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The Application of *Impatiens balsamina* L. and Its Advance Drug Delivery System-Nanoparticles Based: A Comprehensive Review

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Abstract: The water henna plant (*Impatiens balsamina* L.) is a plant species that belongs to the Impatiens genus in the Balsaminaceae family, and it grows widely in South Asia and Southeast Asia. This review discusses traditional uses, phytochemical compounds, nutritional content, pharmacological activity, and development of conventional dosage forms to advanced dosage forms of *I. balsamina* L. Research on pharmacological activities such as infection treatment, antioxidant, immunomodulator, wound healing, antidiabetic, anticancer, antihelmintic and larvicidal, antiallergic, antifibrosis, anti-inflammatory, and antinociceptive, antihyperlipidemic, and antipruritic is in line with the traditional use of this plant in various countries. The content of phytochemical compounds in each part of this plant is quite varied and produces diverse pharmacological activities. Traditional use and the development of advanced dosage forms are some of the promising things about the *I. balsamina* plant in the health sector. However, To obtain optimal benefits from the water henna plant, the harvest time and selection of the right plant parts must be applied, and more research levels of safety of advanced dosage forms, especially those based on nanotechnology, are needed.

Keywords: *Impatiens balsamina* L.; phytochemical compounds; pharmacological activities; traditional uses; advance development.

1. Introduction

Impatiens balsamina L. (*I. balsamina* L.), or what is known as the water henna plant, and has the local name in Indonesia pacar air is a plant that originates from South Asia and Southeast Asia. The water henna plant has thick, non-woody stems with a height of around one meter. The flowers of the water henna plant can be white, red, purple, or pink. In Indonesia, *I. balsamina* L. is widespread in the Pontianak and Bengkulu areas [1]. *I. balsamina* L. is often used by the people of Bengkulu as a wound healer and external infection in the Riau area [2]. Apart from its traditional use, the water henna plant has also been widely studied as an antimicrobial, antipruritic, antitumor, antioxidant, antidiabetic, antihelminthic, antihistamine, antifibrosis, anti-inflammatory, antinociceptive, antihyperlipidemic, wound healer, enzyme inhibitor and immunomodulator, especially immunosuppressant [3-5].

The pharmacological effects of *I. balsamina* L. are caused by secondary metabolite compounds contained in this plant. The secondary metabolite groups contained in water henna plants include flavonoids, saponins, quinones, phenolic acids, nitrogens, coumarins, and other

groups of compounds [6-11]. Besides the secondary metabolites, water henna plants also have primary metabolites such as carbohydrates, amino acids, and proteins [9]. The content of phytochemical compounds in each part of the *I. balsamina* L. plant is quite varied, and it produces various pharmacological effects depending on the phytochemical compounds of this plant, the components used, and the extraction method.

Traditionally, this plant is used to treat various diseases such as bacterial and fungal infections [12], cough medicine with phlegm, skin inflammation, healing burns [9], and to treat sunburn [13]. In its development, several studies have made conventional dosage forms such as creams and gels contain *I. balsamina* L. extract, used to treat bacterial infections that cause various health problems. In more modern research, the water henna plant has also been developed as an antibacterial preparation in the form of nanoemulgel as well as N, Cl Codoped Carbon and a wound healer in the form of Au nanoparticles [14].

Nanoparticles are a kind of technology that makes it possible to manipulate the structure of a compound into nano shapes and sizes, which range from 1-100 nm. One application of nanotechnology in the health sector is called nanomedicine. Nanomedicine can be found in drug delivery, diagnosis, and imaging systems. Nanotechnology has been widely developed in drug delivery systems, especially in treating cardiovascular disease, cancer, musculoskeletal conditions, psychiatric and neurodegenerative diseases, virus infections, bacterial infections, and diabetes [15]. Therefore, in this journal review article, the discussion will be about the content of metabolite compounds in the water henna plant, its traditional uses, the pharmacological effects that are proven in more modern research, and the potential for its development into a pharmaceutical preparation in the form of nanomedicine.

2. Traditional use of *Impatiens Balsamina* L

In Asia, water henna-(*I. balsamina* L.) is widely used as a traditional medicine. Known by the local name "Keembung" in Malaysia, *I. balsamina* L. leaves are used to treat split nails by applying them topically. Apart from that, the herbal part of this plant is also used to treat hypertension by administering decoc orally [16]. In some parts of India, this plant is useful in treating joint pain and is used to remove warts. Crushed leaves are used to treat skin inflammation, and a combination of salt and castor oil is used to treat warts around the fingers and toes that are blistered. In addition, a decoction of the roots is used to treat irregular menstruation. The plant's roots also treat skin inflammation and sore nails. The seeds of this plant are used as an expectorant. The flowers of this plant have mucous properties and are used as a tonic that provides a cooling effect when applied to burns [9]. With its application in cosmetics, *I. balsamina* L. flowers are also processed into henna in this country [17].

Indonesia is another Asian country that widely uses water henna plants for traditional healing. This plant is used as a wound-healing medicine in several provinces, such as West Kalimantan and Bengkulu. This traditional use has also been further studied in terms of histological pathology and has the potential to treat external wounds [1]. The high flavonoid and phenol content in parts of the plant *I. balsamina* L., which also grows widely in Riau province, Sumatera, makes this plant a potential source of pharmacological natural ingredients [2]. In China, *I. balsamina* L. is grown for medicinal purposes [18]. Traditionally, a decoction of the water henna plant is used to treat systemic bacterial and fungal infections. In addition, it is used topically in plaster form to treat local infections [12]. Thai people also use the aerial parts of *I. balsamina* L. to treat abscesses, thorn or glass puncture wounds, in-grown nails, and chronic wounds caused by allergic reactions [3].

In Turkey's Eregli (Zonguldak) and Karabuk regions, the *I. balsamina* L. plant is traditionally used in the health sector. The herbs from this plant are widely used in the treatment of sunburn. Freshwater henna plants are crushed with garlic and salt and then rubbed onto the skin where the hair has been removed first [13].

