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Review Article

Ethnobotany, Pharmacology and Major Bioactive Metabolites from *Impatiens* Genus Plants and their Related Applications

Fabián Vinicio Delgado-Rodríguez*, Nien Tzu Weng-Huang, Arlene Loría Gutiérrez, David Arias-Núñez, Christopher Rosales-Leiva

Instituto de Investigaciones Farmacéuticas (INIFAR), College of Pharmacy, University of Costa Rica, San Pedro de Montes de Oca, San José, COSTA RICA.

ABSTRACT

Impatiens genus comprises several species important for agriculture and food industries, ethnobotany, and research in pharmacology, phytochemistry, biotechnology and pharmaceutical sciences. In this paper, a systematic review of ethnobotanical uses, bioactivities discovered, and research applications reported for *Impatiens* plants and their major bioactive constituents are presented aiming to provide an integrative comprehension of relevance of the genus in the mentioned fields and to give guidance for the further research of unexplored or poorly investigated species of this genus. Through this review, an update on this expanding area of research is also provided. According to revisited information, most of bioactive compounds are phenolics, phytosterols, triterpenoids, and peptides. There is a wide spectrum of applications investigated for *Impatiens* plants extracts and their bioactive metabolites, however, in most cases, they are related to their antimicrobial, cytotoxic, anti-inflammatory, anti-anaphylactic, and antioxidant properties. Further efforts are needed to evaluate the efficacy and safety of *Impatiens* plants extracts and bioactive compounds to get a complete perspective of their potential applications. Most plants from *Impatiens* genus with ethnobotanical interests have been poorly studied, therefore, more research of them will be useful to validate their use, to verify their safety and to isolate their main bioactive compounds.

Keywords: Impatiens, Ethnobotany, Bioactivities, Metabolites, Toxicity, Applications.

Correspondence:
Fabián Vinicio Delgado-Rodríguez
Instituto de Investigaciones Farmacéuticas (INIFAR), College of Pharmacy, University of Costa Rica (11501-2060), San Pedro de Montes de Oca, San José, COSTA RICA.
Email: fabian.delgadorodriguez@ucr.ac.cr

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INTRODUCTION

Balsaminacea family is integrated by two genera, *Hydrocera* and *Impatiens*. *Hydrocera* only has one member corresponding to *Hydrocera triflora* endemic from Southeastern Asia while *Impatiens* has around 1000 species of plants and new species are constantly discovered. Most of *Impatiens* species have a palaeotropical origin,[1,2] however, there are few species endemic from Eurasia, North America, and Central America.[1-5] Several plants of *Impatiens* genus have relevance for agriculture, ethnomedicine and pharmacology. For instance, *I. walleriana* and *I. hawkeri* are ornamental plants with annual wholesales of $65 and $54 million in the United States, respectively.[6,7] Figure 1 contains images of the most relevant species of *Impatiens* genus for the horticulture industry.

Furthermore, *I. balsamina* exemplifies a plant of the genus *Impatiens* relevant due its ethnobotanical use and pharmacological properties. This plant is included in Ayurveda and is used in the traditional medicine of China, Taiwan, and Korea as a remedy for inflammatory diseases and infections.[8] Naphthoquinones, flavonoids and triterpenoids are the principal active compounds responsible of the anti-inflammatory and antimicrobial effects demonstrated by the extracts of *I. balsamina*.[9,10]

Literature indicates a growing interest for the development of products with therapeutic applications using extracts or metabolites from *Impatiens* plants. Soaps prepared using *I. capensis* plant extracts have been investigated for the prevention of dermatitis due to poison ivy/oak contact.[11] A mouthwash with the active principle 2-methoxy-1,4-naphthoquinone (1), a naphthoquinone present in *I. balsamina*, has shown promissory results for its application in oral candidiasis prophylaxis in Human Immunodeficiency Virus (HIV)-infected subjects and denture wearers.[12] Edible species *I. balsamina* and *I. walleriana* have gained attention in food industry due their potential application as functional foods.[13-16]

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Despite the available information related to the chemical constitution and pharmacological activities about Balsaminaceae plants,[9,10,17] we identified the necessity of a deep and integrative review of reported ethnobotanical applications of these plants to guide their further research. Additionally, it is relevant to review the corresponding biological activities in the same way to get an update about this expanding field of research and to define investigation approaches that could be covered to define applications for *Impatiens* plants, including the development of safe and effective products for healthcare from their bioactive extracts and metabolites.

