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Paulownia as a Medicinal Tree: Traditional Uses and Current Advances

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Paulownia is one of the most useful and sought after trees, in China and elsewhere, due to its multipurpose status. Though not regarded as a regular medicinal plant species, various plant parts (leaves, flowers, fruits, wood, bark, roots and seeds) of *Paulownia* have been used for treating a variety of ailments and diseases. Each of these parts has been shown to contain one or more bioactive components, such as ursolic acid and matteucinol in the leaves; paulownin and d-sesamin in the wood/xylem; syringin and catalpinoside in the bark. The fruits contain fatty oils, alkaloids, flavonones as well as flavonoids with antioxidant properties. The flavonoid contents and TROLOX Equivalent Antioxidant Capacity (TEAC) value in fresh and dry leaf extracts of *Paulownia elongata* suggest that this species has potential for advanced medicinal use. *In vitro* grown *Paulownia fortunei* Hemsl. seedlings, inoculated with *Agrobacterium rhizogenes* have a potential to produce hairy roots and synthesize bioactive compounds such as acteosides (verbascosides). With various new studies describing isolation of therapeutic compounds and their probable application in human health, it is an opportune moment to revisit medicinal potential of this tree. In this review, the

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usage of *Paulownia* in traditional medicine has been revisited and current advances in various fields of research in the genus *Paulownia* are summarized.

Keywords: Paulownia; medicinal properties; chemical compositions; pharmacology.

1. INTRODUCTION

While several compounds derived from traditional medicinal plants have found way into modern medicinal practice through extensive research and drug development, there are number of plants with potential medicinal value that are still largely unexplored. *Paulownia* is a deciduous tree which is very well known for its wood quality, while its medicinal properties are just beginning to be realized. The genus *Paulownia*, belonging to monogeneric *Paulowniaceae* family, comprises of nine species: *P. albiphloea*, *P. australis*, *P. catalpifolia*, *P. elongata*, *P. fargesii*, *P. fortunei*, *P. kawakamii*, *P. taiwaniana*, and *P. tomentosa. Paulownia* species are widely distributed in various regions of China and some of the species have also been introduced and cultivated in many countries around the world for their ornamental and timber values [1,2]. *Paulownia* wood is light and flexible, but does not crack or deform easily and is known for its physical strength, texture (light to medium clay-sandy), grain, and color [1]. The wood has considerable moisture resistance and flame retardant properties [3]. Moreover, as a short rotation fast growing tree, *Paulownia* has already attracted attention as a potential bioenergy crop that can help in both carbon sequestration and in producing transportation fuel [4,5].

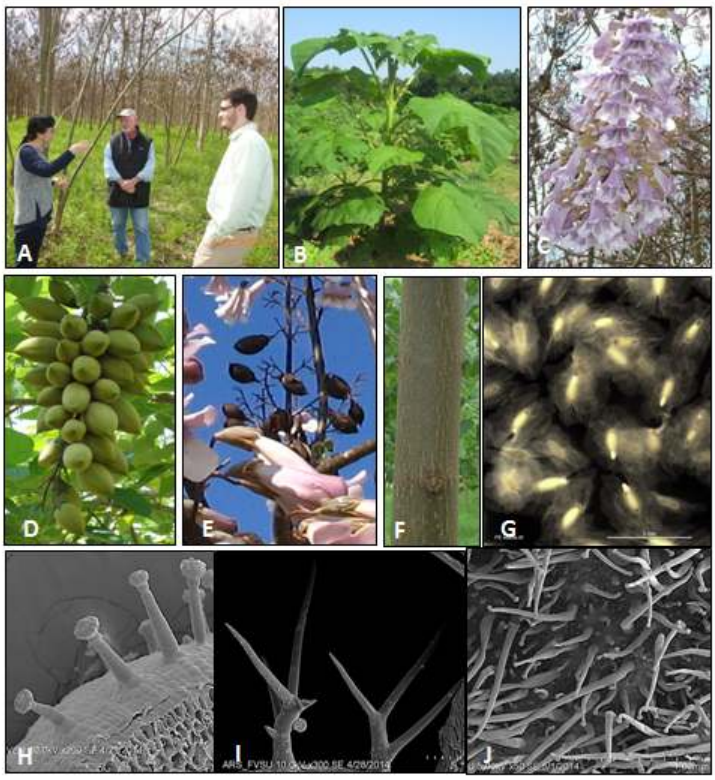

Fig. 1. Research at '*Paulownia* Demonstration Plot' at Fort Valley State University. A. Students interacting with a visitor in the *Paulownia* field, B. *Paulownia elongata* tree during first year with large foliage, C. Flowers in bloom; D and E. Green and mature dried fruits, F. A close up of bark, G. Seed germination of *Paulownia* in the laboratory conditions, H, I, and J. Scanning electron micrograph of glandular and non-glandular trichomes of *Paulownia* present on the leaf