3. Phytochemical compounds and pharmacological effect of *Impatiens balsamina* L

3.1. Phytochemical compounds of I. Balsamina L.

I. balsamina L. is known to contain several active chemical compounds (Table 1) that are beneficial for the body, including compounds in the naphthoquinone group, namely lawsone, lawsone methyl ether, and methylene-3,3'-bi-lawsone 8, 19, 20]. Apart from that, *I. balsamina* L. also contains quercetin, kaempferol, p-hydroxybenzoic acid, p-coumaric acid, uronic acid, flavone glycosides, phenolic compounds, oleanane triterpenoid glycosides, tannins, and saponins [6-11]. In other research, new compounds from the naphthoquinones group were also discovered, namely 1a, 2a-diol-4a-ethoxy-1,2,3,4-tetrahydronaphthalene and 1a, 2a, 4b-triol-1,2,3,4-tetrahydronaphthalene [21].

Table 1. Active substance content in *I. balsamina* L.

Compound family	Common name	Compound name	Plant part	References
Flavonoids	Kaempferol 3,7-digluocoside	5-Hydroxy-2-(4-hydroxyphenyl)-7-[(2S,4S,5S)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one	Flower	[22]
	Kaempferol	3,5,7-trihydroxy-2-(4-hydroxyphenyl)chromen-4-one	Whole plant	[6-11]
	Myricetin	3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl)chromen-4-one	Flower	[23]
	Isoquercertin	2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one	Whole plant	[10]
		Derivatives of 3,5,7-trihydroxy-2-(4-hydroxyphenyl) chromen-4-one	Whole plant	[10]
	Quercetin	2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy chromen-4-one	Whole plant	[9-10]
Saponins		Balsaminside A, B, C, and D	Flower	[22]
Nitrogen Compounds	Balsamitril	2-[(3S)-3-hydroxy-2-oxo-1-benzofuran-3-yl]acetonitrile	White flower	[10]
	Balsamitril-3-O-β-D-glucoside	Balsamitril-3-O-β-D-glucoside	White flower	[10]
Quinones	Tetrahydronapthalene	1a, 2a-diol-4a-ethoxy-1, 2, 3, 4-tetrahydronaphthalene	Stem	[21]
		1a, 2a, 4b-triol-1, 2, 3, 4-tetrahydronaphthalene	Stem	[21]
	2-Methoxy-1,4-Naphthoquinone	2-Methoxynaphthalene-1,4-dione or O-Methyllawsone	Whole plant	[8-10, 19-20]
		Lawsone methyl ether	Leaf	[20]
		Methylene-3,3'-bi-lawsone	Leaf	[20]
		Balsaminone B, D, and E	Flower	[10]
Phenolic acids	Protocatechuic acid	3,4-Dihydroxybenzoic acid	White flower	[10]
	Methylparaben 3-Hydroxycinnamic	Methyl 4-hydroxybenzoate (E)-3-(3-Hydroxyphenyl)prop-2-enoic	White flower	[10]
	Vanillic acid	4-Hydroxy-3-methoxy benzoic acid	White flower	[10]
	p-hydroxybenzoic acid	4-Hydroxybenzoic acid	White flower, stem, root	[9-10, 19]
	Gentisic acid	DHB Asam 5-hidroksisalisilat	Whole plant	[19]
	Ferulic acid	(2E)-3-(4-hidroksi-3-metoksifenil)asam prop-2-enoat	Whole plant	[19]
	P-coumaric acid	4-hydroxy namyc acid	Stem, root	[9,19]

Compound family	Common name	Compound name	Plant part	References
	Sinapic acid	(2E)-3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-enoic acid	Whole plant	[19]
Coumarins	Scopoletin	7-hydroxy-6-methoxy-2H-1-benzopyran-2-one	Whole plant	[8,19]
Other compounds	Tyrosol	4-(2-Hydroxyethyl)phenol	White flower	[10]
	Viloxanthine	2-O-(4-Hydroxybenzoyl)-4-O-β-D-glucopyranosyl-6-hydroxyphenyl acetic acid	Flower	[10]
		(3S, 4R)-3,4-dihydroxy-3,4-dihydronaphthalen-1(2H)-one	White flower	[10]
		trans-(3S, 4R)-3,4-dihydroxy-1-tetralone	White flower	[10]
		β-d-Glucopyranosiduronic acid, (3β)-norolean-3-yl-O-β-d-glucopyranosyl- (1 → 2)-O-[β-d-xylopyranosyl-(1 → 4)]	Flower	[10]
		3-O-β-D-Xylopyranosyl-(1 → 2)-β-D-glucopyranosyl-28-O-β-D-glucopyranosyl oleanolic acid	Flower	[10]
		α-D-Glucopyranosyl-(1 → 1′)-3′-amino-3′-deoxy-β-d-glucopyranoside	Flower	[10]
		6-O-(E)-p-Hydroxy-cinnamoyl-β-d-glucose	Flower	[10]
		6-O-(E)-p-Hydroxy-cinnamoyl-α-d-glucose	Flower	[10]
		1,2-O-(4-Dihydroxybenzoyl)-2,4,6-trihydroxy phenylacetic acid	Flower	[10]
		2-O-(4-Hydroxybenzoyl)-4-O-β-d-glucopyranosyl-6-hydroxyphenyl acetic acid	Flower	[22]
		2-O-(4-Hydroxybenzoyl)-4-O-β-d-glucopyranosyl-6-hydroxyphenyl acetic acid	Flower	[22]
		4-O-β-d-Glucopyranosyl-2,6-dihydroxyphenylacetic acid	Flower	[22]

3.2. Nutritional constituent.

Various nutritional constituents are also found in the water henna plant (I. balsamina L.) (Table 2). The nutritional content of water henna plants includes polysaccharides, proteins, amino acids, lipids, carbohydrates, vitamins, and others. Each part of the water henna plant contains different nutrients.