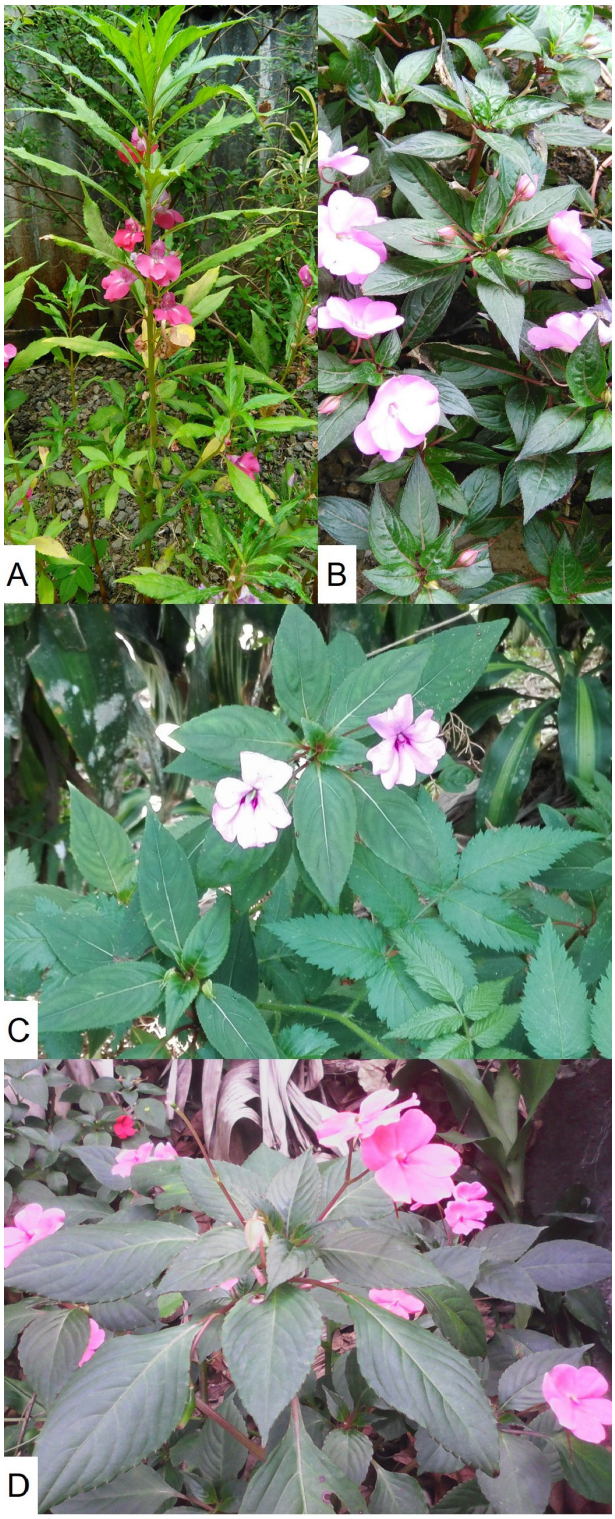


Figure 1: Examples of *Impatiens* species relevant for agriculture, ethnobotany and pharmacology research. (A) *I. balsamina* (cultivated specimen); (B) *I. hawkeri* (cultivated specimen); (C) *I. hawkeri* (naturalized specimen, Coto Brus Region, Costa Rica); (D) *I. walleriana* (naturalized specimen, Coto Brus Region, Costa Rica).

SEARCH METHODOLOGY

The review comprises full-text research articles and book chapters available in the following databases: ACS publications, EBSCOhost, Google Scholar, PubMed, ScienceDirect, SpringerLink, Taylor and Francis Online and Wiley Online Library. For the search in these data bases, the keyword "*Impatiens*" was combined with the terms "Biological activity", "Pharmacology", "Pharmacological activity", "*in vitro* activity", "*in vivo* activity", "Toxicity", "Compounds", "Chemical constituents", "Ethnobotanical use", "Ethnopharmacology" and "Traditional medicine". Boolean operator "AND" was used to combine the search words, this allowed to do an exhaustive search of information available about ethnobotany, pharmacology, and toxicology of plants from *Impatiens* genus considering their major active compounds. References related with sole chemical characterization of extracts and isolation of natural products without biological activity evaluation were excluded. The information from 398 full-text references was selected to prepare the review.

Additional information about ethnobotanical uses of *Impatiens* was obtained from the following electronic databases: Moerman´s online Native American Ethnobotany Database (University of Michigan-Dearborn),[18] Plant Resources of South East Asia (PROSEA foundation),[19] Plant Resources of Tropical Africa (PROTA foundation),[20] Prelude Medicinal Plants Database (Royal Museum for Central Africa),[21] and Subject Database of China Plant (Institute of Botany, Chinese Academy of Science).[22] The botanical recognition of the scientific name of each species reported in the review was corroborated through International Plant Names Index database.[23] Additional 25 references known by authors were used to discuss information and as a complement in the development of the review.

ETHNOBOTANICAL USES

Impatiens alboflava

In Indonesia, flowers are used to treat cancer and fever.[24]

Impatiens apalophylla

In China, decoction from whole plant is used to treat menstruation disorders and blood stasis, including those present after partum. It is also employed to treat rib and abdominal pain. The mashes from whole herb are externally applied to cure pain, injuries, and traumatisms.[22,25,26]

Impatiens arguta

In China, crushed leaves are used as hemostatic.[27] Flowers are used to dissolve clots, to treat amenorrhea pain and to relieve abdominal pain. They are employed to treat postpartum blood stasis, stillbirth, difficult urination, carbuncles, and furunculosis.[22,25] In Bhutan, leaves from *I. arguta* are used to treat old wounds.[28]

Impatiens auricoma

In Mayotte archipelago, leaves decoction is used to treat hemorrhoids.[21]

