenin on lipopolysaccharide induced depressive like behavior in mice. *Neurosci. Lett.*, 2015; 594: 17–22. [CrossRef] [PubMed]
140. Pamunuwa, G.; Karunaratne, D.N.; Waisundara, V.Y. Antidiabetic properties, bioactive constituents, and other therapeutic effects of *Scoparia dulcis*. *Evid. Based Complement. Alternat. Med.*, 2016; 16: 824–830.
141. Tang, R.; Chen, K.; Cosentino, M.; Lee, K.H. Apigenin-7-O- β -D-glucopyranoside, an anti-HIV principle from *Kummerowia Striata*. *Bioorg. Med. Chem. Lett.*, 1994; 4: 455–458. [CrossRef]

142. Ali, F.; Naz, F.; Jyoti, S.; Siddique, Y.H. Health functionality of apigenin: A review. *Int. J. Food Prop.*, 2017; 20: 1197–1238. [CrossRef]
143. Kaur, R.; Sharma, P.; Gupta, G.K.; Ntie-Kang, F.; Kumar, D. Structure activity relationship and mechanistic insights for anti-HIV natural products. *Molecules*, 2020; 25: 2070. [CrossRef] [PubMed]
144. Erlund, I. Review of the flavonoids quercetin, hesperetin, and naringenin: Dietary sources, bioactivities, bioavailability, and epidemiology. *Nutr. Res.*, 2004; 24: 851–874. [CrossRef]
145. Rani, N.; Bharti, S.; Krishnamurthy, B.; Bhatia, J.; Sharma, C.; Kamal, M.A.; Ojha, S.; Arya, D.S. Pharmacological properties and therapeutic potential of naringenin: A citrus flavonoid of pharmaceutical promise. *Curr. Pharm. Des.*, 2016; 22: 1–19. [CrossRef]
146. Jadeja, R.N.; Devkar, R.V. Polyphenols and flavonoids in controlling non-alcoholic steatohepatitis. In *Polyphenols in Human Health and Disease*; Academic Press: San Diego, CA, USA, 2014; 1: 615–623.
147. Mbaveng, A.T.; Zhao, Q.; Kuete, V. Harmful and protective effects of phenolic compounds from African medicinal plants. In *Toxicological Survey of African Medicinal Plants*, 1st ed.; Kuete, V., Ed.; Elsevier: New York, NY, USA, 2014; 1: 20: 577–609.
148. Pinho-Ribeiro, F.A.; Zarpelon, A.C.; Fattori, V.; Manchope, M.F.; Mizokami, S.S.; Casagrande, R.; Verri, W.A. Naringenin reduces inflammatory pain in mice. *Neuropharmacology*, 2016; 105: 508–519. [CrossRef] [PubMed]
149. Zobeiri, M.; Belwal, T.; Parvizi, F.; Naseri, R.; Farzaei, M.H.; Nabavi, S.F.; Sureda, A.; Nabavi, S.M. Naringenin and its nanoformulations for fatty liver: Cellular modes of action and clinical perspective. *Curr. Pharm. Biotechnol*, 2018; 19: 196–205. [CrossRef] [PubMed]
150. Salehi, B.; Fokou, P.V.T.; Sharifi-Rad, M.; Zucca, P.; Pezzani, R.; Martins, N.; Sharifi-Rad, J. The therapeutic potential of naringenin: A review of clinical trials. *Pharmaceuticals*, 2019; 12: 11. [CrossRef]
151. Wang, N.; Li, D.; Lu, N.H.; Yi, L.; Huang, X.W.; Gao, Z.H. Peroxynitrite and haemoglobin mediated nitrative/oxidative modification of human plasma protein: Effects of some flavonoids. *J. Asian Nat. Prod. Res.*, 2010; 12: 257–264. [CrossRef]
152. Arul, D.; Subramanian, P. Naringenin (citrus flavanone) induces growth inhibition, cell cycle arrest and apoptosis in human hepatocellular carcinoma cells. *Pathol. Oncol. Res.*, 2013; 19: 763–770. [CrossRef] [PubMed]

