



Broussonetia papyrifera: Reviewing its Pharmacotherapeutic Potentials

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ABSTRACT

Traditional medicines have long been derived from plants to treat a range of ailments and disorders. Phytochemicals are abundant in many of these medicinal plants, and many of them have potent therapeutic effects. *Broussonetia papyrifera*, also known as paper mulberry, is a well-known traditional natural resource that has been used for decades, and the renowned advancements must be introduced to researchers for further improvement, product development, innovative technology exploration, and the discovery of new concepts. Using publicly available scientific databases / natural products databases, a thorough literature collection on *B. papyrifera*'s unique characteristics, diffusion, plant profile, pharmacological advances, core plant sections, ethnopharmacology, and other important information was completed. This fascinating article highlighted 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. Today's passionate researchers in a number of disciplines may utilise this information to develop a variety of essential formulations for treating a variety of illnesses, including inflammation, disease, high blood sugar, pain, infection, and cellular protection. This study will pave the path for the application of existing nature-based pharmacotherapeutics in human medicine.

Key Words: *Broussonetia papyrifera*, Paper mulberry, Traditional, Ethnopharmacology, Therapeutics, Phytoconstituents

INTRODUCTION

Traditional medicine has long relied on plant species to treat a variety of illnesses and disorders. [1] Some of these medicinal plants are also rich in phytochemicals, which have a wide range of therapeutic uses. [2] French naturalist P.N.V. Broussonet named the genus *Broussonetia* after bringing a male tree of *Broussonetia papyrifera* from a Scottish garden to Paris, France, where a female tree was growing, allowing the fruit to be identified. [3] The family consists of eight species, seven of which are found in Asia and one of which is found in Madagascar. [4] There are 16 or 17 recognised varieties of East Asian plants, as well as 5 wild varieties. [5] *Papyrifera* is a type of paper-making plant. [6] Wild-variety and non-wild-variety papers are interchangeable. [7] The Paper Mulberry (*B. papyrifera* (L.) L'Her. ex Vent.) is a fast-growing shade tree from East Asia belonging to the Moraceae family. In its natural habitat, it is grown for its

bark. [9] Its native habitats include China, Taiwan, Korea, and Japan, as well as Hawaii and Samoa in the Pacific. It has been naturalised throughout Asia, from India and Pakistan to Thailand, Malaysia, the Pacific Islands, and even North America. [11] It can now be found in India and Pakistan at elevations ranging from sea level to 1000 meters. [12]

TAXONOMY

- **Kingdom:** Plantae
- **Sub-Kingdom:** Viridiplantae
- **Infra-Kingdom:** Streptophyta
- **Super-Division:** Embryophyta
- **Division:** Tracheophyta
- **Sub-Division:** Spermatophytina
- **Class:** Magnoliopsida
- **Super-Order:** Rosanae
- **Order:** Rosales

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- **Family:** Moraceae
- **Genus:** *Broussonetia*
- **Species:** *papyrifera*