Apart from its extensive use as a high-quality wood in the industrial and agricultural areas, *Paulownia* has also been used as an herbal medicine in traditional Chinese medicine (TCM). The "Compendium of *Materia Medica*" (a Chinese *Materia Medica* written by Li Shizhen in 1578) mentions *Paulownia* bark for the treatment of hemorrhoids and worms; and the flowers for reducing swelling as well as promoting hair growth [6]. Modern medical research has identified several potential applications for the genus *Paulownia* as an antibacterial, anti-inflammatory, thirst-quenching, diuretic, antihypertensive, hemostatic and insecticidal agent [7]. Insecticidal properties have been linked to chemicals synthesized in glandular trichomes predominantly dispersed on the surface of leaf, flower bud, and flowers [8].

Our research teams at Fort Valley State University and Wayne State University have several active ongoing research projects on *Paulownia* biology (Fig. 1). The various projects mainly focus on micropropagation [2,9]; studying potential as a bioenergy crop [4]; optimization of genetic transformation protocols for further improvement of the tree; reproductive biology; generation of bioenergy and novel bioplastics [10-12]; trichome biology; extraction and identification of valuable phytochemicals [13] and assessing their efficacy in disease models of cancer and obesity. Aerial parts of *Paulownia* tree possess a rich variety of secretory and non-secretory trichomes. Due to their specific glandular structures trichomes secrete, store, and release a wide variety of chemical substances; ranging from insect-attracting nectar or salts to highly specialized (secondary) metabolites. Thus, trichomes perform important biological functions such as discouraging herbivory, attracting pollinators (insects and birds), and maintaining a first line of defense. The biologically active specialized metabolites contained in trichomes could be further assessed for their therapeutic property.

In this mini review, we will briefly describe how traditional usage of *Paulownia* has transitioned into modern pre-clinical research. Though a substantial amount of research has been conducted in the biology of the plant, to the best of our knowledge this is first attempt to comprehensively assess the literature on the medicinal potential of this multipurpose tree. Recent studies using several active components derived from various tree parts of *Paulownia* in different disease models will be succinctly discussed.

2. PLANT PARTS AND THEIR MEDICINAL USE

Paulownia is one of the most exploited medicinal plants in terms of the plant parts that have been used in traditional medicine. In traditional Chinese medicine, the bark, fruit, xylem, and leaves of *P. tomentosa* var*. tomentosa* have been applied to treat or prevent a variety of diseases, such as hemorrhoid, carbuncle, inflammatory bronchitis, gonorrhea, upper respiratory tract infection, parotitis, asthma, traumatic bleeding, erysipelas, bacteriological diarrhea, swelling, bronchopneumonia, enteritis, conjunctivitis, hypertension, and tonsillitis [14,15]. The leaves, wood, and fruits of *P. tomentosa* have been traditionally used for the treatment of tonsillitis, bronchitis, asthmatic attack, and bacterial infections such as enteritis or dysentery. *Paulownia* may also have wound-healing properties, as the leaves have been used for the treatment of frostbite and leg ulcers [16]. Leaves, fruits, and flower are the most important plant parts employed in folk herbal medicine [14,17,18]. Folk remedies in China use mashed *Paulownia* flowers to treat acne vulgaris and the decoction to treat fungal infection on the sole of the foot and the skin between toes [19]. Flowers are also used in treatment of first to second-degree empyrosis [20].

In the following sub-sections, we will summarize some of the modern scientific research pertaining to the efficacy and mechanism of crude extracts or isolated phytochemicals in various *in vitro* as well as *in vivo* disease models.

