Looking Ahead to Reviewing Some Pharmacologically Active Phytoconstituents Present in *Broussonetia papyrifera* (L.) Hert. ex Vent.

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ABSTRACT

Introduction: Plants have long been used to cure diverse ailments and disorders as a source of conventional medicines. Many of these medicinal plants are also fantastic phytochemical sources, many of which have strong therapeutic practices. *Broussonetia papyrifera*, also known as paper mulberry, is a well-known traditional natural resource that has been in application for decades and the renowned advances must be presented to researchers for further betterment, product innovation, exploring novel applications, and uncover miscellaneous ideas.

Aim: Reviewing some pharmacologically active phytoconstituents present in *B. papyrifera* Linn.

Methodology: The systematic literature compilation about the basic aspects, distribution, plant profile, pharmacological advances, key plant parts, ethnopharmacology, and other crucial information about *B. papyrifera* was performed through freely available scientific databases / natural products databases such as ScienceDirect, Google Scholar, PubMed, etc.

Results: This current fascinating article expansively emphasized 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 potentials, anti-inflammatory, anti-diabetic, anti-microbial, anti-nociceptive, anti-gout, and anti-proliferative) mediated by diverse parts (seed, root, leaf, stem, and fruit).

Conclusion: This information will be reasonably functional for the passionate contemporary investigators of several areas (natural products, pharmacognosy, medicine, chemistry, botany, pharmacy, etc.) in developing miscellaneous essential formulations for treating numerous disorders such as inflammation, cancer, high blood sugar, pain, infection, along with exhibiting cellular-protective effects. This study will pave a new way for modern nature-pharmacotherapeutics for human applications.

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

INTRODUCTION

Plants have long been used to cure diverse ailments and disorders as a source of conventional medicines. Many of these medicinal plants are also fantastic phytochemical sources, many of which have strong therapeutic practices. The genus *Broussonetia* was named after P.N.V. Broussonet, a French naturalist, who took a male tree of *B. papyrifera* from a garden in Scotland, and introduced it to Paris, France, where a female tree was growing, thus enabling fruit to be described.¹ The genus contains 8 species, of which 7 are native to Asia and one to Madagascar. There are 16 or 17 recognized varie-

ties of the East Asian species, including 5 wild varieties. The specific name *papyrifera* means paper-bearing. The paper made from wild varieties is inferior to that from non-wild varieties.²

B. papyrifera (L.) L'Her. ex Vent. (Paper mulberry) is a fast-growing shade tree belonging to the Moraceae family that is widely distributed throughout East Asia.³ It is cultivated within its natural range for its bark. It is native to China, Taiwan, Korea, and Japan and possibly native to the Pacific islands of Hawaii and Samoa. From India and Pakistan to Thailand, Malaysia, and the Pacific Islands, and even in

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North America, it has been naturalized in Asia. It is now widely found from sea level to 1000 m altitude in several locations in India and Pakistan.⁴

TAXONOMY

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

TRADITIONAL USES / ETHNOPHARMACOLOGY

B. papyrifera (Moraceae), also known as paper mulberry, grows naturally in Asia and Pacific countries. Its dried fruits have been used as a traditional Chinese medicine for the treatment of ophthalmic disorders and impotency.⁵ The leaves, twig roots, and barks of this plant are widely used to treat gynecological bleeding, dropsy, dysentery diseases as a folk medicine in China.⁶ The dried branches, leaves, and roots of this plant are used as a Korean traditional medicine for various therapeutic purposes, such as a diuretic, tonic, and suppressor of oedema.^{7,8} In particular, isolated metabolites from the roots have multiple biological characteristics including anti-inflammatory,⁹ anti-asthmatic,¹⁰ antioxidant,¹¹ anti-cancer,¹² anti-nociceptive,¹³ anti-microbial,¹⁴ PTP-1B inhibition,¹⁵ and aromatase enzyme inhibition.¹⁶ The extracts of this plant have also been described by the Korea Food and Drug Administration (KFDA) as a medicinal ingredient of Korean traditional medicine, and its effectiveness has been supported by the recent identification of bioactive metabolites, including chalcones, flavonoids, and flavonols with potential therapeutic activities like anti-cancer,¹² α -glucosidase,⁷ anti-cholinesterase,¹⁷ xanthine oxidase,¹¹ and anti-platelet activities.¹⁸