ETHNOPHARMACOLOGY

Paper mulberry, or *B. papyrifera* (Moraceae), is a plant that grows wild in Asia and the Pacific. [13] In Chinese medicine, its dried fruits have historically been used to cure ocular disorders and impotency. [14] This plant's leaves, twig stems, and bark are widely used as a traditional medicine in China to treat gynaecological bleeding, dropsy, and dysentery illnesses. [15] The dried stems, leaves, and roots of this plant are used in Korean traditional medicine as a diuretic, tonic, and edoema suppressor, among other things. Anti-asthmatic, anti-inflammatory, anti-cancer, anti-oxidant, anti-microbial, anti-nociceptive, aromatase enzyme inhibition, and PTP-1B inhibition are among the biological characteristics of isolated metabolites from the roots. [16] The Korean 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 like chalcones, flavonoids, and flavonols with potential therapeutic properties like anti-glucosidase, anti-cancer, xanthine oxidase, anti-cholinesterase, and anti-plat. [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; brousochalcone A; brousochalcone B; brousofluorenone A; brousofluorenone B; broussin; broussinol; broussonin A; broussonin B; broussonin C; broussonin E; broussonin F; broussoside A; broussoside B; broussoside C; broussoside D; broussoside E; broussoside F; broussoside G; broussoside H; broussoside I; broussoside J; broussoside K; broussoside L; broussoside M; broussoside N; broussoside O; broussoside P; broussoside Q; broussoside R; broussoside S; broussoside T; broussoside U; broussoside V; broussoside W; broussoside X; broussoside Y; broussoside Z; broussoside AA; broussoside AB; broussoside AC; broussoside AD; broussoside AE; broussoside AF; broussoside AG; broussoside AH; broussoside AI; broussoside AJ; broussoside AK; broussoside AL; broussoside AM; broussoside AN; broussoside AO; broussoside AP; broussoside AQ; broussoside AR; broussoside AS; broussoside AT; broussoside AU; broussoside AV; broussoside AW; broussoside AX; broussoside AY; broussoside AZ; broussoside BA; broussoside BB; broussoside BC; broussoside BD; broussoside BE; broussoside BF; broussoside BG; broussoside BH; broussoside BI; broussoside BJ; broussoside BK; broussoside BL; broussoside BM; broussoside BN; broussoside BO; broussoside BP; broussoside BQ; broussoside BR; broussoside BS; broussoside BT; broussoside BU; broussoside BV; broussoside BW; broussoside BX; broussoside BY; broussoside BZ; broussoside CA; broussoside CB; broussoside CC; broussoside CD; broussoside CE; broussoside CF; broussoside CG; broussoside CH; broussoside CI; broussoside CJ; broussoside CK; broussoside CL; broussoside CM; broussoside CN; broussoside CO; broussoside CP; broussoside CQ; broussoside CR; broussoside CS; broussoside CT; broussoside CU; broussoside CV; broussoside CW; broussoside CX; broussoside CY; broussoside CZ; broussoside DA; broussoside DB; broussoside DC; broussoside DD; broussoside DE; broussoside DF; broussoside DG; broussoside DH; broussoside DI; broussoside DJ; broussoside DK; broussoside DL; broussoside DM; broussoside DN; broussoside DO; broussoside DP; broussoside DQ; broussoside DR; broussoside DS; broussoside DT; broussoside DU; broussoside DV; broussoside DW; broussoside DX; broussoside DY; broussoside DZ; broussoside EA; broussoside EB; broussoside EC; broussoside ED; broussoside EE; broussoside EF; broussoside EG; broussoside EH; broussoside EI; broussoside EJ; broussoside EK; broussoside EL; broussoside EM; broussoside EN; broussoside EO; broussoside EP; broussoside EQ; broussoside ER; broussoside ES; broussoside ET; broussoside EU; broussoside EV; broussoside EW; broussoside EX; broussoside EY; broussoside EZ; broussoside FA; broussoside FB; broussoside FC; broussoside FD; broussoside FE; broussoside FF; broussoside FG; broussoside FH; broussoside FI; broussoside FJ; broussoside FK; broussoside FL; broussoside FM; broussoside FN; broussoside FO; broussoside FP; broussoside FQ; broussoside FR; broussoside FS; broussoside FT; broussoside FU; broussoside FV; broussoside FW; broussoside FX; broussoside FY; broussoside FZ; broussoside GA; broussoside GB; broussoside GC; broussoside GD; broussoside GE; broussoside GF; broussoside GG; broussoside GH; broussoside GI; broussoside GJ; broussoside GK; broussoside GL; broussoside GM; broussoside GN; broussoside GO; broussoside GP; broussoside GQ; broussoside GR; broussoside GS; broussoside GT; broussoside GU; broussoside GV; broussoside GW; broussoside GX; broussoside GY; broussoside GZ; broussoside HA; broussoside HB; broussoside HC; broussoside HD; broussoside HE; broussoside HF; broussoside HG; broussoside