Table 2. Nutritional constituent in *I. balsamina* L.

Plant part or product used	Nutritional constituents	References
Leaf	Carbohydrates, amino acids, protein	[9,24]
Stem	Carbohydrates, amino acids, protein	[9]
Root	Sugar, Uronic Acid, Carbohydrates, protein, Amino acid	[11,25]
Flower	Lipids, Sugar, Carbohydrates, Vitamin C, Protein, Ash	[26]
Seed	Carbohydrates, protein	[24,27]

3.3. Pharmacological activities of I. balsamina L.

3.3.1. Antibacterial and antifungal.

The water henna plant has been widely studied for its antibacterial and antifungal properties. *I. balsamina* L. is effective as an antibacterial because it contains terpenoids, polyphenols, kaempferol, quercetin, and anthraquinone compounds [28,30]. Inayah *et al.* (2022) reported that purple hexane flower extract with a concentration of 4 mg/mL had the best

percent inhibitory activity against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* with respective inhibitory activity values of 10.8 ± 0.9 mm, 9.1 ± 0.2 mm, and 20.8 ± 0.9 mm [28]. Antimicrobial testing of henna stem extract against 10 microbial strains consisting of *P. italicum, P. digitatum, A. niger, A. oryzae, S. cerevisia Hansen, Candida utilitis, B. subtilis, S. aureus Rosenbach, E. coli,* and *S. boydii*. The test results show that the petroleum ether extract of water henna stems has strong activity with a broad spectrum as an antifungal with MIC value of 250 – 1000 µg/mL. Meanwhile, diethyl ether extract [31] from water henna stems has quite strong activity as an antibacterial with a MIC value of 500 – 1000 µg/mL [29].

The ethanol extract of *I. balsamina* L. has been proven to have antibacterial activity against several gram-positive bacteria, especially *Candida albicans* MIC value of 2.5 – 10 mg/mL and *Candida perfrigens* MIC value of 4 mg/mL. This is due to the presence of quinone, polyphenol, tannin, and terpenoid compounds, which can inhibit bacterial growth [6, 32-33]. The antifungal ability of the methanol extract of *I. balsamina* L. leaves against *R.oryzae* has also been observed. At an extract concentration of 0.896% w/v, it was able to inhibit fungal growth by 50%. The naphthaquinone content is known to be responsible for this antifungal activity [34]. Apart from the flowers, stems, and leaves, the seeds of the water henna plant have also been proven to be effective as an antibacterial. Water henna seed extract has antibacterial activity because it has been proven to contain alkaloids, flavonoids, tannins, and saponins [27,31]. Manikandan *et al.* (2016) proposed that water hexane seed extract was able to inhibit the growth of *S. aureus, E. coli, K. pneumonia, and S. marcescens* with MICs of 25 mg/mL, 50 mg/mL, 75 mg/mL, and 100 mg/mL [27]. Apart from secondary metabolite compounds, peptide compounds in the water henna plant seeds have been proven effective as antifungals. Thevissen *et al.* (2005) isolated four peptides of the Ib-AMP group from the seeds of the water henna plant. Ib-AMP is a peptide containing 5 – 6 arginine residues and 4 cysteine residues originating from disulfide bonds. The research results explain that the Ib-AMP4 compound has the best antifungal activity with an IC_{50} value of 1.2 – 4 µM. In research, it is stated that the antifungal activity of the Ib-AMP compound is influenced by pH; the antifungal activity will decrease with the increased pH [31].

Apart from the compounds already mentioned, the antibacterial and antifungal activity of the water henna plant is also caused by the naphthoquinone compound's content in Or Lawson's compound [12,35]. Lawson's compound is active on 12 bacterial strains, including gram-positive and negative bacteria. The results showed that 7 of the 12 bacteria tested proved to be sensitive to Lawson's compound at a concentration of 30 µg/mL. From these results, testing was continued using 7 sensitive bacterial strains to determine the MIC value. The MIC value obtained from the test results is in the range of 2 – 64 µg/mL. In addition, Yang *et al.* (2001) carried out antifungal testing on 8 strains of fungi that often cause disease in humans. The research results showed that Lawson's compound was proven to be more effective as an antifungal when compared to amphotericin B for all 8 fungal strains except *C. albicans* al-2 with a MIC value of 0.31 – 2.5 µg/mL [12].

Sakunphueak & Panichayupakarananta (2012) compared three Lawson compounds: lawsone, lawsone methyl ether, and methylene-3,3'-bi-lawsone as antifungal and antibacterial. The lawsone methyl ether compound is a strong antifungal that is able to inhibit fungal dermatophytes, including *T. rubrum, T. mentagrophytes*, and *M. gypseum,* with a MIC value of 3.9 – 7.8 µg/mL. Meanwhile, Lawson and methylene-3,3'-bi-lawsone compounds have quite low antifungal effectiveness against dermatophytes, with MIC values of 62.5 – 250 µg/mL and 500 µg/mL, respectively. As an antibacterial compound, lawsone methyl ether has strong

activity in inhibiting gram-positive and negative bacteria with a MIC value of 23.4 – 93.8 µg/mL. In this research, not only were aerobic bacteria able to be inhibited by the compound lawsone methyl ether; anaerobic bacteria such as *H. pylori, S. mutans, and P. acnes* were also proven to be inhibited by this compound [35].

The activity of the Lawson compound as an antibacterial is able to specifically inhibit the growth of *Helicobacter pylori* with an MIC value of 0.156 – 0.625 micrograms/mL [36-37]. Other research also states that the secondary metabolite content of the leaves of the water henna plant has been proven to be able to significantly inhibit the growth of *P. aerugenosa* with a MIC value of 3,125 mg/mL[38].