PHYTOCHEMISTRY

Phytochemicals reported in *B. papyrifera* are: broussonin A; broussonin B; (+)-marmesin; kazinol F; broussonchalcone A; 1-(2,4-dihydroxyphenyl)-3-(4-hydroxyphenyl)-propane; 1-(4-hydroxy-2-methoxyphenyl)-3-(4-hydroxy-3-prenylphenyl)-propane; 3'- γ -hydroxymethyl-(E)- γ -methylallyl-2,4,2',4'-tetrahydroxychalcone-11'-O-coumarate; (2S)-2',4'-dihydroxy-2''-(1-hydroxy-1-methylethyl) dihydrofuro-2,3-h flavanone; isolico flavanol; (2S)-abyssinone II; (2S)-5,7,2',4'-tetrahydroxyflavanone; (2S)-euchrenone

a7; broussonchalcone F; (2S)-naringenin (Syn. Naringetol); albanol A (Syn. Mulberrofuran G); moracin N; isogemichalcone C; chushizisin H; broussonchalcone E; broussonchalcone G; broussonchalcone C; broussonchalcone D; chushizisin I; 5,7,3',4'-tetrahydroxy-3-methoxy-6-geranylflavone; broussonchalcone B; broussonchalcone A; 5,7,3',4'-tetrahydroxy-6-geranylflavone; 4'-O-methyldavidioside; broussonchalcone A; (2R,3R)-lespedezaflavanone C; broussonchalcone F; 5,7,2',4'-tetrahydroxy-3-geranylflavone; kazinol A; kazinol B; gancaonin P; uralenol; (2S)-2',4'-dihydroxy-2''-(1-hydroxy-1-methylethyl) dihydrofuro-2,3-h flavanone; isolico flavanol; chushizisin C; chushizisin D; chushizisin E; chushizisin B; chushizisin A; chushizisin F; (2S)-euchrenone a7; broussonchalcone A; broussonchalcone A; chushizisin G; broussonchalcone; isobavachalcone; broussonchalcone B; (2S)-abyssinone II; bavachin; moracin I; broussonin C; (2S)-7,4'-dihydroxy-3'-prenylflavan; moracin N; demethylmoracin I; moracin D; broussonin F; broussonin; 7,4'-dihydroxyflavan; pinocembrin; resveratrol; isoliquiritigenin; isoliquiritigenin 2'-methoxy ether; 2,4,2',4'-tetrahydroxychalcone; (+)-dihydrokaempferol (Syn. (+)-aromadendrin); norartocarpanone (Syn. Steppogenin); dimethoxy isogemichalcone C; moracin M; (2S)-7,4'-dihydroxyflavan; broussonin E; 1,2,4-dihydroxy-3-(3-methylbut-2-en-1-yl)phenyl-3-(2,4-dihydroxyphenyl)-propan-1-one; 2-{5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-3,4-dihydro-2H-chromen-8-ylamino} pentanedioic acid; papyriflavonol A (Syn. Broussonol E); (2R,3R,5R,6S,9R)-3-hydroxy-5,6-epoxy- β -ionol-2-O- β -D-glucopyranoside; (2R,3R,5R,6S,9R)-3-hydroxyl-5,6-epoxy-acetyl- β -ionol-2-O- β -D-glucopyranoside; quercetin (Syn. 3,3',4',5,7-pentahydroxyflavone); 5,7,3',5'-tetrahydroxyflavanone; luteolin; 5,7,3',4'-tetrahydroxy-3-methoxyflavone; squalene; octacosan-1-ol; lignoceric acid; 4'-hydroxy-*cis*-cinnamic acid octacosyl ester; (-)-marmesin; 8-(1,1-dimethylallyl)-5'-(3-methylbut-2-enyl)-3',4',5,7-tetrahydroxyflavanol; 3'-(3-methylbut-2-enyl)-3',4',7-trihydroxyflavanone; kazinol E; sesquieolignan; 2-(4-hydroxyphenyl)propane-1,3-diol-1-O- β -D-glucopyranoside; 4-hydroxybenzaldehyde; protocathechuic acid; broussonchalcone; nitidine; oxyavicine; lirioidenine; cosmosiin; (+)-pinoselinol-4'-O- β -D-glucopyranosyl-4''-O- β -D-apiofuranoside; luteolin-7-O- β -D-glucopyranoside; lirioidendrin; 3,5,4'-trihydroxy-bibenzyl-3-O- β -D-glucoside; apigenin-6-C- β -D-glucopyranoside; 8,11-octadecadienic acid; broussonchalcone A; broussonchalcone B; broussonchalcone C; broussonchalcone D; broussonchalcone E; syringaresinol-4'-O- β -D-glucoside; *p*-coumaric acid; apigenin; poliothyrsoside; pinoselinol-4'-O- β -D-glucopyranoside; flacourtin; dihydrosyringin; apigenin-7-O- β -D-glucoside; chrysorinol-7-O- β -D-glucoside; isovitexin; luteoloside; orientin; vitexin; isoorientin; 3,4-dihydroxyisolonchocarpin; 4-hydroxyisolonchocarpin; 3'-(3-methylbut-2-enyl)-3',4',7-trihydroxyflavanone; 8-(1,1-dimethylallyl)-5'-(3-methylbut-2-enyl)-3',4',5,7-tetrahydroxyflavanol; broussonfluorenone A; brousson