Impatiens balsamina

In China, aerial parts are used as edible vegetable and as a remedy for articular rheumatism, bruises, and beriberi. Flowers are used to prepare beverages employed to prevent illness, in the form of tea and wine.[9,29-33] Their juice has been used as a natural purple dye for staining cloths and fingernails.[19,25,34,35] Flowers are used externally or orally as treatment for several illnesses, including rheumatic pain, limb numbness, intercostal pain, fractures, pain associated with menorrhagia, amenorrhea, leucorrhea, carbuncle, wounds, furunculosis, swelling, blood stasis, gooseflesh, intoxications, insect and snake bites, and fungal (ringworm, dandruff and nail fungal infections) and parasitic infections.[9,19,22,26,30,31,36,37]

There are other uses reported in China for *I. balsamina*. Decoctions from whole herb are externally used to treat rheumatoid arthritis, cervical osteophytes, and musculoskeletal contractures. They are also used to treat swelling, tinea sore, snake bites, athlete's food, pruritus, bleeding and external infections.[26,34,36,38-40] Tea from whole herb is internally used to treat bacterial and fungal infections.[9,30,31,40,41] Mashes from the same material are applied over affected areas to treat furuncles and carbuncles.[26,42] It is reported that decoction from aerial parts is drunken to ease parturition.[43] It is also used to treat rheumatism, wounds, and foot diseases.[36]

Other specific organs from *I. balsamina* are used in China. Decoction from stems is employed to promote blood circulation and to treat rheumatic paralysis, musculoskeletal contractures, pain, arthritis, intoxications, carbuncles, wounds, swelling, amenorrhea and dysmenorrhea, sores, and pyogenic infections.[22,25,36,44,45] Decoction from older stems with large nodes is used to treat swelling and edema, and to wash abscesses, while dried stems are employed as remedy for difficult labor, pain, leg cramps, and rheumatism. They are also utilized to improve blood circulation. Juice from stems is combined with rice liquor and the mixture is externally used to treat contusions.[37] The decoction or mashes from stems are externally applied to treat bruises, swelling, snake bites, erysipelas, ringworm, and carbuncles.[22] Decoction from leaves is used as anti-inflammatory. Poultices from leaves are applied to wounds, pustules, torn nails, and felons.[19] Seeds are used to promote blood flow, to treat difficult parturition and to relieve post-childbirth pain.[22,25,46] Additionally, seeds have been used as an expectorant and as a bactericide.[15,47] Their decoction is used to treat esophagus and gastric cancer associated abdominal masses, hiccups, amenorrhea, difficult childbirth, bone hyperplasia, dirty teeth, bone choking throat and sores.[15,22,25,26,35-37,48-52] The powder from seeds is externally applicated to treat sores and swelling. Seeds are also utilized to remove teeth with caries.[37] Roots are used to promote blood circulation and to treat edema, rheumatism, tendon pain, bruises, torn nail swelling, and leucorrhea.[19,22,36] The use of *I. balsamina* is not recommended in pregnant women.[26]

In Nepal, the plant extract is used to promote hair growth.[53] In India, *I. balsamina* plant is used as a cathartic, diuretic, and emetic and to treat dysentery and jaundice. Pulverized seeds are used to treat liver disorders.[15,30,32,41,54-56] Leaves from *I. balsamina* are crushed, mixed with water, and given orally to treat malaria.[56] Leaf paste is used to treat cuts, wounds, burns, fractures, and to relieve fever and inflammation.[57-60] It is also used to relieve itching between fingers during monsoons.[61,62] The paste is applied on abdomen to treat urinary disorders. Stems juice is externally applied to threat calluses.[63] Flower tea is used to treat jaundice.[64] Flowers are used as an antiseptic and neuroprotective, and their paste is applied on forehead to treat fever.[65]

In Pakistan, *I balsamina* is used to treat join pain and juice from leaves is used against gastrointestinal disorders.[66,67] In Bangladesh, flowers are used to treat lumbago, neuralgia, burns and scalds.[15] In Sri Lanka, the plant is used to treat boils and burns.[60] In Thailand, the aerial parts are used as tonic and to treat puncture wounds, abscesses in nails, swelling and ulcers associated with allergic reactions to detergents.[36,68-70] Decoction from aerial parts, leaves and roots is drunken to ease parturition and to treat dysmenorrhea and amenorrhea.[43,71,72] *I. balsamina* leaves are used externally to treat abscesses, nail infections, and skin fungal diseases.[73]

In Taiwan, whole plant is used to treat rheumatism, swelling, and fingernail inflammation.[41,46,74] In Japan, petals juice or sochu petal macerate are applied on the skin to alleviate dermatitis, urticaria, burns, and insect bites.[9,32,46,75,76] In Korea, *I. balsamina* is used to treat carbuncles, tuberculosis, scurvy, and dysentery. The stems are used to treat constipation and acute gastritis.[15,36,77,78] The infusion from whole herb is drunk to treat indigestion and sterility, while infusion from flowers and leaves is drunk to treat pollakiuria.[79,80] Beauty-salt™ is a product made of solar salt and *I. balsamina* extract that has been used to treat inflammatory disorders in Korea.[81] In Hawaii, the herb is used as emetic, cathartic, and diuretic. It is utilized to treat ulcers and cancer.[41,82,83] Flowers are used as cooling, tonic, and antiseptic.[82,83]