2.1 Leaves (Fig. 1F)

Flavonoids isolated from *P. tomentosa* leaves have antiradical and cell protective effects [21] (Tables 1 and 2). Aqueous extracts of fresh *P. elongata* leaves and silage show *in vitro* antimicrobial activity against *Salmonella enterica, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pyogenes, Paenibacillus alvei,* and *Candida albicans.* The inhibitory effect is more pronounced against gram-negative bacteria [22]. The leaves from *P. tomentosa* (misidentified as *P. coreana*) contain isoatriplicolide tiglate (PCAC) that induced apoptosis in *in vitro* studies on cervical and breast cancer cell lines [23].

Table 1. A list of chemical compounds that have been isolated from different parts/tissues of various *Paulownia* species

#	Species	Plant part	Compound	Reference
1	*P. tomentosa*	Immature fruit surface	Nine geranylated flavanones: 6-geranyl-5,7-dihydroxy-3',4'-dimethoxyflavanone; 6-geranyl-3',5,7-trihydroxy-4'-methoxyflavanone; 6-geranyl-4',5,7-trihydroxy-3',5'-dimethoxyflavanone; 6-geranyl-4',5,5',7-tetrahydroxy-3'-methoxyflavanone; 6-geranyl-3,3',5,7-tetrahydroxy-4'-methoxyflavanone; 4',5,5',7-tetrahydroxy-6-[6-hydroxy-3,7-dimethyl-2(E),7-octadienyl]-3'-methoxyflavanone; 3,3',4',5,7-pentahydroxy-6-[6-hydroxy-3,7-dimethyl-2(E),7-octadienyl]flavanone; 3,3',4',5,7-pentahydroxy-6-[7-hydroxy-3,7-dimethyl-2(E)-octenyl]flavanone; 3,4',5,5',7-pentahydroxy-3'-methoxy-6-(3-methyl-2-butenyl)flavanone	Asai et al., 2008 [70]
2	*P. tomentosa*	Unripe fruit	Diplacone, Mimulone	Vochyánová et al., 2015 [71]
3	*P. tomentosa*	Fruit	Acteoside; Isoacteoside; Mimulone; Diplacone	Šmejkal et al., 2007 [72]
			Mimulone; Diplacone	Jiang et al., 2004 [73]
			Tomentomimulol; Mimulone B (*C*-geranylated flavonoids)	Schneiderová et al., 2012 [74]
			5,7-dihydroxy-6-geranylchromone; Acteoside; Isoaceteoside; 3'-O-Methyldiplacol; 3'-O-methyl-5'-methyldiplacone; 3'-O-methyl-5'-hydroxydiplacone; Taxifolin; 5,7,4'-trihydroxyflavanone; Tomentodiplacone; Tomentodiplacone B; Cisplatinum; Ara-C	Šmejkal et al., 2008 [64] Navrátilová et al., 2015 [42]
			Tomentodiplacol; 3'-O-methyl-5'-methoxydiplacol; 6-isopentenyl-3'-O-methyltaxifolin; dihydrotricin; 3'-O-Methyldiplacone	Šmejkal et al., 2007 [18]
			Acid; Fatty oil; Flavanon; Alkaloid	Ayan et al., 2003; Zhu et al., 1986 [1,46]
			C-6 geranylated flavanones	Šmejkal, 2013; Hanáková et al., 2015 [68,75]
4	*P. tomentosa*	Flower	Diplacone	Du et al., 2004 [76]
	P. tomentosa	Flower	Paulownin; Isopaulownin	Takahashi and Nakagawa, 1966 [77]
			Furanoquinone	Kang et al., 1999 [17]
			Apigenin; Methanol	Ji et al., 2015 [33]
			Glycerides	Kobayashi et al., 2008 [8]
			Abscisic acid; T-abscisic acid; Luteolin; Apigenin; Tricin; 4',5,7-trihydroxy-3'-methoxyflavone; Paulownin; 3'-methyldiplacol; Diplacone	Meng et al., 2014 [78]
		Essential oil of the flower	Geranyl Geraniol; Nonanal; Heptadecane; Nonadecane; Pentacosane; Hexatriacontane; 1-octen 3-ol; Cis-methyl isoeugenol; Anethole; Neryl acetone; Stearyl aldehyde; Nerolidol	Ibrahim et al., 2013 [34]
5	*P. tomentosa*	Hop	Naringenin	Šmejkal, 2013 [75]
6	*P. tomentosa*	Bark	Apigenin	Si et al., 2009 [79]
			Syringin; Catalpinoside	Ayan et al., 2003; Zhu et al., 1986 [1,80]
7	*P. tomentosa*	Leaf	Ursolic acid; Matteucinol	