HH; broussoside HI; broussoside HJ; broussoside HK; broussoside HL; broussoside HM; broussoside HN; broussoside HO; broussoside HP; broussoside HQ; broussoside HR; broussoside HS; broussoside HT; broussoside HU; broussoside HV; broussoside HW; broussoside HX; broussoside HY; broussoside HZ; broussoside IA; broussoside IB; broussoside IC; broussoside ID; broussoside IE; broussoside IF; broussoside IG; broussoside IH; broussoside II; broussoside IJ; broussoside IK; broussoside IL; broussoside IM; broussoside IN; broussoside IO; broussoside IP; broussoside IQ; broussoside IR; broussoside IS; broussoside IT; broussoside IU; broussoside IV; broussoside IW; broussoside IX; broussoside IY; broussoside IZ; broussoside JA; broussoside JB; broussoside JC; broussoside JD; broussoside JE; broussoside JF; broussoside JG; broussoside JH; broussoside JI; broussoside JJ; broussoside JK; broussoside JL; broussoside JM; broussoside JN; broussoside JO; broussoside JP; broussoside JQ; broussoside JR; broussoside JS; broussoside JT; broussoside JU; broussoside JV; broussoside JW; broussoside JX; broussoside JY; broussoside JZ; broussoside KA; broussoside KB; broussoside KC; broussoside KD; broussoside KE; broussoside KF; broussoside KG; broussoside KH; broussoside KI; broussoside KJ; broussoside KK; broussoside KL; broussoside KM; broussoside KN; broussoside KO; broussoside KP; broussoside KQ; broussoside KR; broussoside KS; broussoside KT; broussoside KU; broussoside KV; broussoside KW; broussoside KX; broussoside KY; broussoside KZ; broussoside LA; broussoside LB; broussoside LC; broussoside LD; broussoside LE; broussoside LF; broussoside LG; broussoside LH; broussoside LI; broussoside LJ; broussoside LK; broussoside LL; broussoside LM; broussoside LN; broussoside LO; broussoside LP; broussoside LQ; broussoside LR; broussoside LS; broussoside LT; broussoside LU; broussoside LV; broussoside LW; broussoside LX; broussoside LY; broussoside LZ; broussoside MA; broussoside MB; broussoside MC; broussoside MD; 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broussoside OP; broussoside OQ; broussoside OR; broussoside OS; broussoside OT; broussoside OU; broussoside OV; broussoside OW; broussoside OX; broussoside OY; broussoside OZ; broussoside PA; broussoside PB; broussoside PC; broussoside PD; broussoside PE; broussoside PF; broussoside PG; broussoside PH; broussoside PI; broussoside PJ; broussoside PK; broussoside PL; broussoside PM; broussoside PN; broussoside PO; broussoside PP; broussoside PQ; broussoside PR; broussoside PS; broussoside PT; broussoside PU; broussoside PV; broussoside PW; broussoside PX; broussoside PY; broussoside PZ; broussoside QA; broussoside QB; broussoside QC; broussoside QD; broussoside QE; broussoside QF; broussoside QG; broussoside QH; broussoside QI; broussoside QJ; broussoside QK; broussoside QL; broussoside QM; broussoside QN; broussoside QO; broussoside QP; broussoside QQ; broussoside QR; broussoside QS; broussoside QT; broussoside QU; broussoside QV; broussoside QW; broussoside QX; broussoside QY; broussoside QZ; 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broussoside WE; broussoside WF; broussoside WG; broussoside WH; broussoside WI; broussoside WJ; broussoside WK; broussoside WL; broussoside WM; broussoside WN; broussoside WO; broussoside WP; broussoside WQ; broussoside WR; broussoside WS; broussoside WT; broussoside WY; broussoside WZ; broussoside XA; broussoside XB; broussoside XC; broussoside XD; broussoside XE; broussoside XF; broussoside XG; broussoside XH; broussoside XI; broussoside XJ; broussoside XK; broussoside XL; broussoside XM; broussoside XN; broussoside XO; broussoside XP; broussoside XQ; broussoside XR; broussoside XS; broussoside XT; broussoside XU; broussoside XV; broussoside XW; broussoside XX; broussoside XY; broussoside XZ; broussoside YA; broussoside YB; broussoside YC; broussoside YD; broussoside YE; broussoside YF; broussoside YG; broussoside YH; broussoside YI; broussoside YJ; broussoside YK; broussoside YL; broussoside YM; broussoside YN; broussoside YO; broussoside YP; broussoside YQ; broussoside YR; broussoside YS; broussoside YT; broussoside YU; broussoside YV; broussoside YW; broussoside YX; broussoside YY; broussoside YZ; broussoside ZA; broussoside ZB; broussoside ZC; broussoside ZD; broussoside ZE; broussoside ZF; broussoside ZG; broussoside ZH; broussoside ZI; broussoside ZJ; broussoside ZK; broussoside ZL; broussoside ZM; broussoside ZN; broussoside ZO; broussoside ZP; broussoside ZQ; broussoside ZR; broussoside ZS; broussoside ZT; broussoside ZU; broussoside ZV; broussoside ZW; broussoside ZX; broussoside ZY; broussoside ZZ.