153. Hernandez-Aquino, E.; Muriel, P. Beneficial effects of naringenin in liver diseases: Molecular mechanisms. *World J. Gastroenterol*, 2018; 24: 1679–1707. [CrossRef]
154. Kapoor, R.; Rizvi, F.; Kakkar, P. Naringenin prevents high glucose induced mitochondria mediated apoptosis involving AIF, Endo-G and caspases. *Apoptosis*, 2013; 18: 9–27. [CrossRef] [PubMed]
155. Kapoor, R.; Kakkar, P. Naringenin accords hepato protection from streptozotocin induced diabetes in vivo by modulating mitochondrial dysfunction and apoptotic signalling cascade. *Toxicol. Rep.*, 2014; 1: 569–581. [CrossRef]
156. Middleton, E.; Kandaswami, C.; Theoharides, T.C. The effects of plant flavonoids on mammalian cells: Implications for inflammation, heart disease and cancer. *Pharmacol. Rev.*, 2000; 52: 673–751. [PubMed]
157. Rocha, L.D.; Monterio, M.C.; Teodoro, A.J. Anticancer properties of hydroxycinnamic acids: A review. *J. Cancer Res. Clin. Oncol*, 2012; 1: 109–121. [CrossRef]
158. Badhani, B.; Sharma, N.; Kakkar, R. Gallic acid: A versatile antioxidant with promising therapeutic and industrial applications. *RSC Adv.*, 2015; 5: 27540–27557. [CrossRef]
159. Heleno, S.A.; Martins, A.; Queiroz, M.J.; Ferreira, I.C. Bioactivity of phenolic acids: Metabolites versus parent compounds: A review. *Food Chem*, 2015; 173: 501–513. [CrossRef]
159. Yokozawa, T.; Chen, C.P.; Dong, E.; Tanaka, T.; Nonaka, G.I.; Nishioka, I. Study on the inhibitory effect of tannins and flavonoids against DPPH radical. *J. Agric. Food Chem*, 1998; 56: 213–222.
160. Akinmoladun, A.C.; Ibukun, E.O.; Afor, E.; Obuotor, E.M.; Farombi, E.O. Phytochemical constituent and antioxidant activity of extract from the leaves of *Ocimum gratissimum*. *Sci. Res. Ess*, 2007; 2: 163–166.
161. Kumar, N.; Goel, N. Phenolic acids: Natural versatile molecules with promising therapeutic applications. *Appl. Biotechnol. Rep.*, 2019; 24: e00370. [CrossRef]
162. Del-Rio, D.; Costa, L.G.; Lean, M.E.J.; Crozier, A. Polyphenols and health. *Nutr. Metab. Cardiovasc. Dis.*, 2010; 20: 1–6. [CrossRef] [PubMed]
163. Anand, K.K.; Singh, B.; Saxena, A.K.; Chandan, B.K.; Gupta, V.N.; Bhardwaj, V. 3,4,5-Trihydroxy benzoic acid (Gallic Acid) the hepatoprotective principle in the fruits of *Terminalia bellerica* bioassay guided activity. *Pharmacol. Res.*, 1997; 36: 315–321. [CrossRef] [PubMed]
164. Anand, K.K.; Singh, B.; Saxena, A.K.; Chandan, B.K.; Gupta, V.N.; Bhardwaj, V. 3,4,5-Trihydroxy benzoic acid (Gallic Acid) the hepatoprotective principle in the fruits of

- Terminalia bellerica bioassay guided activity. *Pharmacol. Res.*, 1997; 36: 315–321. [CrossRef] [PubMed]
165. Da Silva, S.; Chaar, J.; Yano, T. Chemotherapeutic potential of two gallic acid derivative compounds from leaves of *Casearia sylvestris* (Flacourtiaceae). *Eur. J. Pharmacol.*, 2009; 608: 76–83. [CrossRef] [PubMed]
166. Chanwitheesuk, A.; Teerawutgulrag, A.; Kilburn, J.D.; Rakariyatham, N. Antimicrobial gallic acid from *Caesalpinia mimosoides* Lamk. *Food Chem.*, 2007; 100: 1044–1048. [CrossRef]
167. Kahkeshani, N.; Farzaei, F.; Fotouhi, M.; Alavi, S.S.H.; Bahramsoltani, R.; Naseri, R.; Momtaz, S.; Abbasabadi, Z.; Rahimi, R.; Farzaei, M.H.; et al. Pharmacological effects of gallic acid in health and diseases: A mechanistic review. *Iran. J. Basic Med. Sci.*, 2019; 22: 225–237.
168. Park, J.; Han, W.; Park, J.; Choi, S.; Choi, J. Changes in hepatic drug metabolizing enzymes and lipid peroxidation by methanol extract and major compound of *Orostachys japonicus*. *J. Ethnopharmacol.*, 2005; 102: 313–318. [CrossRef]
169. Choubey, S.; Goyal, S.; Varughese, L.R.; Kumar, V.; Sharma, A.K.; Beniwal, V. Probing Gallic Acid for Its Broad-Spectrum Applications. *Mini Rev. Med. Chem.*, 2018; 18: 1283–1293. [CrossRef]
170. Chung, K.T.; Wong, T.Y.; Wei, C.; Huang, Y.W.; Lin, Y. Tannins and human health: A review. *Crit. Rev. Food Sci. Nutr.*, 1998; 38: 421–464. [CrossRef]
171. Hussein, I.A.S.; Mona-Mansour, M.S.M. Polyphenols: Properties, occurrence, content in food and potential effects. *J. Environ. Sci. Eng.*, 2017; 6: 232–261.
172. Tillman, P.B. Determination of nutrient values for commercial amino acids. *J. Appl. Poult. Res.*, 2019; 28: 526–530. [CrossRef]
173. WHO; FAO; UNO. Protein and amino acid requirements in human nutrition, report of a joint WHO/FAO/UNU expert consultation. In WHO Technical Report Series No; WHO: Geneva, Switzerland, 2007; 935. Available online: <https://apps.who.int/iris/handle/10665/43411> (accessed on 1 May 2021)
174. Azwanida NN. *Med Aromat Plants*, 2015; 4(196): 2167- 2412.
175. Abubakar AR, Haque M. *J Pharm Bioallied Sci.*, 2020; 12(1): 1-10.
176. Chaturvedi AP, Kumar M, Tripathi YB. *Int. Wound J.*, 2013; 10(6): 675-82.
177. Roy K, Chakraborty M, Theengh A. *Int. J. Pharm. Sci. Res.*, 2021; 12(1): 554-558.