In Philippines, leaves are heated and applied with oil on forehead to treat headache.[84] Leaves are pounded and externally used to dissolve felons.[15,37] Ground leaves and flowers are externally applied to treat burns, insect bites and swollen muscles.[85] In Malaysia, whole plant decoction is used to treat hypertension and leaves paste is used to treat split nails, felons and to soothe skin irritation.[15,86-89] Leaves are utilized to treat snake bites.[41] In Indonesia, the whole herb has ritual uses[90] and is utilized as an antimalarial and as remedy for felons and wounds.[37,91] Leaves are considered edible material, they are ground with black pepper and ginger and the mixture is taken to treat beriberi.[19,92] Leaves and stems are used as an anti-infective for wounds.[36,93] Flowers are used as a component of concoctions used to prepare traditional beauty masks.[94] Boiled seeds and flowers are used to treat cancer and fever.[24,95] In Brunei, root decoction is taken to treat irregular menstruation.[15,19,32] In Indochina, the decoction made from leaves is used to wash the hair and to help it to grow.[37]

In Mauritius, decoction from stems and roots of *I. balsamina* is drunk to ease childbirth. Juice from the stem is used as emetic, cathartic, and diuretic. Flowers are used for lumbago, intercostal neuralgia and to remove blood stasis.[21,96] Leaf poultices are applied for wound healing and to treat paronychia.[21,96-98] Leaves are used to relieve surgery pain and to facilitate parturition.[21,97,98]

In Türkiye, the herb is pounded with garlic and applied in the head after shaving the hair to treat sunstroke.[99] The plant is also used to treat heart stroke and hair loss.[36] In Canary Islands, leaves are used to treat wounds, hemorrhoids, and diabetes.[100] In Ecuador, the infusion from fresh leaves and flowers is drunk to cure internal infections.[101] In Colombia, flower decoction is drunk and its ointment is externally applied to treat snake bites.[102] In Guyana, leaves are mashed and mixed with salt and castor oil to treat whitlow and ingrown toenails.[103]

Impatiens baronii

In Madagascar, decoction from aerial parts is used as a febrifuge.[104]

Impatiens bicolor

In Pakistan, juice and powder from stems and seeds are used as diuretic and to treat kidney stones and joints pain.[105] The paste made from leaves is externally applied to treat joint pains.[89,106] Seeds are eaten as a brain tonic.[107] Extracts from whole plant are used as laxative and cooling agents.[106] Fruits and seeds are used as antihypertensives, diuretics, cooling agents and tonics.[86,108,109] In India, fruits are used as edible material.[110] Leaves are given to buffalos to promote milk production.[109]

Impatiens bicornuta

In Nepal, whole plant decoction is used to treat inflammation. Leave paste is used to treat joints pain.[111]

Impatiens blepharosepala

In China, whole herb is used to treat rheumatic pain in joints, fractures, and amenorrhea. Roots are used as a treatment for anemia, trauma, and bleeding.[22]

Impatiens brachycentra

In Pakistan, seeds are chewed as tonic, and they are used to treat anxiety and joints pain. The oil from seeds has the same uses.[112] Flowers, leaves and roots are used as cathartics, emetics, and diuretics.[113] Poultices made of seeds are used topically to treat burns.[114]

Impatiens burtonii

In Cameroon, infusion from leaves is drunken to treat female infertility.[21,115] Leaves and stems are macerated and drunk by pregnant women to treat swelling of inferior limbs. Macerate from leaves is used to clean babies.[116]

Impatiens capensis

This plant is mainly used by American Natives of United States and Canada. The plant is an ingredient of green corn medicine used in Cherokee tribe as an emetic and to prevent colic and parasitosis. Decoctions and infusions from whole herb are taken to promote appetite and diuresis. They are used to treat chest cold, stomach cramps, and burns. Their external application is used to treat soreness, sprains, and bruises and to wash liver spots. Decoctions and infusion from leaves are used as a remedy for jaundice and measles. Decoction from stems is drunk to ease childbirth. Infusions from roots are used to bath babies with hives and are drunk to promote diuresis. Herbal decoctions and infusions that includes *I. capensis* as an ingredient are employed to treat fever, difficult urination, kidney diseases, and edema. Plant juice is rubbed on head to treat headache and is externally applied on skin to cure nettle sting and poison ivy/oak rash. Poultices from crushed whole plants, leaves, flowers, or stems are externally applied to heal burns, bruises, wounds, rash, and eczema, especially those related to poison ivy/oak contact. Crushed leaves are rubbed on children to treat stomachache. Baths made from spicebush berries and *I. capensis* are used to treat heart failure. The plant is used as a sources of dyes.[11,18,117-121] Decoction from *I. capensis* is used as an abortive in Croatia.[122]

