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BROUSSONETIA PAPYRIFERA LINN: DEEP INSIGHTS INTO ITS DOMINANT PHARMACOLOGICAL PERSPECTIVES

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ABSTRACT

Plants have long been used as a source of traditional drugs to treat a variety of illnesses and diseases. Many of these medicinal plants are also excellent sources of phytochemicals, and many of them have powerful therapeutic properties. Broussonetia papyrifera, also known as paper mulberry, is a well-known conventional natural resource that has been used for decades, and the renowned advancements must be introduced to researchers for more improvement, product creation, innovative technology exploration, and the discovery of new concepts. The comprehensive literature collection regarding *B. papyrifera*'s specific features, dissemination, plant profile, pharmacological developments, core plant sections, ethnopharmacology, and other critical knowledge was done using publicly accessible scientific databases / natural products databases. The general aspects, plant profile, traditional uses, distribution, major phytoconstituents, and significant pharmacotherapeutic attributes (antiviral, anti-cancer, anti-oxidant, cytotoxic potentials, anti-inflammatory, anti-diabetic, anti-microbial, anti-nociceptive, anti-gout, and anti-proliferative) mediated by various parts were all highlighted in this fascinating article. This knowledge would be useful to today's ardent researchers in a variety of fields in creating a variety of important formulations for treating a variety of diseases, including inflammation, disease, high blood sugar, discomfort, infection, and cellular protection. This research will pave the way for current nature-based pharmacotherapeutics to be used in human medicine.

KEYWORDS: *Broussonetia papyrifera*, Paper mulberry, Traditional, Ethnopharmacology, Therapeutics, Phytoconstituents.

INTRODUCTION

Plant species have often been used as a source of traditional medicine to treat a variety of illnesses and disorders.[1] Some of these medicinal herbs are also excellent phytochemical sources, with a variety of therapeutic applications.[2] P.N.V. Broussonet, a French naturalist, named the genus Broussonetia after bringing a male tree of *Broussonetia papyrifera* from a Scottish garden to Paris, France, where a female tree was developing, allowing the fruit to be identified.[3] There are eight species in the family, seven of which are found in Asia and one in Madagascar.[4] East Asian plants are divided into 16 or 17 accepted varieties, with 5 wild varieties.[5] Papyrifera refers to a plant that creates paper.[6] Wild-variety paper is equivalent to non-wild-variety paper.[7] Paper Mulberry (*B. papyrifera* (L.) L'Her. ex Vent.) is a fast-growing shade tree in the Moraceae family that is found in East Asia.[8] It is grown for its bark in its native habitat.[9] It is indigenous to China, Taiwan, Korea, and Japan, as well as Hawaii and Samoa in the Pacific.[10] It has been naturalized in Asia, from India and Pakistan to Thailand, Malaysia, the Pacific Islands, and also North America.[11] It can now be identified in a number of places in India and Pakistan, ranging from sea level to 1000 meters.[12]

TAXONOMY

- **Kingdom:** Plantae
- **Sub-Kingdom:** Virdiplantae
- **Infra-Kingdom:** Streptophyta
- **Super-Division:** Embryophyta
- **Division:** Tracheophyta
- **Sub-Division:** Spermatophytina
- **Class:** Magnoliopsida
- **Super-Order:** Rosanae
- **Order:** Rosales
- **Family:** Moraceae
- **Genus:** *Broussonetia*
- **Species:** *papyrifera*

ETHNOPHARMACOLOGY

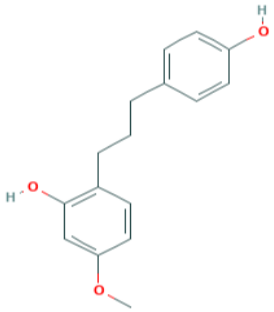
B. papyrifera (Moraceae), also known as paper mulberry, is a plant that grows wild in Asia and the Pacific.[13] Its dried fruits have traditionally been used in Chinese medicine to treat

ophthalmic diseases and impotency.[14] In China, the leaves, twig stems, and barks of this plant are commonly used as a traditional medicine to cure gynecological bleeding, dropsy, and dysentery diseases.[15] This plant's dried stems, leaves, and roots are used in Korean traditional medicine for a variety of medicinal uses, including as a diuretic, tonic, and edema suppressor. Isolated metabolites from the roots, in fact, have a variety of biological properties, including anti-asthmatic, anti-inflammatory, anti-cancer, anti-oxidant, anti-microbial, anti-nociceptive, inhibition of the aromatase enzyme, and Protein-Tyrosine Phosphatase 1B (PTP-1B) inhibition.[16] The Korea Food and Drug Administration (KFDA) has classified the extracts of this plant as a medicinal ingredient in Korean traditional medicine, and their efficacy has been backed up by the discovery of bioactive metabolites such as chalcones, flavonoids, and flavonols with potential therapeutic properties such as anti-glucosidase, anti-cancer, xanthine oxidase, anti-cholinesterase, and anti-platelet.[17]