3.3.2. Antioxidant and antityrosinase.

The *in vitro* antioxidant activity of ethanolic extracts from whole plants of three species of Impatiens (*I. balsamina, I. hawkeri*, and *I. walleriana*) was evaluated using the radical trapping activity of 2,2-diphenyl-1-picrylhydrazyl (DPPH), potassium ferricyanide-reducing antioxidant ability (PFRAP) and oxygen radical absorbance capacity (ORAC). The antioxidant activity values of the three plant species were respectively in the range of 0.1-0.44mg/mL in the DPPH method, 26.97-98.49 µmol TE/g in the PFRAP method, and 784.35-1528.13 µmol TE/g g on the ORAC method. This value is in the same concentration range as extracts with high antioxidant activity. The content of phenolic compounds is known to be responsible for providing antioxidant activity [6]. Research on the antioxidant activity of water-soluble polysaccharide fractions from the roots and aerial parts of four other Impatiens species (*I. glandulifera Royle, I. parviflora DC., I. balsamina* L., and *I. noli-tangere* L.) was tested by DPPH and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonate) (ABTS) methods. The highest DPPH and ABTS trapping abilities were found in extracts of aerial parts of *I. balsamina* L. with EC_{50} values of 0.24 mg/mL and 0.32 mg/mL [11].

Extracts (ethanol, methanol, and acetone) of the aerial parts of the water henna plant containing phenolic and flavonoid compounds have been observed for their antioxidant activity using the DPPH method. Extracts of various types show different patterns of antioxidant activity. The flower extract showed the highest activity in all types of solvents, followed by the leaf extract and then the stem extract in DPPH (more than 80%). Apart from that, flower extracts are also able to inhibit tyrosinase activity by chelating copper in the active site, which causes enzyme inactivation [3].

The methanol extracts of the leaves and stems of *I. balsamina* L. were separately observed for their activity using DPPH, ABTS, Iron chelating, and FRAP tests. The IC_{50} values produced by the methanol extract of leaves and stems, respectively, were (0.282, 0.284, 0.604, 0.705) mg/mL and (0.380, 0.358, 0.994, 0.856) mg/mL in the DPPH, ABTS, Iron chelating, and FRAP [39]. In other research, there were significant differences in antioxidant capacity between samples at different harvest times. Respectively, the average FRSA value produced in the ethanol extract of water henna stems and leaves was 12.93 mg/mL and 67.32 mg/mL, where there was an increase in the FRSA value of 5.2 times along with the delay in harvest time. This causes differences in the total phenolic and flavonoid content, influencing antioxidant properties produced [33].

Essential oils from herbs and roots of species Impatiens plants containing most of the compounds linalool, hexanal, and benzaldehyde were evaluated to determine antioxidant capacity using the DPPH method. Anti-radical activity of herbal oils of *I. glandulifera* (3.96 ±

0.03µg/mL), *I. noli-tangere* (4.76 ± 0.05 µg/mL), *I. balsamina* L. (16.14 96 ± 0, 68 µg/mL). Meanwhile, the EC_{50} value of ascorbic acid is 2.06 ± 0.01 µg/mL [40].

The antioxidant activity of the ethanol extract of *I. balsamina* L. seeds was observed *in vitro* using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical trap method. An IC_{50} value of 320 µg/mL was found in DPPH free radical trapping activity. This shows an almost identical value compared to the standard Ascorbic Acid, which has an IC_{50} of 310 µg/mL [41].

3.3.3. Anticancer.

The methanol extract of the water henna plant has anticancer properties, as proven by the increase in the production of t-bid protein in cancer cells. The t-bid protein is a precursor for the synthesis of AMPK compounds, namely compounds that play an important role in regulating cell apoptosis. In research conducted by Shin and Kwon (2015), exposure to 60 µg/mL methanol extract for 24 hours was able to reduce the viability of HSC-2 human oral cancer cells. The methanol extract of the water henna plant was proven to be able to significantly inhibit several proteins that inhibit the formation of AMPK, namely p mTOR and p p70S6 kinase. It was able to inhibit p p38 or p ERK, although not significantly. Apart from that, the methanol extract of the water henna plant was able to increase the t-bid protein, although not significantly [42].

One of the compounds that play an important role in anticancer activity is triterpenoid glycoside compounds, namely imbaloside A, imbaloside B, and imbaloside C. These three triterpenoid glycoside compounds were tested for their effectiveness as an anticancer against four cancer cells, namely A549, SK-OV-3, SK- MEL-2, and BT549. The imbaloside B compound was proven to inhibit the growth of BT549 cancer cells with an IC_{50} value of 26.4 µM. Meanwhile, the imbaloside C compound was proven to inhibit the growth of A549 and BT549 cancer cells with IC_{50} values of 29.8 µM and 29.2 µM [43]. In addition, 20 µg/mL and 40 µg/mL methanol extracts were also proven to significantly inhibit the growth and stimulate apoptosis of carcinoma cancer cells by reducing Akt expression [44].

Ethyl acetate extract from the semen of the water henna plant was proven to inhibit the proliferation and apoptosis of prostate cancer cells via the AKT/ERK pathway with the strongest inhibitory dose, namely 40-80 µg/mL [45]. Previous research discovered that the compound responsible for being antitumor was 2-methoxy-1,4-naphtoquinone or what is more commonly referred to as Lawson's compound. Lawson's compound is able to inhibit hepatocellular carcinoma (HepG2) cells with an IC_{50} value of 6.47 ± 0.05 mg/mL [46]. The mechanism of anticancer action of the MNQ compound against lung cancer cells is to stimulate the generation of ROS, which causes oxidative DNA damage and activates the JNK and p38MAPK signaling pathways. In research conducted by Ong *et al.* (2015), Lawson's compound was able to significantly inhibit the growth of lung cancer cells (A549) at a concentration of 10 µM after exposure for 24 hours [47]. The anticancer activity of Lawson's compound has been proven to be able to prevent the growth of breast cancer cells, especially breast cancer cells that do not have 3 general receptors, namely HER 2, ER, and PR. Lawson's compound with an IC_{50} of 29 µM has been proven to significantly inhibit glucose uptake in cancer cells so that cancer cells cannot carry out cellular metabolic processes [48].