8	*P. tomentosa*	Xylem	Paulownin; D-Sesamin	
		Leaf	Glycerides	Kobayashi et al., 2008 [8]
			Flavonoids	Zima et al., 2010; Šmejkal et al., 2007 [18,21]
9	*P. tomentosa*	Extract	Ursolic acid; Oleanolic acid	Liu et al., 2007 [81]
			Paulownioside	Plouvier, 1947; Adriani et al., 1981 [82,83]
			Tomentoside; 7-hydroxytomentoside	Damtoft and Jensen, 1993 [84]
	P. tomentosa	Extract	(+)-Piperitol; Daphneside	Ina et al., 1987 [85]
			Phenylethanoid glycosides *Campneosid I*	Radev, 2010 [52]
10	*P. tomentosa* var. *tomentosa*	Bark	Eight phenolic compounds: glucodistylin, luteolin, ellagic acid, cistanoside F, campneoside II, isocampneoside II, verbascoside, and isoverbascoside	Si et al., 2013 [47]
			Nine phenolic extractives: two flavonoids (naringenin, and quercetin), two phenolic acids (cinnamic acid, and gallic acid), and five phenylpropanoid glycosides (cistanoside F, acteoside, isoacteoside, campneoside II, and isocampneoside II	Si et al.,2011 [86]
11	*Paulownia imperialis*	Extract	Azulene; Bisabolols; Apigenin; Glycosides; Flavonoids; Uvzymes^{tm}	Campo Res., 2013 [87]
12	*P. imperialis; P. fortunei*	Extract	Chlorophyll a; Chlorophyll b; β-Carotene; Violaxanthin; Proline	Ayala-Astorga et al., 2010 [88]
13	*P. tomentosa*	Fruits	*C*-geranyl flavonoid: Mimuline	An et al., 2014 [43]
	P. tomentosa	Extract	*C*-geranylated flavanone: Tomentodiplacone B (TOM B)	Kollár et al., 2011 [61]
	P. coreana	Leaf	Isoatriplicolide Tiglate (PCAC)	Jung et al., 2012 [23]
14	*Paulownia* sp.	Wood	Cellulose; Hemicellulos Pentozan; Lingin	El-Showk and El-Showk, 2003 [89]
		Xylem	Paulownin and d-sesamin	Zhu et al., 1986 [1]
		Seed	Sterols and tocopherols	Angelova-Romova et al., 2011 [48]
		Bark and leaf	Glycoside	Kazi et al., 1931 [49]
	Paulownia sp.	Extract	Iridoid glycosides; Phenyl- propanoid; Lignin glycosides; Flavonoids; Sesquiterpene; Triterpenes	Cao et al., 2008 [51]
			Syringin	

Table 2. A comprehensive list of ailments for which various plant parts of *Paulownia* species have been used

#	Species	Plant parts	Used for	Reference
1	*Paulownia tomentosa*	Stem bark	Gonorrhea and erysipelas	Kang et al., 1999 [17]
2	*P. tomentosa*	Fruit, leaf and wood	Bronchitis	Zhu et al., 1986 [1]
3	*P. tomentosa*	Fruit and leaf	Hair regeneration and scalp stimulant	
			Tonsillitis, bronchitis, asthmatic attack, and bacterial infections such as enteritis or dysentery	Kang et al., 1999; Jiang et al., 2004; Šmejkal et al., 2007 [14,17,18]
4	*P. tomentosa*	Leaf	Antiradical and cell protective effects	Zima et al., 2010; Šmejkal et al., 2007 [18,21]
5	*P. tomentosa*	Fruit	Airway inflammation	Chen et al., 2007 [90]
			Antioxidant activity	Zima et al., 2010 [21]
			Inhibitory activity against bacteria and yeast	Šmejkal, 2007 [18]
			Antibacterial and antileishmanial activity	Navrátilová et al., 2015 [42]
		Fruit	Anti-inflammatory and antiphlogistic potential	Hanáková et al., 2015 [68]
		Fruit (unripe)	Reduction of symptoms of colitis in male Wistar rats	Vochyánova et al., 2015 [71]
		Fruit	Hypotensive effect	Duke et al., 1985 [91]
		Wood	Bacterial infection	
6	*P. tomentosa*	Flower	Anti-viral activity against EV71 and CAV 16 - caused hand, foot and mouth disease	Ji et al., 2015 [33]
			Antioxidant activity	Meng et al., 2014 [78]
			Antimicrobial activity; Antibacterial activity	Ibrahim et al., 2013 [34]
			Against Acne vulgaris	Guo et al., 2011 [19]
			First to second-degree empyrosis	Luo et al., 2010 [20]
	P. tomentosa	Flower	Hypotensive, anti-inflammatory, antispasmodic, anti-oxidant and vasorelaxant activities; Anti-tumorigenic effect in vitro as well as in vivo	Loizzo et al., 2007; Gerritsen et al., 1995; Ko et al., 2004; Capasso et al., 1991; Cos et al., 1998; Zhang et al., 2000; Czyz et al., 2005; Parajuli et al, 2009 [24-31]
			Bacterial inhibitor	Wei et al., 2006 [32]
			Neuroprotective effects	Kim et al., 2010 [38]
7	*P. elongata*	Leaf	Antimicrobial activity	Popova and Baykov, 2013 [22]
			Decreasing erythrocyte and leukocyte counts; Reducing blood glucose	Varlyakov et al., 2013 [23]
8	*P. fortunei*	Seed	Diabetes and its complications	Kim et al., 2011 [38]