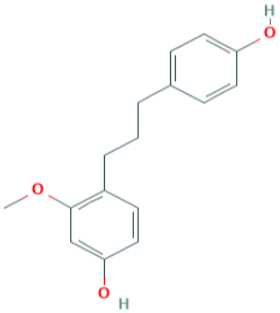
COMPREHENSIVE PHYTOCHEMISTRY

Phytochemicals reported in *B. papyrifera* are: (+)-dihydrokaempferol; (+)-marmesin; (–)-marmesin; (2*S*)-abyssinone II; (2*S*)-naringenin; (2*S*)-7,4'-dihydroxyflavan; 2,4,2',4'-tetrahydroxychalcone; 3,4- threo-1-(4-hydroxyphenyl)glycerol; 4'-hydroxy-*cis*-cinnamic acid octacosyl ester; 4-hydroxybenzaldehyde; 4-hydroxyisolonchocarpin; 7,4'-dihydroxyflavan; β-sitosterol; apigenin; apigenin-7-*O*-β-D-glucoside; arbutin; bavachin; broussochalcone A; broussochalcone B; broussofluorenone A; brussofluorenone B; broussin; broussinol; broussonin A; broussonin B; broussonin C; broussonin E; broussonin F; broussoside A; broussoside B; broussoside C; broussoside D; broussoside E; broussoaurone A; broussoflavan A; broussoflavonol A; broussoflavonol B; broussoflavonol C; broussoflavonol D; broussoflavonol E; broussoflavonol F; broussoflavonol G; broussonpapyrine; chelerythrine; chrysoriol-7-*O*-β-orientin; chushizisin A; chushizisin B; chushizisin C; chushizisin D; chushizisin E; chushizisin F; chushizisin G; chushizisin H; chushizisin I; *cis*-coniferin; *cis*-syringin; coniferyl alcohol; cosmosiin; curculigoside C; curculigoside I; D-galacitol; D-glucoside; demethylmoracin I; dihydroconiferyl alcohol; dihydrosyringin; dihydroxyisolonchocarpin; dimethoxy isogemichalcone C; ergosterol peroxide; erythro-1-(4-hydroxyphenyl)glycerol; flacourtin; ferulic acid; fucosterol; gancaonin P; graveolone; isobavachalcone; isogemichalcone C; isolicoflavonol; isoliquiritigenin; isoorientin; isoterihanine; isovitexin; kazinol A; kazinol B; kazinol E; kazinol F; lespedezaflavanone C; lignoceric acid; liriodendrin; liriodenine; luteolin; luteolin-7-*O*-β-D-glucopyranoside; luteoloside; moracin D; moracin I; moracin M; moracin N; mulberrofuran G; nitidine;

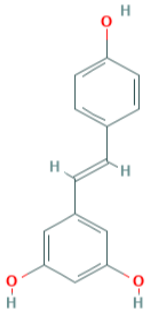
norartocarpanone; octacosan-1-ol; oxyavicine; papyriflavonol A; pinocembrin; pinoresinol-4'-*O*-β-D-glucopyranoside; *p*-coumaraldehyde; *p*-coumaric acid; poliothyrsoside; protocatechuic acid; quercetin; resveratrol; sesquineolignan; squalene; sulfuretin; syringaresinol-4'-*O*-β-D-glucoside; uralenol; and vitexin.[18] The structures of some dominant pharmacologically active phytoconstituents are depicted in **Figure 1**.



