**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, anticancer, 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
- **Super-Division:** Spermatophytina
- **Class:** Magnoliopsida
- **Super-Order:** Rosanae
- **Order:** Rosales

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**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-nocioceptive, 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; (2S)-abysinone II; (2S)-naringenin; (2S)-7,4′-dihydroxyflavan; 2,4′,4″-tetrahydroxychalcone; 3,4′-threo-1-(4-hydroxyphenyl)glycerol; 4′-hydroxydihydroxyflavan; 2,4,2′,4′-tetrahydroxychalcone; 3,4-(+)-dihydrokaempferol; (+)-marmesin; (−)-marmesin; isogemichalcone C; ergosterol peroxide; erythro-1-(4-hydroxyphenyl)glycerol; flacourtin; ferulic acid; fucosterol; gancaoin P; graveolone; isobavachalcone; isogemichalcone C; isoloflavonol; 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; poliothyroside; protocatechuic acid; quercetin; resveratrol; sesquineolignan; squalene; sulforafin; 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-alpha, 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-nocioceptive 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 broussochalcone A, broussochalcone B, 4-hydroxyisolochocarpin, papyriflavonol A, 3′-(3-methylbut-2-enyl)-3′,4,7-trihydroxyflavane, kazinol...
A, kazinol B, broussoflavan A, kazinol F, and kazinol J, all isolated from 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 bladder cancer.

Guo et al. extracted and distilled several active compounds from EtOAc mulberry bark extract (papyriflavonol A, broussochalcone A, uralenol, broussoflavonol 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 phytoconstituents from B. papyrifera branches, was shown to have a significant inhibitory effect on the well-known anti-diabetic drug voglibose (IC50 = 23.4 M). Ryu et al. isolated 12 polyphenols from the chloroform extract of B. papyrifera stems. Papyriflavonol A (IC50 = 2.1 M), deoxyxojirimycin (IC50 = 3.5 M), broussoflurenone A (IC50 = 27.6 M), and brossoflurenone B (IC50 = 33.3 M) have all been reported as potential -glucosidase inhibitors, in addition to the standard voglibose (IC50 = 23.4 M). Inhibitors of sugar-derived glucosidase showed comparable effectiveness.

**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 bladder cancer.

**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, flavonol from B. papyrifera showed significant antihypertensive microbe action.

**Anti-diabetic Activity** [24]

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**Anti-gout Activity** [25]

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