Impatiens chinensis

In China, decoction from whole plant is used as a remedy for fever, pain, intoxication, low blood flow, dysentery, diarrhea, urinary infections, pulmonary tuberculosis, child pneumonia, swelling, abscesses, and carbuncles.[22,25,26] The plant mashes are used externally to treat carbuncles, furuncles, and malignant boils. The use of this plant is not recommended to pregnant women.[26] In India, plant juice is used to treat burns and internally to treat gonorrhea.[123] The plant is used to relieve pain, to promote blood circulation and to treat urinary infections.[124]

Impatiens clavigera

In China, whole plant is used to treat skin injuries and burns. It is used to treat carbuncles swelling and poison.[22,25]

Impatiens cyanantha

In China, whole plant is used to relax and activate tendons and to treat injuries, traumatisms, and snake bites.[25] It is used for abdominal pain, children malnutrition, swelling and pain.[22]

Impatiens davidii

In China, plant decoction is used to treat abdominal pain, indigestion, infantile malnutrition, swelling and pain.[22,26]

Impatiens dichroa

In Central African Republic, macerate from stem and leaves is drunk to treat headache.[21]

Impatiens dycentra

In China, seeds and whole herb decoctions are used to promote blood circulation and to remove blood stasis. They are used as diuretic and detoxification agent. Smashed whole herb is externally applied to treat bruises.[22]

Impatiens edgeworthii

In Pakistan, seeds are chewed as a tonic and to treat anxiety and joints pain. The oil from seeds has the same uses.[112] Extracts from whole plant and flowers are used as antimicrobials to treat urinary infections, gonorrhea, and fever.[109,125-127] Powder or extracts from whole herb are used to treat kidney stones, hyperacidity, and pain.[109,128] Paste from whole plant and poultices from seeds are used topically to treat burns.[60,114,125-127,129] Flowers are used externally to treat burns.[109] Fruits with seeds are taken to treat sexual disfunction.[130]

Impatiens ethiopica

In Ethiopia, *I. ethiopica* roots powder is warmed and applied on wounds.[131]

Impatiens glandulifera

In Pakistan, *I. glandulifera* is used to treat joints pain.[66,67] Seeds are chewed as tonic and as treatment to anxiety and joints pain. The oil from seeds has the same applications.[112] The paste made from roots or extracts from roots are applied to cool hands and feet. Roots, leaves and flowers powders and decoctions are used as antidepressant, anxiolytic, hypnotic and to treat snake bites.[128,132-134] Leaves are applied externally to treat burns.[109] The infusion from flowers are used for eye washes.[125] Juice from flowers is used as a cooling and tonic agent.[67,109] Flowers are also utiized to treat joints pain and as cathartic, diuretic, and emetic.[109] In India, flowers are used to treat snake bites.[133] Paste from leaves is used as a cooling agent for hands and feet.[135] Fruits, seeds, leaves, and stems are used as edible material.[136,137] Paste and powder from the leaves of *I. glandulifera* are externally used to treat sun burns and joints pain.[138]

Impatiens griffithii

In Malaysia, flowers are used for dyeing fingernails.[19]

Impatiens hawkeri

In Papua New Guinea, *I. hawkeri* is considered as a magical and ceremonial plant.[139,140] Leaves are used to treat scabies[141] and are eaten by women to promote pregnancy.[142] They are mixed with leaves from *Coleus scutellarioides* and then rubbed on the abdomen of pregnant women to relieve labor pains. Leaves are chewed by women to promote labor. Juice from leaves is rubbed in the legs of small children with walking retardation. The cooked whole plant is given to children with stomachache.[19,142,143] In Brazil, it is reported that in close environments, the plant can induce tearing, headache, and allergy.[144]

Impatiens henryi

In China, whole herb is used to treat rheumatic pain.[22]

Impatiens holocentra

In China, whole plant is used as fodder.[145]

Impatiens irvingii

In Guinea, flowers macerate is used as an antidiabetic.[146] In Liberia, leaves are used as edible material. In Democratic Republic of Congo, Gabon and Sudan, the plant is used to produce vegetable salt. In Democratic Republic of Congo, stem juice is instilled in nostrils to treat headaches and stems oil is rubbed to treat bone tuberculosis. Herbal decoctions including *I. irvingii* roots are used to treat female infertility. In Ivory Coast, the plant is used as a treatment for schistosomiasis.[20,21]

Impatiens latifolia

In India, the plant is considered as edible material.[147] Leaves are used to relieve headache and gastrointestinal disorders.[148]

Impatiens lecomtei

In China, whole herb is used to treat livestock sores and is given to them after birth.[149]

Impatiens lemannii

In Pakistan, whole plant infusion is drunk to relieve pain.[128]

Impatiens leptocaulon

In China, the decoctions or wine macerates from roots of *I. leptocaulon* are taken to promote blood circulation and are used as analgesic. They are also employed to treat rheumatoid arthritis and limb numbness. The mashes from roots are applied externally to treat bruises, swelling, and pain.[22]

Impatiens longialata

In China, whole herb is used to promote blood circulation, muscle relaxation, and regulation of menstruation.[22]

Impatiens loulanensis

In China, whole plant is used to relax and to activate tendons, and to treat injuries, traumatisms, and snake bites.[25]