9	*P. tomentosa* var. *tomentosa*	Bark	Antioxidant activity	Jiang, 2003; Si et al., 2013 [14,48]
		Bark, fruit, xylem, and leaf	Hemorrhoid; Carbuncle; Inflammatory bronchitis; Gonorrhea; Upper respiratory tract infection; Parotitis; Asthma; Traumatic bleeding; Erysipelas; Bacteriological diarrhea; Swelling; Bronchopneumonia; Enteritis; Conjunctivitis; Hypertension; Tonsillitis	Jiang, 2003; Jiangsu New Medical College, 1977 [14,15]
			Anti-inflammatory and analgesic properties; Boosting immunity; Lowering blood glucose	Li et al., 2007 [68]
	P. coreana	Leaf	Anticancer activity against breast and cervical cancer cell lines	Jung et al., 2012 [47]
	P. tomentosa	Fruits	Anticancer activity against human lung adenocarcinoma cells	An et al., 2014 [44]
	P. tomentosa	Extract	Anti-inflammatory	Hošek *at al*., 2010 [94]
	P. tomentosa	Extract	Anticancer agent	Kollár et al., 2011 [63]
10	*Paulownia* sp.	Leaf and flower	Fertilizer; Fodder	Rahman et al., 2013 [95]
		Leaf	Frostbite; Leg ulcers	Zhao, 2003 [16]
	Paulownia sp.	Flower	Bronchial asthma	Zhang et al., 2002 [36]
	Paulownia sp.	Flower	Asthmatic trachea inflammation;	Chen and Li, 2007 [35]
		Bark	Hemorrhoids; Insecticide; Swelling; Hair growth induction;	The Editorial Committee of Flora of China, 1979 [6]
11	*Paulownia* sp.	Extract	Antibacterial; Anti-inflammatory; Thirst-quenching; Diuretic; Antihypertensive; Hemostatic, Insecticidal effects	Qu et al., 2011 [7]
			Hemostasis	Cao et al., 2008 [53]
			Tinea pedis	Guo et al., 2011 [19]
		Fruit	Inhibitory activity against gram-positive bacteria	Si et al., 2009 [81]
		Bark	Wild bee stings	Zhao, 2003 [16]

Varlyakov et al. [24] tested the influence of the intake of *P. elongata* leaves on blood parameters of three yearling sheep, Stara Zagora x Pleven Blackhead crosses. Their results revealed a significant decrease in erythrocyte and leukocyte counts which was most pronounced in the postprandial hours. In addition, their study showed that the leaves of *P. elongata* possess ability to significantly reduce blood glucose concentration.

Fresh and dried methanolic leaf extracts of *P. elongata* and *P. fortunei* show significant level of antioxidant activities [9]. *P. fortunei* leaves (both fresh and dry) show higher values in total polyphenol content averaging 250 mg/g GAE compared to *P. elongata* (75 mg/g GAE). The flavonoid content in *P. fortunei* leaf extract was also higher than that in *P. elongata*. Moreover, the TEAC (TROLOX equivalent antioxidant capacity) assay of the leaf extracts revealed that *P. fortunei* has higher average TEAC value (2000 µmol/g) for both fresh and dry methanolic extracts compared to the *P. elongata* leaf extracts (average of 1375 µmol/g) [9].