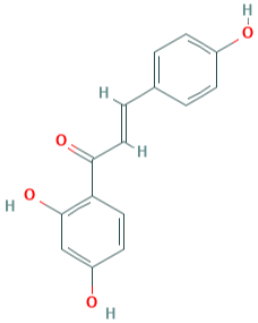
Broussonin A



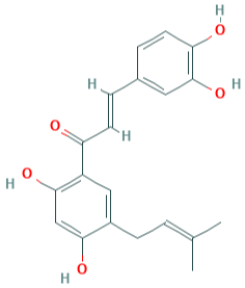
Broussonin B



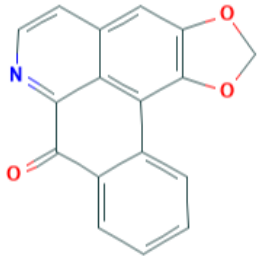
Resveratrol



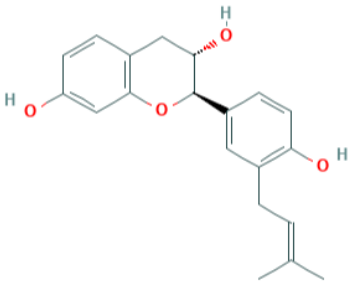
Isoliquiritigenin



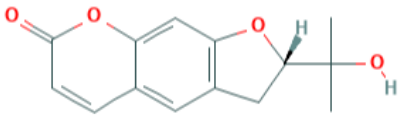
Broussochalcone A



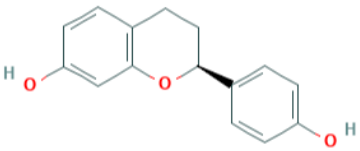
Liriodenine



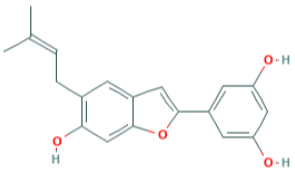
Broussinol



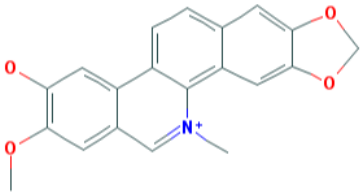
Marmesin



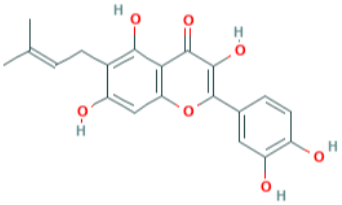
7,4'-dihydroxyflavan



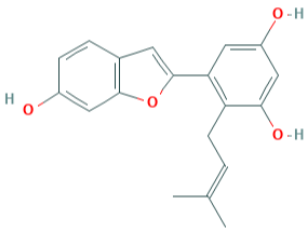
Moracin N



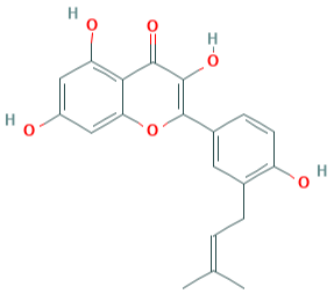
Isoterihanine



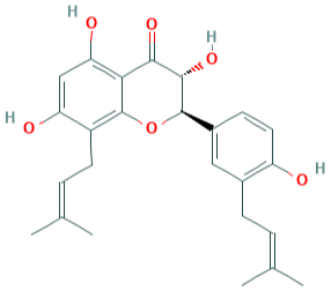
Gancaonin P



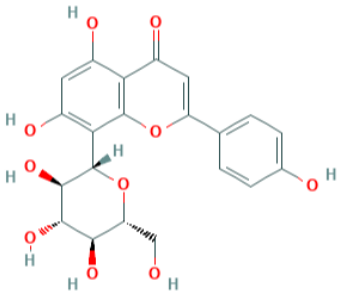
Demethylmoracin I



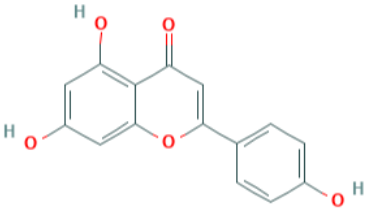
Isolicoflavonol



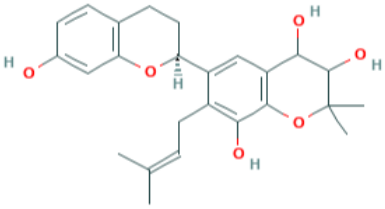
Lespedezaflavanone C