fluorenone B; threo-1-(4-hydroxy-3-methoxyphenyl)-2-{4-(*E*)-3-hydroxy-1-propenyl-2-methoxyphenoxy}-1,3-propanediol; arbutine; dihydro-coniferyl alcohol; coniferyl alcohol; ferulic acid; *p*-coumaraldehyde; *cis*-syringin; *cis*-coniferin; erythro-1-(4-hydroxyphenyl) glycerol; threo-1-(4-hydroxyphenyl) glycerol; curculigoside I, curculigoside C, (2*S*)-2',4'-dihydroxy-2''-(1-hydroxy-1-methylethyl)-dihydrofurano-2,3-h-flavanone; erythro-1-(4-hydroxy-3-methoxyphenyl)-2-{4-(*E*)-3-hydroxy-1-propenyl-2-methoxy-phenoxy}-1,3-propanediol; 3-2-(4-hydroxyphenyl)-3-hydroxymethyl-2,3-dihydro-1-benzofuran-5-ylpropan-1-ol; 5,7,3',4'-tetrahydroxy-3-methoxy-8-geranylflavone; 5,7,3',4'-tetrahydroxy-3-methoxy-8,5'-diprenylflavone; chelerythrine; isoterhanine; β -sitosterol; fucosterol; ergosterol peroxide; D-galacitol; sulfuretin; and gaeveolone.¹⁹

PHARMACOTHERAPEUTIC EFFECTS

Anti-inflammatory activity

Bioactivity-guided fractionation and metabolite study from the methanolic extracts of root bark of *Broussonetia papyrifera* (L.) L. Her. ex Vent. led to the isolation of twenty compounds; six 1,3 diphenylpropanes, flavanone, two chalcones, five flavans, dihydroflavonol, and five flavonols, including five new compounds. From the screening for inhibition of nitric oxide (NO) and pro-inflammatory cytokines (TNF- α and IL-6) in LPS-stimulated RAW264.7 cells, few compounds exhibited potent anti-inflammatory effects by reducing NO production through downregulating iNOS, COX-2, TNF- α expression, and iNOS protein expression. This study, therefore, reveals that *B. papyrifera* is a valuable source of phytoconstituents for pharmaceuticals and functional foods for anti-inflammatory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and atopy.²⁰

Anti-SARS CoV-2 activity

A group of polyphenolic compounds was isolated from this medicinal plant of which a chalconoid derivative showed the best inhibitory potential against both Mpro and PLpro (IC₅₀ of 27.9 μ M and 112.9 μ M, respectively).²¹