Impatiens masisiensis

In Democratic Republic of Congo, plant juice is taken or externally applied to treat snake bites. Leaves decoction is used to treat hematuria. Crushed leaves and stems are applied to treat skin injuries, mosquito bites and livestock theileriosis.[21]

Impatiens meruensis

I. meruensis is utilized as edible plant in Uganda.[150]

Impatiens microcentra

In China, roots are used as antipyretic and analgesic. Plant is used for muscle pain and sore throat relief.[22]

Impatiens mooreana

In New Guinea, petals and young leaves from *I. mooreana* are rubbed on skin to treat burns.[37,151]

Impatiens niamniamensis

In Congo Democratic Republic, the juice from leaves is instilled in each nostril to treat pneumonia. The decoction from leaves is used as treatment for gonorrhea and epilepsy. Mashes from whole plants are applied externally to promote wound healing.[152] Leaves are considered edible material and are used to produce vegetable salt. In Congo, leaves are eaten to cure heart illnesses. In both countries mentioned, leaves poultices and dressings are used to treat wounds, sores, and painful conditions.[20]

Impatiens noli-tangere

In Romania, the plant is used as anti-inflammatory, astringent, hemostatic and to promote wound healing.[153] Herbal baths with *I. noli-tangere* have been reported as treatments for general weakness and musculoskeletal weakness or disability in extremities.[154] Tincture from leaves is used as an astringent and diuretic remedy. Dry leaf powder is used as a purgative, laxative, and emetic agent.[155] In China, decoctions from roots, flowers and whole plants are used to reduce blood stasis and to treat irregular menstruation, dysmenorrhea, bruises, rheumatism, and scrotal eczema.[22] Decoction from of *I. noli-tangere* whole plants is employed to clear "heat" (a set of symptoms that include fever, unconsciousness, delirium, dysphoria, thirst, constipation, oral ulcers, mouth sore, and dry eye).[156] The mashes of the plant are externally used to treat bruises, rheumatic pain, and scrotal eczema.[26]

Impatiens notolopha

In China, aerial parts are used as edible material.[157]

Impatiens nzoana

Leaves have been used in Liberia to treat involuntary urination on bed.[158]

Impatiens omeina

In China, roots are used as an analgesic.[22]

Impatiens parviflora

In Czechia, seeds are edible and are recognized by their nutty pleasant flavor.[159] In Uzbekistan and Kyrgyzstan, whole herb is used as antimicrobial, hemostatic and as treatment for uterine diseases.[160-162]

Impatiens pallida

This plant is mainly used by American Natives of United States and Canada. The plant is also used as an ingredient of green corn medicine used by Cherokee tribe. Crushed herb and juice are rubbed on skin to treat wounds, bruises, mosquito bites and poison ivy/oak related rash and eczema. Herb and leaves infusions or decoctions are drunk to treat fever, measles, and pain during parturition. Infusion from roots is used to bath babies with hives. Crushed leaves are rubbed on children abdomen to treat stomachache.[18]

Impatiens platypetala

Leaves are used in Indonesia to treat skin eruptions and as a diuretic for children.[19,37]

Impatiens pritzelii

In China, the rhizomes of *I. pritzelii* var. *hupehensis* are used to promote blood circulation and to treat rheumatism, limb numbness, bleeding, joints swelling and pain, wounds, burns, traumatisms, abdominal pain and distention, enteritis, dysentery, diarrhea, acute stomachache, amenorrhea, and dysmenorrhea.[25,163-167] Fresh leaves are mashed to treat bruises, traumatic bleeding, boils and snake bites.[22]

Impatiens puberula

In Nepal, whole plant is used to treat indigestion.[111]

Impatiens pterosepala

In China, whole plant is applied for wounds treatment.[22]

Impatiens pulchra

In China, stems and leaves are boiled and eaten.[168]

Impatiens racemosa

In India, the paste from leaves and roots is mixed with mustard oil and applied externally to treat rheumatic pains.[169] Leaves are

used for gastrointestinal disorders.[148] Fruits are used in Bhutan to treat cold and cough.[28]

Impatiens rothi

In Ethiopia, root powder is warmed and applied on wounds.[131]

Impatiens scabrida

In Pakistan, whole herb is used as a laxative and diuretic on farm animals.[170,171] In India, *I. scabrida* is used as fodder plant and stems are used as an abortifacient.[172,173] In Nepal, the plant is used to feed farm animals suffering fever, fruits are use as edible material and oil from seeds is used to relieve muscle pain and fever.[174-176]

Impatiens siculifera

In China, roots, whole plants and seeds are used as circulatory tonics and as remedies to treat rheumatoid pain and numbness, edema, swelling, inflammation, burns, scalds, bruises, carbuncles, and fractures.[22,26,177,178] Stems are used to treat fever, intoxications, phlegm, pain, injuries, and burns.[25] Decoction from whole plants is used to treat "heat". Mashes of the plant are used to treat burns and wounds.[26]