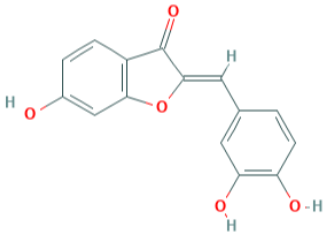
Vitexin



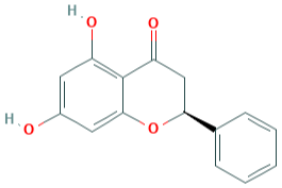
Apigenin



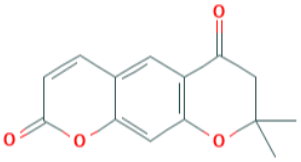
Broussoflavan A



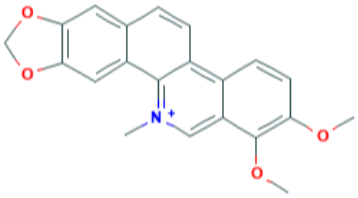
Sulfuretin



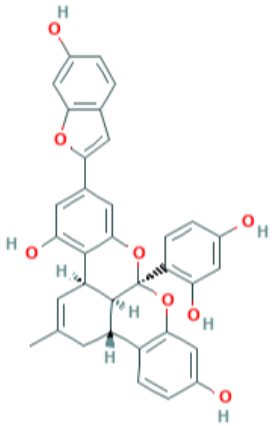
Pinocembrin



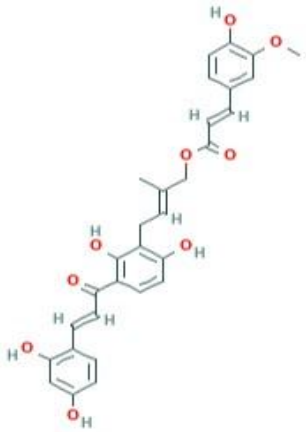
Graveolone



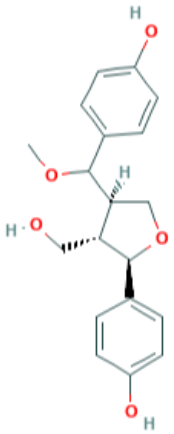
Chelerythrine



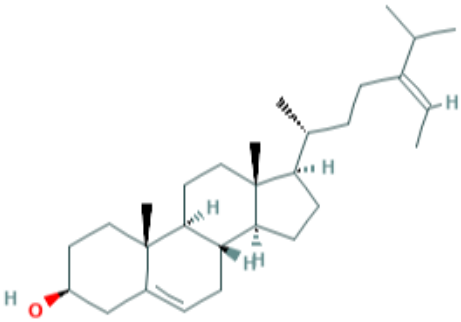
Mulberrofuran G



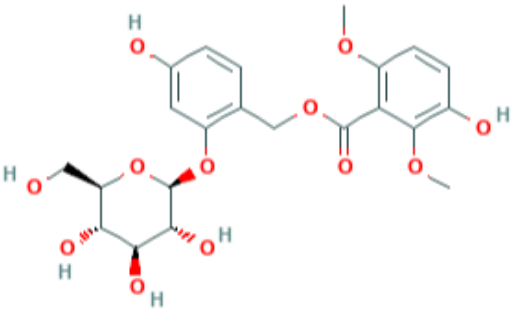
Isogemichalcone C



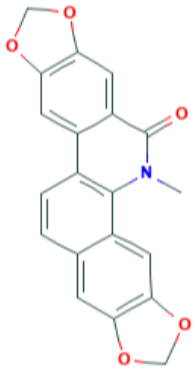
Chushizisin G



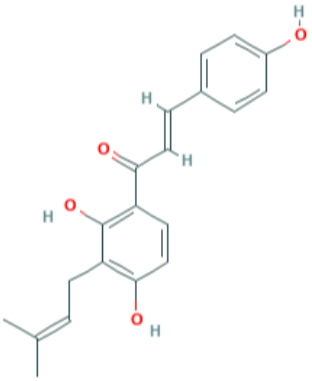
Fucosterol



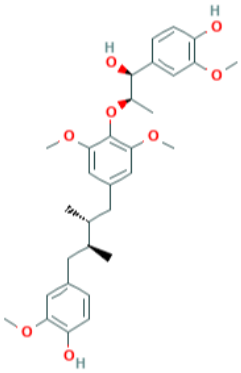
Curculigoside C



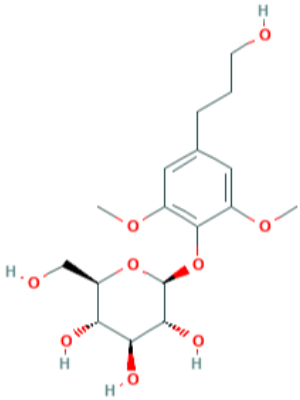
Oxyavicine



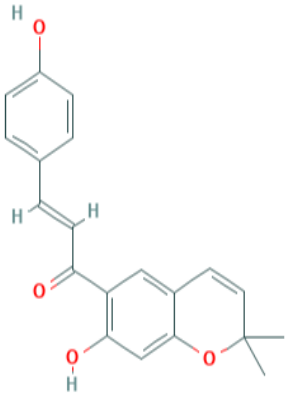
Isobavachalcone



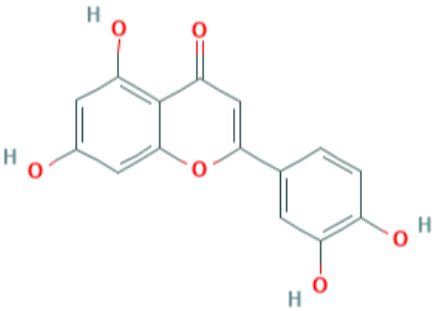
Sesquineolignan