(4-hydroxyphenyl)glycerol; flacourtin; ferulic acid; fucosterol; gancaonin P; graveolone; isobavachalcone; isogemichalcone C; isolicoflavonol; isoliquiritigenin; isoorientin; isoterhanine; isovitexin; kazinol A; kazinol B; kazinol E; kazinol F; lespezezaflavanone C; lignoceric acid; liriiodendrin; liriiodenine; luteolin; luteolin-7-*O*- β -D-glucopyranoside; luteoloside; moracin D; moracin I; moracin M; moracin N; mulberrofuran G; nitidine; norartocarpanone; octacosan-1-ol; oxyvicine; papyriflavonol A; pinocembrin; pinoresinol-4'-*O*- β -D-glucopyranoside; *p*-coumaraldehyde; *p*-coumaric acid; poliothyrsoside; protocatechuic acid; quercetin; resveratrol; sesquieolignan; squalene; sulfuretin; syringaresinol-4'-*O*- β -D-glucoside; uralenol; and vitexin.^[18]

DOMINANT PHARMACOLOGICAL ACTIVITIES

Anti-inflammatory and activity ^[19]

The methanolic extracts of *B. papyrifera* (L.) L. Her. ex Vent. included six 1,3 diphenylpropanes, flavanone, two chalcones, five flavans, dihydroflavonol, and five flavonols. In LPS-stimulated RAW264.7 cells, a few substances exhibited significant anti-inflammatory actions by reducing nitric oxide activity by downregulating the protein expression of i-Nitric Oxide Synthase, cyclooxygenase-2, tumour necrosis factor- α , and i-Nitric Oxide Synthase. *B. papyrifera* seems to be a useful source of phytoconstituents for anti-inflammatory illnesses such as asthma, chronic obstructive pulmonary disease (COPD), and atopy in medicines and functional foods as a consequence of this study.

Various sections of *B. papyrifera* were tested for anti-nociceptive and anti-inflammatory activity in a rat model using chemically induced pain and inflammation. All parts of *B. papyrifera*, including the radix, root, and fruits, efficiently block both the writhing reaction induced by 1% acetic acid and the late phase licking response induced by 1% formalin. Radix and fruits were shown to reduce edoema produced by 1% carrageenan after 1-2 hours, as well as extravasations of abdominal Evan's blue caused by inflammatory mediators like serotonin and sodium nitroprusside. The presence of betulinic acid, an active component that reduced serotonin and carrageenan-induced paw edoema, was responsible for this finding.

Anti-SARS CoV-2 activity ^[20]

Among a group of polyphenolic compounds isolated from this medicinal plant, a chalconoid derivative showed the greatest inhibitory activity against Mpro and PLpro (IC₅₀ of 27.9 M and 112.9 M, respectively). The major active components were brousochalcone A, brousochalcone B, 4-hydroxyisolonchocarpin, papyriflavonol A, 3'-(3-methylbut-2-enyl)-3',4,7-trihydroxyflavane, kazinol

A, kazinol B, brousoflavan A, kazinol F, and kazinol J, all isolated from *B. papyr* Papyriflavonol A, a prenylated flavone derivative, inhibited PLpro most effectively, with an IC₅₀ of 3.7 M, outperforming non-prenylated flavone derivatives quercetin and kaempferol (IC₅₀ of 8.6 M and 16.3 M, respectively). This demonstrated the significance of the prenyl group in forming stronger hydrophobic interactions with the enzyme and improving flavone backbone hydroxylation.

Anti-cancer Activity ^[21]

The active chemicals in *B. papyrifera* have been shown to be effective in the treatment of human bladder cancer, including drug-resistant strains, and a potential medical foundation has been established. Cell proliferation, apoptosis, and autophagy were studied to see whether phytoconstituents caused cytotoxicity in human bladder cancer cells, particularly the cisplatin-resistant T24R2. The chemical may be utilised to develop effective anti-cancer drugs for individuals suffering from urinary bladder cancer.

Guo et al. extracted and distilled several active compounds from EtOAc mulberry bark extract (papyriflavonol A, brousochalcone A, uralenol, brousoflavonol B, and 5,7,3',4'-tetrahydroxy-3-methoxy-8,5'-diprenylflavone), all of which had significant anti-proliferative effects in ER-positive MCF-7 cells. The phytochemicals brousoflavonol B (IC₅₀ = 4.19 M) and 5,7,3',4'-tetrahydroxy-3-methoxy-8,5'-diprenylflavone (IC₅₀ = 4.41 M) were the most significant components, followed by icaritin (IC₅₀ = 4.41 M). Brousochalcone A and brousoflavonol B were shown to significantly inhibit tumour growth by reducing ERK phosphorylation in the BCAP-37 xenograft BALB/c nude mice model at a dose of 1 M. Compounds dramatically reduced oestrogen receptor (ER) synthesis, according to Western blot analysis.