Impatiens stuhlmannii

In Congo Democratic Republic, juice from whole herb is topically used to promote wound healing.[152] It is taken to improve virility and is used as a tonic and a remedy for anemia and cachexia.[21] In Uganda, leaves, stems and flowers are crushed and applied externally to treat lupus, skin rash, wounds, swelling, ulcers and infections.[21,179] In Rwanda, herbal decoctions including *I. stuhlmannii* leaves are used to treat paralytic diseases (hemiplegia, paraplegia, and polio). Fruits and leaves are used to treat external parasitosis. In Burundi, leaves are given to livestock to treat theileriosis.[21]

Impatiens sulcata

In China, seeds are used as edible material, the plant paste is applied to prevent urticaria and its mucilage is used as a abortifacient.[25,180] In Nepal, fruits are used as edible material and seed oil is used externally to relieve body pain and fever.[176]

Impatiens textorii

I. textorii is used in Japan, Korea, and Northeast China to treat allergic disorders, inflammation, ulcers, and infections in skin. The whole plant extract has been used as a detoxifying agent and as treatment for carbuncles, contusions, and superficial infections, including fingernail inflammations.[22,181-183] In China, decoctions from roots are used to promote circulation and to treat abdominal pain and swelling. Mashes from roots are externally used to treat pain, carbuncle sores, bruises, and snake bites.[22] In Korea, *I. textorii* is considered as a poisonous plant.[184]

Impatiens tienchuanensis

In China, stems and seeds are used for pain relief.[22]

Impatiens tinctoria

In Ethiopia, *I. tinctoria* subsp. *abyssinica* powdered roots are given to cattle to treat blackleg.[21,185] Leaves, stems and fruits are used to treat external parasitosis.[21] Red dye from tubers of *I. tinctoria* is used as cloth dye and as a beauty treatment, it is applied on skin to toughen it and to prevent fungal infections.[20,186-188] Root decoction is used to treat abdominal pain and as a purgative.[20] Root powder from *I. tinctoria* is warmed and applied on palm wounds.[131] Stems are chewed to treat mouth and throat problems.[20,187] In Kenya, decoction from roots is used to promote fertility.[21,189]

Impatiens trilobata

In Bangladesh, the plant is used to treat boils.[60]

Impatiens tripetala

In India, the plant is used to promote appetite.[190]

Impatiens uliginosa

In China, poultices from whole herb are used to treat snake bites, wounds, abscesses, ulcers, burns, scabies, herpes, psoriasis on hands and feet and scrotal eczema. Whole herb and roots are used internally or externally to relax muscles and to treat mouth sores, leprosy, plague, tuberculosis, migraine, apoplexy, colds, cough, epistaxis, hemoptysis, hematemesis, irregular menstruation, dysmenorrhea, postpartum bleeding, edema, rheumatism, arthritis, vomiting, diarrhea, difficult urination, bladder and kidney stones, acute nephritis, urinary tract infection, hematuria, hypertension, esophageal cancer, polydipsia, abdominal pain (pain in liver, spleen and stomach), jaundice, brain and tendon disorders, impotence and tonsillitis. Flowers are used to promote hair growth, to moist skin, and to dispel "cold" (a term used in Traditional Chinese Medicine as a reference for symptoms that include hypothermia, cold limbs, lost appetite, diarrhea, nausea, and vomiting).[156] The fruit is used for irregular menstruation.[22] The plant is used as a source of dyes for nails.[191]

Impatiens urticifolia

In Nepal, root paste is used to treat skin burns. Juice form leaves are used to treat urinary infections.[60,111]

Impatiens walleriana

In Ethiopia, roots are used by women to strength hair and are given to pigs as fodder.[21,192] In Tanzania, *I. walleriana* stems are used to treat liver pain while roots are used as abortifacient.[15,143,193] In Malawi, boiled roots and stems are also used as an abortifacient.[21] In Indonesia, flowers are used to treat cancer and fever.[24] In Brazil, the plant is used to treat uterus infections.[194] In Costa Rica, leaves, and young shoots from *I.*

walleriana are rubbed on the skin to relieve insect bites pruritus and to heal hand wounds.[103,195]

BIOLOGICAL ACTIVITIES

Antimicrobial activity

There is wide variability among reported results for the evaluation of the antimicrobial activity of different extracts from *Impatiens* plants. Phatthalung *et al.* reports that ethanol extract from *I. balsamina* stems has weak activity against *Acinetobacter baumannii*, reducing its growth to 9.77% at concentration of 250 μg/mL under broth dilution assay.[196] According to Grosvenor *et al.*, the ethanol extract from *I. balsamina* stems and leaves has antibacterial activity against *Staphylococcus aureus* based on agar diffusion assay results.[93] Naitullah *et al.* reports that ethanol extract from *I. balsamina* leaves shows antifungal activity against *Candida albicans* with Inhibition Zone Diameters (IZD) from 6.00 to 13.66 mm according to agar diffusion assays.[197] The ethanol extract from *I. balsamina* leaves has antibacterial activity against *Propionibacterium acnes* with IZD in the range of 11.4-17.9 mm based on the same assay.[198] The ethanol (70%) extract from *I. balsamina* leaves has antibacterial activity against *Escherichia coli* and *Shigella sonnei* when 2.5 mg are applied in agar diffusion assay obtaining IZD values ranging from 13.7 to 14.7 mm. This extract can act synergically with chloramphenicol against both microorganisms.[199]