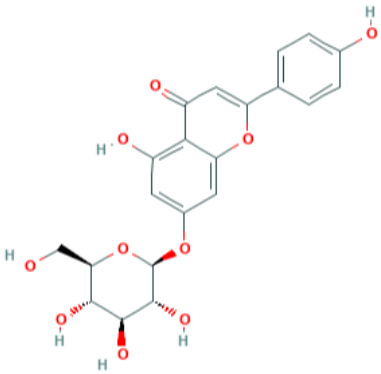
Dihydrosyringin



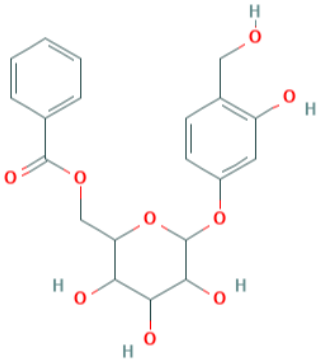
4-hydroxyisolonchocarpin



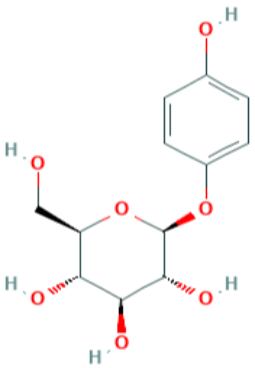
Luteolin



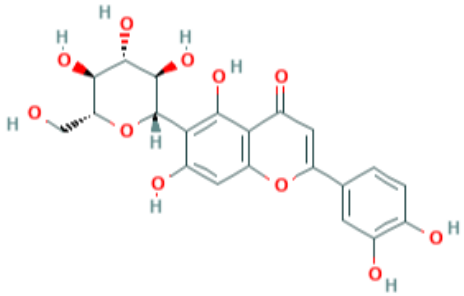
Cosmosiin



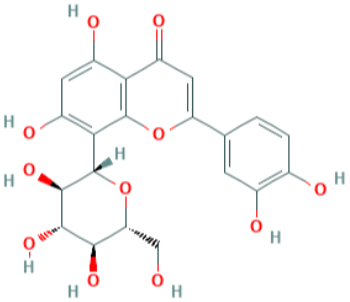
Flacourtin



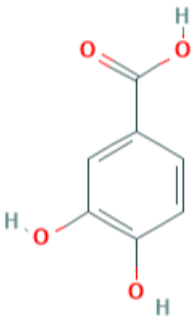
Arbutin



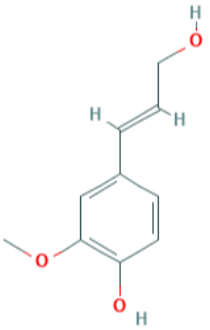
Isoorientin



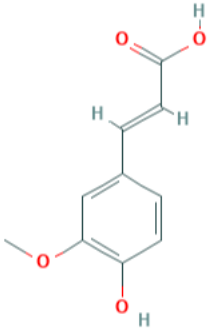
Orientin



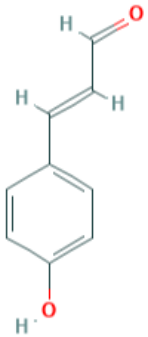
Protocatechuic acid



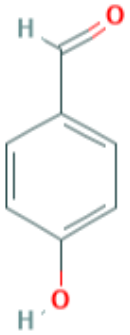
Coniferyl alcohol



Ferulic acid



***p*-coumaraldehyde**



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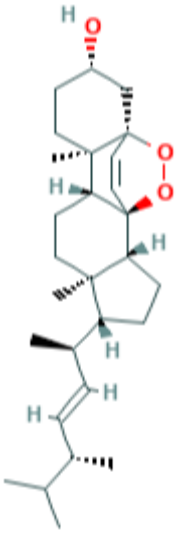

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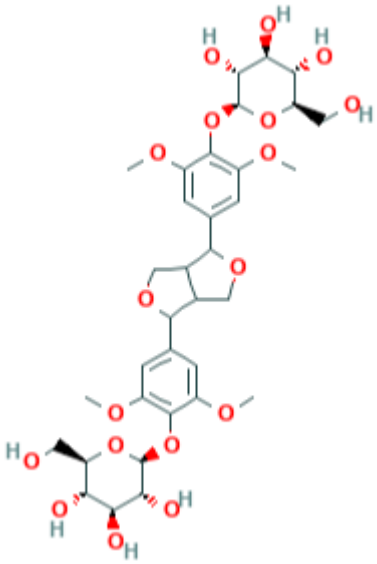
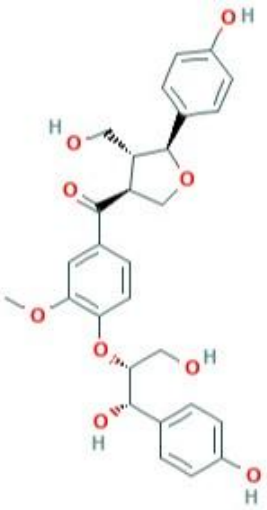
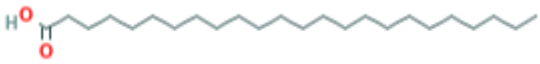