The inhibitory potential of ten polyphenols derived from *B. papyrifera* roots, i.e. 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 were tested against the two SARS CoV proteases with a more potent inhibition recorded against PLpro than that of 3CLpro. The most potent PLpro inhibition was exhibited by the prenylated flavone derivative viz. papyriflavonol A with an IC₅₀ value of 3.7 μ M, exceeding the inhibitory potential of non-prenylated flavone derivatives viz. quercetin

and kaempferol (IC₅₀ of 8.6 μ M and 16.3 μ M, respectively). This signified the crucial role of the prenyl group in forming stronger hydrophobic interactions with the enzyme as well as the increase in the hydroxylation in the flavone backbone.^{22,23}

Anti-cancer Activity

The active compounds from *B. papyrifera* were found to be used for the treatment of human bladder cancer including drug-resistant forms and to establish a potential rationale for their clinical application. The cytotoxic effects of the compound were tested by analyzing cell proliferation, apoptosis, and autophagy where the results suggest that phytoconstituents induces cytotoxic effects in human bladder cancer cells, including the cisplatin-resistant T24R2. The compound may be a candidate for the development of effective anti-cancer drugs on human urinary bladder cancer.²⁴

Anti-nociceptive activity

Various parts of *B. papyrifera* were studied for its anti-nociceptive and anti-inflammatory activity by chemical-induced pain and inflammation in the rodent model.²⁵ All the parts of *B. papyrifera* viz., radix, leaf, and fruits effectively inhibit both writhing response induced by 1% acetic acid and late phase licking response caused by 1% formalin. It was observed that radix and fruits reduce the edema induced by 1% carrageenan at 1-2 hrs, also radix reduced the abdominal Evan's blue extravasations caused by inflammatory mediators including serotonin and sodium nitroprusside. This effect has been attributed due to the presence of one active ingredient, betulinic acid, which inhibited the paw edema caused by serotonin and carrageenan.²⁶

Anti-oxidant activity

Brousochalcone A (BCA), a prenylated chalcone was originally isolated from the cortex of *B. papyrifera* Vent and the cortex of this plant has been used as traditional medicine for decades.²⁷ BCA is a powerful natural anti-oxidant that may be primarily attributed due to its free radical-scavenging activity. Moreover, BCA was also found to suppress LPS-induced iNOS protein expression by preventing I κ B α degradation in RAW 264.7 macrophages. The free radical-scavenging activity of BCA and its inhibition of iNOS protein expression may have therapeutic potential because excessive free radicals and NO production have been associated with various inflammatory diseases.²⁸

Anti-bacterial Activity

Sohn *et al.* reported that a prenylated flavonol compound, Papyriflavonol A (Pap A) was isolated from the mulberry roots and evaluated its antimicrobial activity. The results revealed that the minimum inhibitory concentration (MIC) of Pap

A against *Candida albicans* and *Saccharomyces cerevisiae* were between 10 µg/mL and 25 µg/mL, and its anti-fungal activity was mediated by its ability to disrupt cell membrane integrity. In addition, Pap A had a lower toxic effect than amphotericin B. For the tested strains, the hemolysis ratio of human erythrocytes was less than 5%.²⁹ Geng *et al.* reported that flavonols in *B. papyrifera* showed significant *in vitro* anti-oral microbial activity.³⁰

Anti-proliferative Activity

Guo *et al.* isolated and purified few active compounds (papyriflavonol A, brousochalcone A, uralenol, brousoflavonol B, and 5,7,3',4'-tetrahydroxy-3-methoxy-8,5'-diprenylflavone) from EtOAc extract of mulberry bark where all of them showed significant anti-proliferative effects on ER-positive breast cancer MCF-7 cells *in vitro*. The phytochemicals; brousoflavonol B with $IC_{50} = 4.19 \mu M$ and 5,7,3',4'-tetrahydroxy-3-methoxy-8,5'-diprenylflavone with $IC_{50} = 4.41 \mu M$ were the most effective components than the positive control, icaritin. In an established human breast cancer BCAP-37 xenograft BALB/c nude mice model, brousochalcone A and brousoflavonol B were found to significantly reduce the tumor growth significantly at a concentration of 1 µM by reducing ERK phosphorylation. Western blot indicated that the compounds strongly downregulated the expression of estrogen receptor- α (ER- α).³¹