3.3.4. Antipruritic and antidermatitis.

Lawson and kaempferol are the compounds responsible for acting as antifoulants in the water henna plant. In a study conducted by Oku and Ishiguro, 35% ethanol of white flower petals was proven to treat and prevent dermatitis in NC strain mice. NC strain mice were acclimatized in a clean room with a temperature of 22 – 24°C and humidity of 60 ± 5%. After that, the mice were placed in a polysulphonic cage and given Kimtowel bedding. Scratching behavior in mice was observed, as well as the presence or absence of redness (hemorrhage) in the areas around the ears, cheeks, and back of the neck. NC mice that were given ethanol extract of the white flower of the water henna plant at 100 mg/kg body weight experienced a significant reduction in scratching habits compared to negative controls. Apart from that, giving 100 mg/kg BW of mice ethanol extract of the white flower of the water henna plant also reduced the percentage of dermatitis compared to the negative control [49].

Further research stated that apart from Lawson's compound, there are compounds isolated from the corolla of *I. balsamina* L., namely Impatienolate and Balsaminolate, which are sodium salts of 1,4-naphthoquinone. Based on test results using the COX Inhibitor Screening Assay Kit, both compounds are reported to have activity in reducing swelling (which is one of the symptoms of dermatitis). The IC_{50} values of 1 and 2 against COX-2 were 0.2 µM and 9.4 µM [50]. In other research, it was proven that *I. balsamina* L. extract containing Lawson compounds reduced itchy dermatitis rashes caused by exposure to poison ivy in humans. Research conducted by Motz *et al.* (2012) was aimed at looking at the effectiveness of antidermatitis due to exposure to poison ivy in 15 human subjects with an age range of 18 – 65 years. The antidermatitis effectiveness was compared between whole simpilicia, water extract of *I. balsamina* L., and soap preparations containing *I. balsamina* L. extract. The study results showed that fresh Simplicia *I. balsamina* L. was proven to reduce redness by 50% compared to the control. Meanwhile, the water extract of *I. balsamina* L. was only able to reduce redness on the subjects' hands by 28.5% compared to the control group. The best results were obtained in soap preparations containing 150 mL of *I. balsamina* L. water extract with a redness percentage of 33%. [51].

3.3.5. Antidiabetic.

The antidiabetic activity of the hydroalcoholic extract of *I. balsamina* L. roots *in vitro* was observed using the alpha-amylase inhibitory activity method. The IC_{50} value of the extract is 0.316 mg/mL. Meanwhile, as a comparison, the IC_{50} value of acarbose is 0.206 mg/mL. The compounds that play a role are mainly flavonoids and anthraquinone glycosides [25]. Several compounds isolated from *I. balsamina* L. flowers showed antidiabetic activity. The highest activity in one of the compounds was identified as having an IC_{50} value of 0.72 µg/mL, whereas acarbose, as a comparison, showed an IC_{50} value of 3.36 µg/mL [52]. In another study, the antidiabetic activity of the ethanol extract of *I. balsamina* L. seeds was also observed using a similar method. The highest activity was observed at a seed ethanol extract concentration of 500 µg/mL [41].

3.3.6. Antihelmintics and larvacides.

The hydroalcoholic extract of henna root (*I. balsamina* L.) at a concentration of 50 mg/mL was observed for its ability to cause paralysis and death of Pheretima posthuma worms using the Adult Motilit Assay (AMA) method. At this concentration, paralysis was observed

in the worms at 8 minutes ± 0.707 and death at 11 minutes ± 0.235. Meanwhile, albendazole, used as a comparison, showed paralysis of the worms at 0.5 ± 0.009 minutes and death at 1 ± 0.004 minutes. Tannin and phenolic compounds are known to play a role in this activity [25]. Water henna seed oil at concentrations of 10 and 50 mg/mL caused paralysis of the Pheretima Posthuma worm at 24 ± 0.12 and 18 ± 0.12 minutes, more than 90 minutes to cause the worm's death. Meanwhile, a concentration of 100 mg/mL was observed to cause paralysis and death at 13 ± 0.13 and 62 ± 0.12 minutes respectively [53].

Extracts from various solvents (crude benzene, chloroform, ethyl acetate, and methanol) of water henna leaves were observed for their ability to kill larvae (larvicidal). Observations of larval death were carried out after 24 hours of treatment. The highest larvicidal activity was observed in the methanol extract of *I. balsamina* L. leaves against *An. Stephensi, Ae. aegypti, and Cx. quinquefasciatus* with LC_{50} and LC_{90} values 98.04; 119.68, 125.06 and 172.93, 210.14, 220.60 mg/L respectively [54].

3.3.7. Antihistamines.

The antihistamine effect of the white petals of the henna plant extracted using 35% ethanol as a solvent was observed using the Passive cutaneous anaphylaxis (PCA) reaction method in mice induced by hen egg-white lysozyme (HEL). It was observed that the flower extract of the water henna plant was able to provide significant anti-anaphylactic effects at local doses > 0.01 mg/kg BW of rats and was able to prevent symptoms and fatal anaphylactic shock at a dose of 256 mg/kg BW of rats injected intravenously [55]. Using blood pressure monitoring in ddY mice given exogenous histamine where histamine is the main mediator of allergic hypotension. In the same extract, the anti-anaphylactic effect of the ethanol extract of white petal I balsamine was shown to be different from that of diphenhydramine (DPH), which is a typical H1 blocker [56]. However, water henna plant flower extract can incompletely inhibit the first stage of hypotension caused by histamine. The compounds responsible for this activity are characterized as kaempferol 3-glucoside, kaempferol 3-rutinoside, kaempferol 3 rhamnosyl glucoside, quercetin, quercetin 3-glucoside and 2-hydroxy 1,4-naphthoquinone [57].