The chemicals isolated from the leaves (liriodendrin, (+)-pinoresinol-4'-O-D-glucopyranosyl-4''-O-D-apiofuranoside, and apigenin-6-C-D-glycopyranside) exhibit cytotoxic potentials (against HepG2 cell line), with IC₅₀ values of 14.56 g/mL, 19.53 g/mL, and 17.19 g/mL. From an ethyl acetate extract of a culture of the endophytic fungus *Alternaria* species G7 discovered in *B. papyrifera*, Zhang et al. isolated and identified altertoxin-IV as well as nine additional chemicals (using bioassay-guided fractionation). The compounds had impressive cytotoxic activity against three cancer cell lines (MG-63, A549, and SMMC-7721), with IC₅₀ values of 2.11 g/mL, 1.47 g/mL, and 7.34 g/mL, respectively, for 3,4',5'-trihydroxy-5-methoxy-6H-benzo[c]chromen-6-one. In the presence of altersolanol A, the cell lines SMMC-7721 (IC₅₀ = 2.92 g/mL) and MG-63 (IC₅₀ = 0.53 g/mL) showed significant cytotoxicity.

Anti-oxidant activity ^[22]

The prenylated chalcone brousochalcone A (BCA) was found in the cortex of *B. papyrifera* Vent, which has been used in herbal therapy for decades. BCA is a powerful natural antioxidant that may neutralise free radicals. In RAW 264.7 macrophages, BCA inhibited I κ B degradation, which reduced LPS-induced iNOS protein production. BCA's free radical-scavenging activity and suppression of iNOS protein production may have therapeutic benefits since excessive free radicals and NO generation have been related to a variety of inflammatory illnesses.

Anti-bacterial Activity ^[23]

Papyriflavonol A (Pap A), a prenylated flavonol molecule produced from mulberry roots, was studied for its antibacterial properties. The researchers discovered that the minimum inhibitory concentration (MIC) of Pap A against *Candida albicans* and *Saccharomyces cerevisiae* was between 10 and 25 g/mL, and that its antifungal activity was controlled by its capacity to disrupt cell membrane integrity. Furthermore, Pap A was less toxic than amphotericin B. For the strains tested, the hemolysis ratio of human erythrocytes was 5%. In vitro, flavonols from *B. papyrifera* showed significant anti-oral microbial action.

Anti-diabetic Activity ^[24]

Ryu et al. isolated 12 polyphenols from the chloroform extract of *B. papyrifera* stems. Papyriflavonol A (IC₅₀ = 2.1 M), deoxynojirimycin (IC₅₀ = 3.5 M), brousoflurenone A (IC₅₀ = 27.6 M), and brousoflurenone B (IC₅₀ = 33.3 M) have all been reported as potential α -glucosidase inhibitors, in addition to the standard voglibose (IC₅₀ = 23.4 M). Inhibitors of sugar-derived glucosidase showed comparable effectiveness. Broupapyrin A, a newly isoprenylated flavonol isolated from *B. papyrifera* branches, was shown to have a significant inhibitory effect on the well-known anti-diabetic target enzyme PTP-1B, with an IC₅₀ of 0.8-30 M.

Anti-gout Activity ^[25]

The most potent inhibitors of xanthine oxidase were found to be brousochalcone A (IC₅₀ = 5.8 M) and 3,4-dihydroxyisolonchocarpin (IC₅₀ = 7.7 M). The most effective candidate was found to be Brousochalcone A.

CONCLUSION

This fascinating article expanded on 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, and significant pharmacotherapeutic attributes (antiviral, anti-cancer, anti-oxidant, cytotoxic,

anti-inflammatory, anti-inflammatory) of (seed, root, leaf, stem, and fruit). This information would be very useful to today's enthusiastic researchers in a variety of areas (natural products, pharmacognosis, anatomy, chemistry, botany, pharmacy, and so on) in developing many key formulations to cure a variety of diseases. This study will pave the way for synthetic nature-based pharmacotherapeutics that are man-made.

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CONFLICT OF INTEREST

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

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