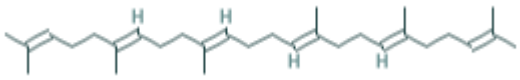
Liriodendrin



Chushizisin H

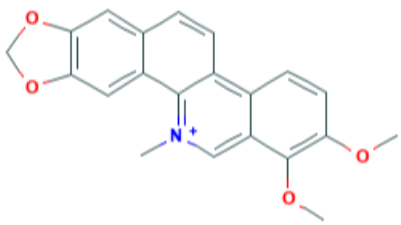


Lignoceric acid

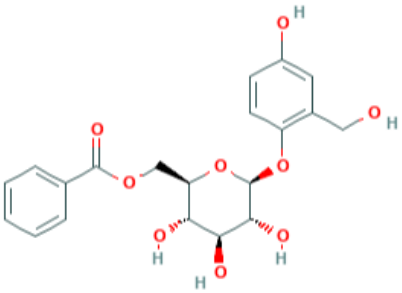


Squalene

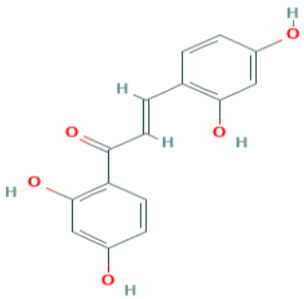
Octacosan-1-ol



Broussonpapyrine



Poliothyrsoside



2,4,2’,4’-tetrahydroxychalcone

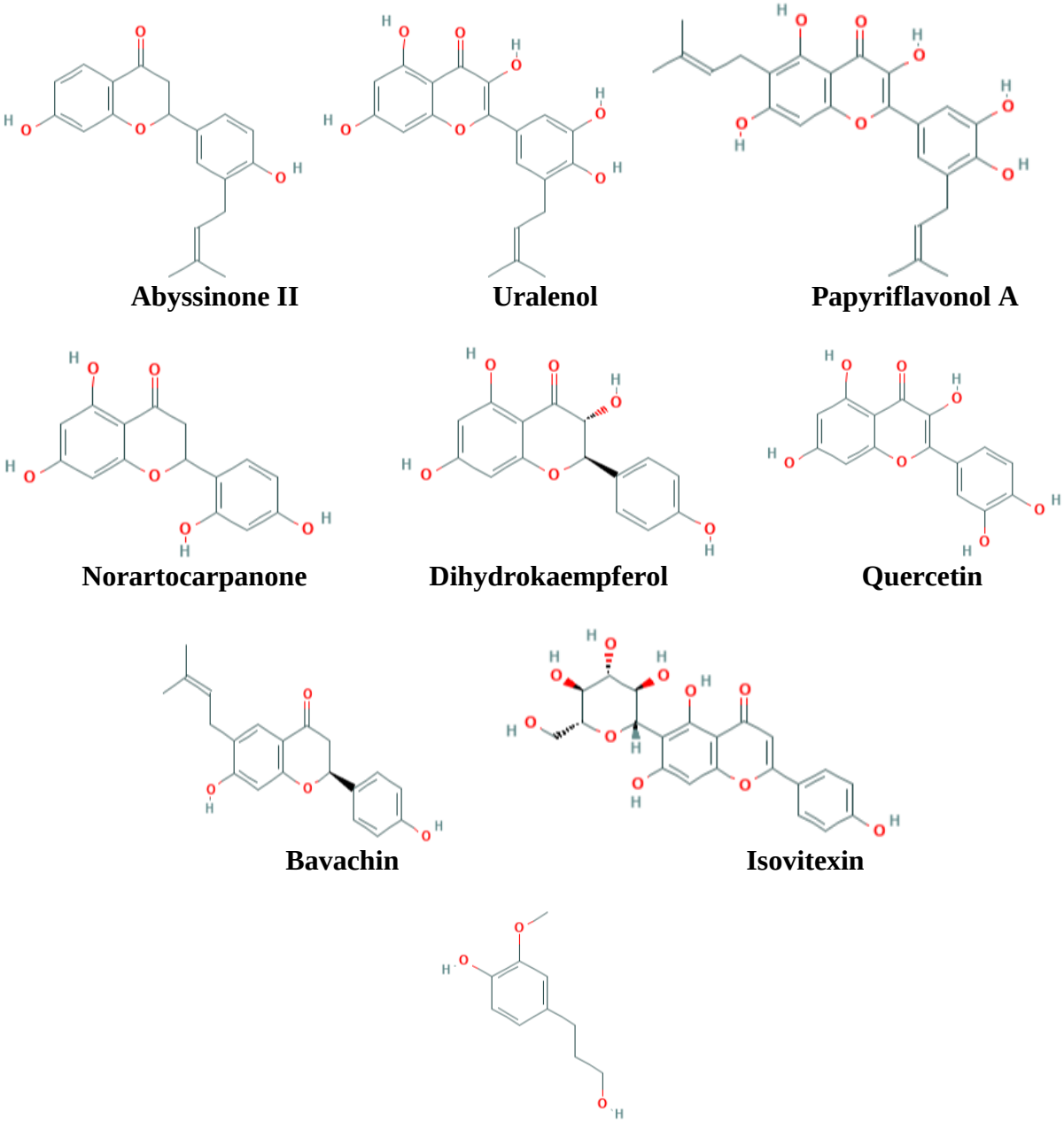


Figure 1: Phytoconstituents present in *Broussonetia papyrifera* Linn.

DOMINANT PHARMACOLOGICAL ACTIVITIES

Anti-inflammatory activity[19]

Six 1,3 diphenylpropanes, flavanone, two chalcones, five flavans, dihydroflavonol, and five flavonols were isolated from the methanolic extracts of *B. papyrifera* (L.) L. Her. ex Vent. Few compounds showed potent anti-inflammatory effects by minimizing nitric oxide activity by downregulating i-Nitric Oxide Synthase, cyclooxygenase-2, tumor necrosis factor-alpha, and i-Nitric Oxide Synthase protein expression in LPS-stimulated RAW264.7 cells. As a result of this research, *B. papyrifera* seems to be a beneficial source of phytoconstituents for

anti-inflammatory diseases like asthma, chronic obstructive pulmonary disorder (COPD), and atopy in pharmaceuticals and functional foods.

Chemical-induced pain and inflammation in the rodent model is used to test various sections of *B. papyrifera* for anti-nociceptive and anti-inflammatory action. Both the writhing reaction triggered by 1% acetic acid and the late phase licking response triggered by 1% formalin are effectively inhibited by all sections of *B. papyrifera*, including the radix, root, and fruits. Radix and fruits were found to decrease the edema induced by 1 percent carrageenan after 1-2 hours, as well as the extravasations of abdominal Evan's blue caused by inflammatory mediators including serotonin and sodium nitroprusside. This result was attributable to the involvement of betulinic acid, an active component that inhibited serotonin and carrageenan-induced paw edema.

Anti-coronavirus activity[20]