3.3.8. Antifibrosis.

The anti-hepatic fibrosis activity of the saponin triterpenoid compound from henna plant extract was tested using the t-HSC/Cl-6 cell proliferation inhibition method. From the research results, it can be concluded that *I. balsamina* L. extract is able to reduce the proliferation of t-HSC/Cl-6 cells with an IC_{50} value of 13.9 micromolar [22]. Further research was carried out on the compounds 9S-(1- methoxycarbonyl 4,5-di hydroxy)phenyl furano naphthoquinone and 2-methoxy-10 -hydroxy-30 -methoxy[3,20 -binaphthalene]-1,4- dione which are derivatives new from the 1,4-naphthoquinone group compound. The research results showed that both compounds were able to potently inhibit the proliferation of t-HSC/Cl-6 cells with IC_{50} values of 30.54 and 40.67 µg/mL, respectively [23,52].

3.3.9. Antinociceptive.

The antinociceptive effect of water henna plants was tested on the ethanol extract of water henna flowers using several methods, namely acetic acid induction, hot plate test, tail immersion test, formalin test, hole cross test, and open field test *in vivo* on Swiss albino mice. The acetic acid and formalin induction test aims to determine the antinociceptive effect on pain

stimulation by chemical compounds and peripheral nerves. In the acetic acid induction test, ethanol extract of water henna flowers with a concentration of 100 mg/kg BW of mice was proven to have the same effectiveness in inhibiting abdominal construction as 10 mg/kg BW of rats of diclofenac sodium. Meanwhile, in the formalin test, the ethanol extract of henna flowers, water, 400 mg/kg BW, mice had the best percent inhibition of licking in the late phase compared to the control group [58].

The hot plate and tail immersion tests are intended to determine the antinociceptive effect of heat stimulation. The hot plate test found that 200 mg/kg BW of mice with ethanol extract of water henna flowers could significantly increase the reaction time to heat compared to the control group. Meanwhile, in the tail immersion test, ethanol extract of water henna flowers 100 mg/kg BW of mice was able to increase the latency time to hot water. Overall, test results show that the ethanol extract of *I. balsamina* L. provides significant peripheral and central antinociceptive effects by inhibiting COX, LOX, and other inflammatory mediators. In addition, several compounds in the ethanol extract of *I. balsamina* L. are able to bind to the μ-opioid receptor and inhibit the activity of adenylyl cyclase [58].

3.3.10. Anti-inflammatory.

The anti-inflammatory activity of ethanol and water extracts from the roots and stems of *I. balsamina* L. was evaluated using the edema method on the soles of the feet induced with carrageenan in albino Wistar rats. The ethanol extract of *I. balsamina* L. roots at a dose of 50mg/kg administered orally was observed to show the highest anti-inflammatory activity [59]. The sodium salt compound 1,4-naphthoquinones isolated from water henna flowers has significant inhibitory activity against cyclooxygenase-2 (COX-2), which triggers inflammation, as observed with the COX Inhibitor Screening Assay Kit. The inhibitory effect of the compound is shown by an IC_{50} value of 0.2 μM, which is also the same as the IC_{50} value of NS-398 (selective COX-2 inhibitor) [50]. In another study, the anti-inflammatory activity of the ethanol extract of *I. balsamina* L. seeds was also observed using the bovine serum albumin (BSA) denaturation assay method. The extract also showed excellent anti-inflammatory activity, with the IC_{50} values of the standard and extract being 196 μg/mL and 210 μg/mL, respectively [41]. The anti-inflammatory activity of the aqueous extract of *I. balsamina* L. leaves was also carried out by Ningthoujam and Soibam (2022). The Tests were carried out using a Cotton pellet implantation, Granuloma pouch, and formaldehyde arthritis method in albino rats method at three concentrations (500mg, 1,000mg, 2,000mg)/kg. Using the Cotton pellet implantation and Granuloma pouch methods showed inhibition of granuloma formation and inhibition of exudate formation by 8.79%, 29.13%, 44.83%, and 36.34%, 50%, 68.3% with a p-value <0.001% at the three concentrations used respectively. Apart from that, this water extract also significantly inhibited formaldehyde-induced swelling in rats' feet ($p<0.05$-0.001) [60].

3.3.11. Antihyperlipidemia.

The methanol extract of water henna leaves was observed for its antihyperlipid activity in Sprague Dawley rats with induced hypercholesterolemia. At a dose of 400mg/kg BW of mice, the methanol extract of henna leaves reduced total LDL-cholesterol and increased HDL-cholesterol in mice. The resulting hypolipidemic activity was correlated with the presence of flavonoids in the methanol extract of henna leaves [61].

3.3.12. Wound healing.

The activity of 96% ethanol extract of *I. balsamina* leaves on wound healing was observed. The results of observing the area of the wound, which is represented as an AUC value, indicate total healing activity. The extract dose of 10.5 mg/mL provided the best wound healing effectiveness because it produced a significant difference in AUC values compared to the normal, negative, and povidone-iodine groups. It is known that flavonoid compounds, tannins, and quinones play a role in accelerating wound healing [1].

3.3.13. Immunomodulator.

The immunomodulatory effect of the water henna plant was carried out *in vivo* on Balb/C albino mice induced by red blood sheep and ink B17. The test results showed that in 125 mg/kg BW of mice, the ethyl acetate fraction of the water henna plant reduced B cell activity, equivalent to the activity of methylprednisolone 15 mg/kg BW of mice. In tests using B17 induction ink, the ethyl acetate fraction of water henna plants 125 mg/kg BW of mice was proven to be able to reduce the phagocytic index value by 0.86 compared to the negative control which had a phagocytic index of 1. The ethyl acetate fraction of water henna plants was also proven to reduce the index value. Liver and spleen organs were compared to negative controls, indicating inhibitory activity on mice's lymphocyte cell proliferation[3].