Anti-diabetic Activity

Ryu *et al.* isolated 12 polyphenols from the chloroform extract of the roots of *B. papyrifera*. Among them, papyriflavonol A ($IC_{50} = 2.1 \mu M$), deoxynojirimycin ($IC_{50} = 3.5 \mu M$), brousoflurenone A ($IC_{50} = 27.6 \mu M$), and brousoflurenone B ($IC_{50} = 33.3 \mu M$) have been identified as potential α -glucosidase inhibitors in comparison to the standard voglibose ($IC_{50} = 23.4 \mu M$). The activity was similar to sugar-derived α -glucosidase inhibitors.³²

Lou *et al.* reported broupapyrin A, a new isoprenylated flavonol isolated from the branches of *B. papyrifera* in exhibiting a significant inhibitory effect on the well-known anti-diabetic target enzyme PTP-1B with an IC_{50} value of $0.83 \pm 0.30 \mu M$.³³

Anti-gout Activity

Researchers found that brousochalcone A ($IC_{50} = 5.8 \mu M$) and 3,4-dihydroxyisolonchocarpin ($IC_{50} = 7.7 \mu M$) were the major contributors to the inhibition of xanthine oxidase. The compound brousochalcone A was identified as the most effective candidate.³⁴

Cytotoxic activity

Ran *et al.* reported the cytotoxic potentials (against HepG2 cell line) of the compounds (liriodendrin, (+)-pinorensinol-

4'-O- β -D-glucopyranosyl-4''-O- β -D-apiofuranoside, and apigenin-6-C- β -D-glycopyranside) that were isolated from the leaves with the IC_{50} values of 14.56 µg/mL, 19.53 µg/mL, and 17.19 µg/mL, respectively.³⁵

Zhang *et al.* isolated and reported a new compound altertoxin-IV together with nine known compounds from the ethyl acetate extract (through bioassay-guided fractionation) of a culture of the endophytic fungus *Alternaria species* G7 present in *B. papyrifera*. The compounds presented impressive cytotoxic activities against three cancer cell lines (MG-63, A549, and SMMC-7721), of which 3,4',5'-trihydroxy-5-methoxy-6H-benzo[c]chromen-6-one demonstrated noteworthy cytotoxic activity with IC_{50} values of 2.11 µg/mL, 1.47 µg/mL, and 7.34 µg/mL, respectively. The compound altersolanol A also presented a considerable cytotoxic activity against two cell lines; SMMC-7721 ($IC_{50} = 2.92 \mu g/mL$) and MG-63 ($IC_{50} = 0.53 \mu g/mL$).³⁶

CONCLUSION

This current fascinating article expansively emphasized 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 potentials, anti-inflammatory, anti-diabetic, anti-microbial, anti-nociceptive, anti-gout, and anti-proliferative) mediated by diverse parts (seed, root, leaf, stem, and fruit). This information will be reasonably functional for the passionate contemporary investigators of several areas (natural products, pharmacognosy, medicine, chemistry, botany, pharmacy, etc.) in developing miscellaneous essential formulations for treating numerous disorders. This study will pave a new way for modern nature-pharmacotherapeutics for human applications.

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Conflict of Interest

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

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Authors Contribution

Madhukar Vitthalrao Shende: Physically wrote the full manuscript.

Debarshi Kar Mahapatra: Performed the literature review, set references uniformly, drawn graphical abstract, and prepared the structured abstract.

Atul Arjun Baravkar: Proofread, did necessary changes/corrections, and provided suggestions.

Nilesh Ashokrao Nalawade: Removed plagiarized contents, corrected grammar, and attended all the revisions.

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GRAPHICAL ABSTRACT

Looking Ahead to Reviewing Some Pharmacologically Active Phytoconstituents Present in *Broussonetia papyrifera* (L.) Hert. ex Vent.

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