2.2 Flowers (Fig. 1B)

Among various parts of *Paulownia* tree, the flowers seem to be the most used plant part with multiple usages in folk herbal medicine [14,17]. Extracts of *P. tomentosa* flowers have been of particular research interest due to the presence of flavonoids, specifically Apigenin. Apigenin has been shown to have hypotensive [25], anti-inflammatory [26], antispasmodic [27], antioxidant [28], and vasorelaxant [29] properties. Additionally, apigenin has been reported to exert its anti-tumorigenic effect *in vitro* as well as *in vivo* not only via the inhibition of tumor cell proliferation, but also via the impairment of the invasive potential of tumor cells [30,31].

Paulownia flower extracts inhibit the growth of certain bacteria; the strongest effect was seen on *Staphylococcus aureus*, whereas the effect on *Aspergillus niger*, *Saccharomyces cerevisiae,* and *Penicillium chrysogenum* were not so significant [32]. Methanol extracts from dried flowers of *P. tomentosa* have shown potential antiviral activity against enterovirus 71 (EV 71) and Coxsackie virus A16 (CAV 16), - the two main pathogens causing hand, foot and mouth disease (HFMD) [33]. Ibrahim et al., [34] reported broad spectrum antimicrobial activity of the essential oils derived from *P. tomentosa* flowers against *Bacillus subtilis* NRRL B-543*,* *Staphylococcus aureus* NRRL B-313, and *Escherichia coli* NRRL B-210.

The flavonoids extracted from *Paulownia* flowers have been shown to suppress asthmatic trachea inflammation, while the essential oil from the flowers also alleviated the allergic airway inflammation in mice [35]. Similarly, *Paulownia* flower extract showed potential efficacy against bronchial asthma in *Cavia porcellus* [36].

The sesquiterpene derivatives of *P. tomentosa* flowers may exert neuroprotective effects by inhibiting glutamate toxicity [37].

2.3 Fruits (Figs. 1C and 1D)

It has been noted that certain compounds of *Paulownia* fruits may have high inhibitory activity against *Staphylococcus epidermidis*, a pathogenic gram-positive bacteria [38]. A study reported that the *P. tomentosa* fruits can be a feasible source of natural antioxidant substances [21]. Purification of the methanol extract of *P. tomentosa* fruits yielded potent acetylcholinesterase (hAChE) and butyrylcholinestrase (BChE) inhibitory flavonoids which have been linked to amelioration of Alzheimer's symptoms in addition to being a rich source of various geranylated flavonoids [39]. The antibacterial activity of compounds tomentodiplacone C (1), tomentodiplacone D (2), tomentodiplacone E (3), tomentodiplacone G (5), mimulone C (8), mimulone D (9), tomentodiplacone B (11), diplacone (12), 3'-*O*-methyl-5'-hydroxydiplacone (13), 3'-*O*-methyl-5'-*O*-methyldiplacone (14), mimulone (15), and 3'-*O*-methyldiplacol (16) against different Methicillin-resistant *Staphylococcus aureus* (MRSA) stains have been reported [40-42]. Several geranylated flavonoids from methanolic extract of *P. tomentosa* fruits show remarkable inhibitory activity against SARS viral protease because of an unusual 3, 4-dihydro-2H-pyran motif, which targets the cysteine residues on the RNA virus's replicase protein: the papain-like protease [39]. Moreover, anti-microbial activity of six geranylated flavonoids derived from *P. tomentosa* fruits and their synergistic activity with conventional antibiotics have also been reported [42]. Mimulone, a *C*-geranyl flavonoid, isolated from the *P. tomentosa* fruits has been shown to induce autophagy in human lung cancer cell lines through p53-mediated regulation of AMPK/mTOR signaling, leading to apoptotic death of the tumor cells [43]. It was discovered that the fruits of

*P. tomentosa (*misidentified as *P. coreana)* contain eleostearic acid, fatty oil, flavonoids and alkaloids [44].