4. The Developed conventional form

Several conventional dosage forms containing active compounds from the *I.balsamina* L. plant have been developed. In general, this dosage form is more widely used in delivering traditional medicines to produce antibacterial pharmacological effects. Lengkoan *et al*. (2017) have developed a gel containing henna flower extract as a hand antiseptic. The gel produces a good inhibitory effect on the growth of one type of bacteria, *S. aureus*, at a water henna ethyl acetate extract concentration of 10% and 15% [62]. A similar dosage form was also developed by Ismarani *et al*. (2014). At a concentration of 15% methanol extract of water henna leaves and stems, the resulting gel was able to provide inhibition of the growth of S. epidermidis and P. acnes bacteria of 17.13 mm ± 0. 44 mm and 16.13 mm ± 0.35 mm respectively in the best formulation [63].

Another dosage form that has also been developed is a cream containing methanol extract of *I. balsamina* L. stems and leaves. Its antibacterial activity was tested using the disc diffusion method, producing an inhibitory power against *P. acnes* of 8.37 mm ± 2,205 mm to 17.42 mm ± 3,029 mm at an extract concentration of 10-20% in the formulation [64]. The effectiveness of the methanol extract of *I. balsamina* L. leaves as an antibacterial was also tested in cream preparations. In the same extract concentration range, the resulting inhibitory power against the growth of *P. acnes* and *S. epidermidis* bacteria was (9.93 ± 2.458 to 16.96 ± 0.682) mm and (11.28 ± 22.676 to 21.10 ± 0.492) mm using the Kirby-Bauer disc diffusion method [65].

5. Advanced drug delivery system-nanoparticles based on *Impatiens balsamina* L

An advanced drug delivery system is fast, sustainable, and efficient. Nanomedicine is one application of an advanced drug delivery system based on nanotechnology in the health sector [15]. In general, nanomedicine produces high treatment target selectivity, can be used as

a carrier for active ingredients to promote tissue repair and regeneration [66], reduces toxicity, increases efficacy [67and increases active substance compounds' solubility. Which is lipophilic, increases drug absorption in the body, and improves its pharmacokinetic properties [68]. Nanomedicine allows drug compounds to enter body cells because their size ranges from 1 – 100 nm. The types of nanomedicine used in the pharmaceutical industry can be micelles, liposomes, dendrimers, carbon nanotubes, metallic nanoparticles, or quantum dots [15].

Several natural drug delivery systems from the plant *I. balsamina* L. have been developed. This delivery system has been tested to determine the pharmacological effects produced and compared with controls. The following are nanotechnology-based dosage forms that have been made, summarized in Table 3.

Table 3. Pharmacological effect of *I. balsamina* L. nanotechnology-based drug delivery system.

Natural Products	Form of Drug Delivery System	Test Model	Result on control	Pharmacological Effects	Ref
I. balsamina L.'s leaf extract	Nanoemulgel	Antibacterial Mueller-Hinton agar (MHA) against *S.epidermidis* bacteria	Shows the existence of an inhibition zone measuring 6 mm	Increased bacterial inhibition zone measuring 22 mm. Indicates the level of significance compared to the control group ($p < 0.05$)	[69]
I. balsamina. L' stem extract	N,Cl-Codoped Carbon Dots	Antibacterial tryptone soy broth (TSB) agar plates against 6 species of gram-positive bacteria.	MIC values of *S. aureus*, *E. faecium*, *B. subtilis* (2, 1.2, 2.4) $mg.mL^{-1}$ respectively	Increased inhibitory effect against gram-positive bacteria. MIC values of *S. aureus*, *E. faecium*, *B. subtilis* (0.08, 0.2, 0.16) $mg.mL^{-1}$ respectively	[14]
Extract of *I. balsamina* L plant	Au Nanoparticles	Excision wound model and thermal wound model in Swiss albino mice	The control group took 12 days and 3 weeks for healing and epithelializatio n of the excision wound In the thermal injury model, the healing time was 3 weeks	Maximum healing and epithelialization time are approximately 9 days and 2 weeks. In the group of animals treated with AuNPs, the degree of injury contraction was much lower ($p < 0.05$) compared with the control group of animals. 100% thermal wound healing time is 13 days.	[70]
I. balsamina L.'s flower extract	Ag Nanoparticles	Anticancer test *In Vitro* (U937, COLO205, B16F10, HepG2, HeLa) cell	The positive control group produced a higher level of cytotoxicity against cells	Strong cell anti-proliferative activity with lower cytotoxicity	[71]
I. balsamina L's flower extract and Tagetes *erecta* L.'s extract	Nanoparticle extract incorporated in cream	*In Vitro* antioxidant test with 2,2-Diphenyl-1-picrylhydrazyl (DPPH)	No testing was done on the controls	At a concentration of 1% *I. balsamina* L. red flower extract in the form of nanoparticles, the antioxidant activity reached 92.26%	[72]
Lawsone methyl ether isolated from *I. balsamina* L.	Chitosan-Dextran Sulfate Nanoparticles	*In Vitro* release test	Demonstrates less controlled release of Lawsone methyl ether (relatively high release at the beginning)	Release occurs slowly and continuously of Lawsone methyl ether	[73]

The monotherapy approach developed from the plant extract of *I. balsamina* L. shows an increase in the pharmacological activities tested. The nanoemulgel in research [69] is a combination of nanoemulsion incorporated into a hydrogel base [74], where the nanoemulsion

itself has advantages, including high drug-loading capacity, solubilization capacity, and ease of production, has good stability and release control [68]. Nanoemulgel has been proven to have better penetration into the skin [74], thereby enabling increased drug delivery and resulting pharmacological activity.