A chalconoid derivative had the strongest inhibitory ability against Mpro and PLpro (IC_{50} of 27.9 μM and 112.9 μM, respectively) among a community of polyphenolic compounds extracted from this medicinal plant. Broussochalcone A, broussochalcone B, 4-hydroxyisolonchocarpin, papyriflavonol A, 3'-(3-methylbut-2-enyl)-3',4,7-trihydroxyflavane, kazinol A, kazinol B, broussoflavan A, kazinol F, and kazinol J, all extracted from *B. papyrifera* origins, were the main active constituents. The prenylated flavone derivative papyriflavonol A showed the most efficient PLpro inhibition, with an IC_{50} value of 3.7 μM, outperforming non-prenylated flavone derivatives quercetin and kaempferol (IC_{50} of 8.6 μM and 16.3 μM, respectively). This indicated the importance of the prenyl group in creating deeper hydrophobic relationships with the enzyme as well as an improvement in flavone backbone hydroxylation.

Anti-cancer Activity[21]

The active compounds from *B. papyrifera* were discovered to be used in the management of human bladder cancer, even drug-resistant varieties, and a possible basis for their medicinal usage was developed. The compound's cytotoxic effects were examined by looking at cell proliferation, apoptosis, and autophagy, with the findings showing that phytoconstituents cause cytotoxicity in human bladder cancer cells, including the cisplatin-resistant T24R2. The compound may be used to produce successful anti-cancer medications for people with urinary bladder cancer.

Guo et al. extracted and distilled several active compounds (papyriflavonol A, broussochalcone A, uralenol, broussoflavonol B and 5,7,3',4'-tetrahydroxy-3-methoxy-8,5'–diprenylflavone) from EtOAc mulberry bark extract, all of which had important anti-proliferative effects on ER-positive MCF-7 cells *in vitro*. The most important components were the phytocompounds; broussoflavonol B with IC_{50} = 4.19 μM and 5,7,3',4'-tetrahydroxy-3-methoxy-8,5'-diprenylflavone with IC_{50} = 4.41 μM than positive power, icaritin. BCAP-37 xenograft BALB/c nude mice model, broussochalcone A and broussoflavonol B were found to substantially suppress tumor development at a concentration of 1 μM by decreasing ERK phosphorylation. Western blot showed that compounds highly down-regulated estrogen receptor-α (ER-α) production.