2.4 Wood and Bark (Fig. 1F)

Paulownia wood serves for making paper pulp, musical instruments, furniture, and is also used in construction [45,46]. Although the xylem contains paulownin and d-sesamin [1], the actual medicinal usage of the wood has barely been reported. In *P. tomentosa* (misidentified as *P. coreana*)*,* constituents of syringin, paulownin and eleostearic acid have been identified from stems and roots and these compounds contribute to the diverse medicinal uses [45].

Apart from traditional usage in hemorrhoids or to kill worms, as mentioned above, reports on the medicinal usage of the bark is also quite rare. There is one report on its usage for the treatment of wild bee stings [16], while the antioxidant activity of extracts from *P. tomentosa* var. *tomentosa* bark has also been demonstrated [14,47] that might lead to medicinal applications. The latter study showed that isocampneoside II plays a critical role in neuroprotection by acting as a free radical scavenger and antioxidant.

2.5 Root

Roots have been used to treat chronic retrograde inflammation of the shoulder joint capsule and surrounding ligaments, muscles, tendons and bursa mucosa, also known as scapulohumeral periarthritis in medical terms [16].

2.6 Seed (Fig. 1E)

Acetone extract of *P. tomentosa* (misidentified as *P. coreana*) seeds have been used in treating diabetic complications. One study showed that the isolated active compound, phenylethanoid glycoside isocampneoside II, acts to inhibit aldose reductase and prevents the polyol pathway from proceeding [44]. *Paulownia* seeds can also be used as a non-traditional material for the production of oil which is rich in bioactive compounds such as sterols and tocopherols for nutritive purposes [48].

3. MEDICINAL COMPOUNDS REPORTED FROM VARIOUS *Paulownia* species

The study of chemical constituents on the genus *Paulownia* started in the early 1930s. Japanese researchers were the first to work on this field. In 1931, glycoside compounds from the *Paulownia* bark and leaves were isolated [49]. The following sections briefly discuss research on select active components derived from *Paulownia*.

3.1 Glycosides

Glycosides are a large and very significant class of carbohydrate derivatives that are characterized by replacement of the anomeric hydroxyl group by some other substituent [50]. With the advancement in chromatographic methods and modern spectroscopic techniques, studies on natural products from the genus *Paulownia* continue to reveal new compounds. The most notable ones are iridoid glycosides, phenyl-propanoid, lignin glycosides, flavonoids, sesquiterpene, and triterpenes. Many of these compounds have been proven to contain a certain degree of bioactivity [51]. Phenylethanoid derivatives which are incorporated by ether or ester bond to iridoid glycosides have recently been isolated [52]. Phenylethanoid glycosides Campneosid I extracted from *P. tomentosa* have a high biological activity. Campneosid I was found to have significant antibacterial activity against several pathogenic strains of *Streptococcus* and *Staphylococcus* including *S. aureus* [53].

3.2 Syringin

Lignin analysis of *Paulownia* wood exhibited presence of the bioactive compound called syringin [54]. Syringin is a phenylpropanoid glycoside pertaining to eleutheroside derivative. The pharmacological properties of syringin include free radicals scavenging, neuronal cell damage prevention, apoptosis inhibition, anti-diabetic effect, anti-inflammatory potential, anti-nociceptive effect, and anti-allergic actions [55]. In addition, *Paulownia* has been reported to have insect-resistant, neuroprotective, antioxidant, and hemostatic effects [51].

3.3 Flavonoids

Flavonoids comprise a large group of hydroxylated polyphenolic compounds having a benzo-γ-pyrone structure and are commonly found in plants. They are synthesized by the phenylpropanoid pathway. Secondary metabolites of phenolic nature including flavonoids are synthesized in response to various stress conditions and are responsible for a variety of pharmacological activities (Table 1 and 2) [56-58]. The four main groups of flavonoids

are flavones, flavanones, catechins, and anthocyanins [59]. The geranylated flavanone from *P. tomentosa* was shown to inhibit levels of nitrite oxide in LPS stimulated rat macrophages [60]. On the other hand, specific geranylated flavanone tomentodiplacone B (TOM B) inhibited the proliferation of human moncytic leukemia cells [61].