The water henna plant extract enhances the pharmacological activities of nanoparticle formulation, also observed in research by Liu *et al.* (2021) by carrying out delivery modifications in the form of nanomedicine Carbon dots (CDs), which is one of the innovative nanoparticle delivery because CDs are able to provide green fluorescence and when combined with ingredients nature which has the potential to act as an antibacterial and as a precursor [14]. The delivery system in the form of Gold nanoparticles (Au Nps) extract from *I. balsamina* L. showed similar results. This modification has advantages as a medical carrier because it is biocompatible, hydrophilicity, non-immunogenic, and low toxicity. Gold nanoparticles are also highly uptaken by body cells; this allows for increased pharmacological activity [75].

Similar to the use of Au Nps, the Ag Nps delivery system was also developed and widely applied in cancer drug delivery because it is able to reduce side effects and increase the efficiency of cancer therapy [76] by increasing solubility, stability, and biodistribution [77]. The research of Panichayupakarant *et al*. (2013), which developed Chitosan-Dextran Sulfate Nanoparticles (CDNP), also showed an increase in the properties of the active ingredient isolated from the water henna plant, which would influence the resulting pharmacological activity [73]. CDNP is formed due to electrostatic interactions between chitosan and dextran sulfate. The components that make up CDNP are chitosan, which is biocompatible, non-toxic, and biodegradable [73], and dextran sulfate, which is a polymer that is easily degraded, making this form of delivery widely used in the pharmaceutical field [78].

6. Future perspective of *Impatiens balsamina* L. for delivering natural products into pharmacologycal effect

The large number of pharmacological activities produced by the *I. balsamina* L. plant with traditional and advanced processing gives this species the potential for further development. By modifying the delivery system, several developments have shown increased pharmacological activity produced by the secondary metabolite compounds contained therein, such as quercetin, phenolics, and coumarin. These activities include antibacterial and wound healing [14, 69, 70].

Several studies have proven that developing nanoparticle dosage forms can increase the effectiveness and absorptivity of active compounds, both from natural and synthetic substances. One example is increasing GI uptake of the quercetin compound encapsulated using nanoemulsion. The nanoemulsion carrier in the quercetin compound is also able to protect quercetin from degradation or metabolism in the body [79]. The nanoemulsion delivery system also enhances antioxidant activity and tyrosinase enzyme inhibition activity of kepok banana (*Musa* sp.) extract [80]. Furthermore, it is known that many nanoparticle products containing natural ingredients such as honey, plant herbs, and even animal fat have been developed to treat various types of wounds [81]. In other research, it was stated that phenol compounds had a much better level of effectiveness in fighting lung cancer when encapsulated into nanocarriers. Phenolic compounds encapsulated in nanocarriers can increase lung cancer cell apoptosis by 45% when compared to pure phenolic compounds (20%) [82]. Other research has proven that coumarin compounds encapsulated in solid lipid nanoparticle suspension (SLN suspension) can increase antimicrobial effectiveness against *Staphylococcus aureus* bacteria

with a MIC value of 3.92 µg/mL for coumarin powder to 1.08 µg/mL for SLN coumarin suspension. In addition, compared with single coumarin, the antibacterial onset time of coumarin in SLN suspension is much faster, around 8 hours after administration [83]. The three active compounds whose activity increased in research [79, 82, 83] are active compounds shown in many other studies as compounds responsible for various pharmacological activities of water henna plants.

Based on data showing increased pharmacological activity with modifications to the carrier system, strategies like this can be used to increase other activities, as discussed above. Further studies should be designed in this area to improve treatment efficiency in the future. The advantages of nanotechnology-based delivery systems that can be used as natural product carriers to increase the pharmacological activity of I. *balsamina* L. are illustrated in Figure 1.

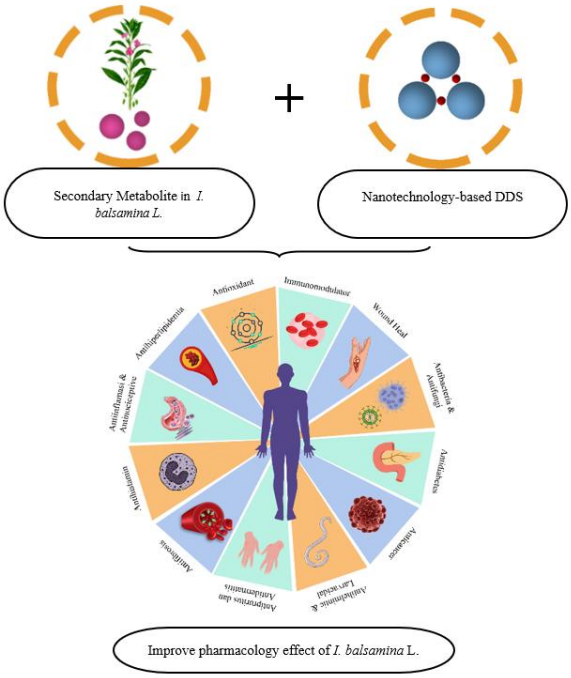

Figure 1. The advantages of nanotechnology-based drug delivery systems for delivering natural products to produce pharmacological effects.

Based on the best observations regarding investigations into *I. balsamina* L. nanotechnology, no studies have been observed that conclude there are safety data and undesirable effects. Future further studies need to be designed and added clearly. This draft safety data includes dose, particle size, toxicity, etc.

8. Conclusions

I. balsamina L. is a plant growing widely in Asia with many phytochemical compounds and nutrients. The main phytochemical compounds contained therein are phenolics, flavonoids, and quinones. Every part and compound contained in this plant has benefits for humans, both with simple processing and with advanced methods. The harvest time and selection of the right plant parts must be applied to obtain optimal benefits from the water henna plant. Nanotechnology-based modifications can also be used to increase the pharmacological activity of water henna plants. The absence of safety testing and undesirable effects in Advanced drug delivery system-nanoparticle processing need to be considered in the future.

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Conflicts of Interest

The authors declare no conflict of interest.

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