The compounds (liriodendrin, (+)-pinoresinol-4'-O-D-glucopyranosyl-4″-O-D-apiofuranoside, and apigenin-6-C-D-glycopyranside) extracted from the leaves have cytotoxic potentials (against HepG2 cell line) with IC_{50} values of 14.56 μg/mL, 19.53 μg/mL, and 17.19 μg/mL. Zhang et al. extracted and identified altertoxin-IV, as well as nine other compounds, from an ethyl acetate extract of a culture of the endophytic fungus Alternaria species G7 found in *B. papyrifera* (using bioassay-guided fractionation). The compounds showed remarkable cytotoxic activity against three cancer cell lines (MG-63, A549, and SMMC-7721), with IC_{50} values of 2.11 μg/mL, 1.47 μg/mL, and 7.34 μg/mL, respectively, for 3,4',5'-trihydroxy-5-methoxy-6H-benzo[c]chromen-6-one. SMMC-7721 (IC_{50} = 2.92 μg/mL) and MG-63 (IC_{50} = 0.53 μg/mL) cell lines displayed substantial cytotoxic behavior in the presence of altersolanol A.

Anti-oxidant activity[22]

Broussochalcone A (BCA), a prenylated chalcone, was discovered in the cortex of *B. papyrifera* Vent, which has been used in herbal medicine for decades. BCA is a potent natural antioxidant known for its ability to scavenge free radicals. BCA was also observed to inhibit IkB degradation in RAW 264.7 macrophages, which suppressed LPS-induced i-Nitric Oxide Synthase protein expression. Since excessive free radicals and nitric oxide development have been linked to multiple inflammatory diseases, BCA's free radical-scavenging behavior and inhibition of iNOS protein expression may have therapeutic effects.

Anti-bacterial Activity[23]

Sohn et al. investigated the antimicrobial function of Papyriflavonol A (Pap A), a prenylated flavonol compound derived from mulberry roots. The findings showed that Pap A's minimum

inhibitory concentration (MIC) against *Candida albicans* and *Saccharomyces cerevisiae* was between 10 µg/mL and 25 µg/mL, and that its antifungal action was regulated by its ability to interrupt cell membrane integrity. Additionally, Pap A was less harmful than amphotericin B. The hemolysis ratio of human erythrocytes was <5% for the strains studied. Flavonols in *B. papyrifera* displayed strong anti-oral microbial activity *in vitro*, according to Geng et al.

Anti-diabetic Activity[24]

From the chloroform extract of *B. papyrifera* stems, Ryu et al. extracted 12 polyphenols. In addition to the normal voglibose (IC_{50} = 23.4 µM), papyriflavonol A (IC_{50} = 2.1 µM), deoxynojirimycin (IC_{50} = 3.5 µM), brossoflurenone A (IC_{50} = 27.6 µM), and brossoflurenone B (IC_{50} = 33.3 µM) have been reported as possible α-glucosidase inhibitors. Sugar-derived-glucosidase inhibitors had similar efficacy. Broupapyrin A, a recent isoprenylated flavonol extracted from *B. papyrifera* branches, was found to have an important inhibitory impact on the well-known anti-diabetic target enzyme PTP-1B, with an IC_{50} value of 0.8 µM - 30 µM, according to Lou et al.

Anti-gout Activity[25]

Broussochalcone A (IC_{50} = 5.8 µM) and 3,4-dihydroxyisolonchocarpin (IC_{50} = 7.7 µM) were discovered to be the most significant inhibitors of xanthine oxidase. Broussochalcone A was discovered to be the most successful candidate.

CONCLUSION

This fascinating article expanded the general aspects, plant profile (Kingdom, Sub-Kingdom, Infra-Kingdom, Division, Sub-Division, Super-Division Class, Order, Super-Order, Family, Genus, and Species), traditional uses, distribution, major phytoconstituents, significant pharmacotherapeutic attributes (anti-viral, anti-cancer, anti-oxidant, cytotoxic, anti-inflammatory, anti-inflammatory) (seed, root, leaf, stem, and fruit). This knowledge would be fairly practical for ardent contemporary researchers in many fields (natural goods, pharmacognosis, anatomy, chemistry, botany, pharmacy, etc.) in designing different important formulations to treat multiple disorders. This research will open a new path for man-made synthetic nature-pharmacotherapeutics.

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CONFLICT OF INTEREST

The authors declare no Conflict of Interest regarding the publication of the article.

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