Naringenin chalcone in plants is the precursor of benzene propane made by flavonoid biosynthetic pathway. This was elegantly demonstrated via fermentative production of chalcone by *Escherichia coli* carrying an artificially assembled gene clusters for phenylpropanoid pathways [62]. It showed that in plants the biosynthetic pathway was almost entirely established based on the heterologous microorganism for the production of flavanones from the amino acid precursors, phenylalanine, and tyrosine [62]. Phenylalanine deamination occurs when it yields cinnamic acid by the action of phenylalanine ammonia-lyase (PAL) which is also considered as the first step in the phenylpropanoid pathway in plants. Cinnamic acid is hydroxylated by cinnamate-4-hydroxylase (C4H) to p-coumaric acid, and then by the action of 4-coumarate: coenzyme A (CoA) ligase, it is then activated to p-coumaroyl-CoA. Chalcone synthase (CHS) catalyze the stepwise condensation of three acetate units from malonyl-CoA with p-coumaroyl-CoA to yield naringenin chalcone. Naringenin chalcone is transferred to naringenin by chalcone isomerase (CHI) or nonenzymatically *in vitro* [63].

Staphylococcus aureus, *S. pyogenes*, and *S. faecium* are inhibited by campneoside-I isolated from the genus *Paulownia* [64]. Eight *C*-6-geranylflavonoids were isolated from an ethanol extract of *P. tomentosa* fruits and their inhibitory activities against seven bacteria and yeast have been reported [65]. Based on the experimental studies on pharmacological action of paulownin, it has been revealed that the compound has significant health benefits including anti-inflammatory and analgesic properties, boosting immunity, and lowering blood glucose; and has little toxicity [66].

Dai et al. [67] have recently reported on the identification of six flavonoids (apigenin, quercetin, apigenin-7-O-β-d-glucoside, quercetin-3-O-β-d-glucoside, 3'-methoxyluteolin-7-O-β-d-glucoside, and tricin-7-O-β-d-glucopyranoside) in rat plasma after oral administration of *P. tomentosa* flower extract. Another recent study has identified twenty-three different C-Geranylated Flavanones from *P. tomentosa* fruits, out of which at least five had anti-inflammatory activity potentially influencing the NF-κB signaling pathway [68], specifically by inhibiting the expression of TNF-α mRNAs.

As discussed earlier, the extracts of *P. tomentosa* flowers have been of particular research interest due to the presence of flavonoids, specifically apigenin. It is worth mentioning that apigenin, a naturally occurring plant flavone, has been shown to have significant anti-inflammatory, antioxidant and anti-carcinogenic properties. In the past few years tremendous progress has been made in the study of biological effects of apigenin on both cellular and molecular levels. Apigenin has considerable potential for development as a cancer chemopreventive agent, although human clinical trials testing the efficacy of supplementation of apigenin as a cancer chemopreventive agent have not been performed [69].

4. CONCLUSION

Plants present an enormous reservoir of bioactive compounds that can be used to prevent or treat various ailments. *Paulownia* has a long history of use in traditional Chinese medicine and there are many reports on isolation and analysis of its bioactive compounds. Various extracts and active compounds derived from *Paulownia* have an assortment of pharmacological actives with potential clinical usage. Currently, there has been a renewed interest in the study of *Paulownia* for its phytochemical composition, pharmacological effects and potential clinical applications. Although the chemical constituents and medicinal uses of the genus *Paulownia* could be quite diverse, the studies so far have focused mostly on the *P. tomentosa* species, while the other species are less explored. Similarly, studies on the medicinal properties of *Paulownia* have been confined to the extracts from flowers and fruits, whereas the wood, bark, and roots have not been studied well. Although *Paulownia* extracts contain phytochemicals that are also found in other medicinal plants, what could set *Paulownia* apart from others is the relative abundance of geranylated flavanones in its extracts, compared to that in other common medicinal herbs. Geranylated flavanones appear to have much higher potency compared to non-modified counterparts, probably because of their higher lipophilicity and increased affinity for biological membranes. Although studies have

identified several bioactive phytochemicals and have associated them with various health benefits, there is still a lack of scientific studies demonstrating the actual mechanism of action against the diseases. Moreover, studies on anti-microbial and anti-cancer activities of *Paulownia* extracts are so far limited to *in vitro* studies using primary cultures or cell lines, though Wistar rats have been successfully used as a model of colitis to test *Paulownia* derived compounds. With the application of new technologies and methods, relevant studies on all plant parts and all species of *Paulownia* will continue to reveal its potent phytochemical content. More scientific studies using *in vivo* disease models are warranted to elucidate the medicinal properties and underlying mechanisms of *Paulownia*.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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