Voravuthikunchai *et al.* indicates that aqueous extract from *I. balsamina* leaves is inactive against *E. coli* O157:H7 strains.[200] However, Hartanti *et al.* reported that aqueous extract from *I. balsamina* stems has antibacterial activity against *S. aureus* according to agar diffusion assay with IZD value of 16.43 mm when 20 μL of the extract are applied on test bacterial culture.[201] Comparison of the antibacterial activity of the ethanol and aqueous extracts from *I. balsamina* against *S. aureus* demonstrated that the ethanol extract is more potent with Minimal Inhibitory Concentration (MIC) and Minimal Bactericidal Concentration (MBC) of 6.3 and 25 mg/mL, respectively.[202] Kamble *et al.* reported the comparison of the antibacterial activity of the aqueous and ethanol extracts from *I. balsamina* leaves against *E. coli, Bacillus subtilis,* and *Pseudomonas aeruginosa*, using agar diffusion assay, results showed that ethanol extract has the best antibacterial profile with IZD values ranging from 10 mm to 19 mm.[203]

Methanol and chloroform extracts from *I. balsamina* leaves have antimicrobial activity against *Pseudomonas putida, Vibrio cholerae, Shigella flexneri* and *Streptococcus pyogenes* with IZD values in the range of 6-22 mm.[204] The hexane extract from the leaves of *I. balsamina* has antibacterial activity against *S. aureus, Klebsiella pneumonia, Proteus vulgaris, E. coli, Serratia marcescens,* and *P. aeruginosa* with MIC and MBC ranging from 25 to 100 mg/mL.[205]

Determination of the antimicrobial activity of the hexane, petroleum ether, acetone, methanol, and aqueous extracts from *I. balsamina* whole plants against *Shigella boydii, Salmonella* Paratyphi*, P. vulgaris, S. aureus, C. albicans,* and *Cryptococcus neoformans*, using agar diffusion assay, showed IZD values ranging from 1 mm to 36 mm.[206] The comparative evaluation of the antimicrobial activity of the ethanol, benzene, chloroform, methanol, petroleum ether, and aqueous extracts from leaves and roots of *I. balsamina* on *B. cereus, K. pneumoniae, S. aureus, E. coli, S. typhimurium, P. aeruginosa, C. albicans, Aspergillus niger, Aspergillus flavus, Penicillium* sp., and *Trichoderma reesei* showed that ethanol extract is the most active with MIC values in the range of 1-4 mg/mL.[207]

Ethanol, petroleum ether, and ethyl acetate extracts from seeds of *I. balsamina* have shown antimicrobial activity against *Bacillus anthracis, E. coli*, and *A. niger* with IZD values ranging from 7.03 to 23 mm according to agar diffusion assay.[208] Ethanol extracts from flowers and seeds of *I. balsamina* have demonstrated activity under the same assay against *S. aureus, P. aeruginosa* and *E. coli* with IZD values in the range of 3.50-23.00 mm. Flower extract is the most active with IZD ranging from 7.83 to 23.00 mm.[209] The hexane, ethyl acetate, and ethanol extracts from *I. balsamina* flowers showed IZD ranging from 6.6 to 20.8 mm against *S. aureus, E. coli*, and *C. albicans*.[210]

The comparative analysis of the antimicrobial activity of the petroleum ether (60-90°C), diethyl ether, chloroform, methanol, and water extracts from *I. balsamina* stems against *B. subtilis, S. aureus, E. coli, S. boydii, Saccharomyces cerevisiae, Candida utilis, A. niger, Aspergillus oryzae, Penicillium italicum,* and *Penicillium digitatum* demonstrated that petroleum ether and diethyl ether extracts are the most potent against test microorganisms (MIC ranges of 125-1000 μg/mL and 500-1000 μg/mL, respectively). Diethyl ether extract is active against all test strains while petroleum ether is not active against *E. coli*.[29]

The evaluation of the antimicrobial activity of the ethanol (70% v/v) extracts from stems or leaves of *I. balsamina* recollected at different harvest times showed that extracts from leaves have the best results in agar diffusion assay with IZD values ranging from 8 to 15 mm after their application at concentration of 4 mg/mL in agar plates inoculated with *Vibrio parahaemolyticus, Listeria monocytogenes, S. aureus, B. cereus, S. typhimurium, E. coli, C. albicans*, or *Clostridium perfringens*. All test strains were susceptible to leaves extracts.[211]

The ethanol (80:20 v/v, acidified with trifluoro acetic acid 0.5% v/v) extracts from orange and pink flowers of *I. balsamina* have shown antimicrobial activity on *B. cereus, S. aureus, L. monocytogenes, E. coli, P. aeruginosa, S. typhimurium, Aspergillus fumigatus, Aspergillus versicolor, A. niger, Penicillium funiculosum, Penicillium ochrochloron,* and *Penicillium verrucosum* var. *cyclopium* with MIC and MBC/Minimal Fungicidal Concentration

(MFC) values in the ranges of 0.006-0.20 and 0.012-0.40 mg/mL, respectively.[212]

The evaluation of the antibacterial activity of the ethanol extracts from *I. balsamina* fruits, whole plants, seeds and the mixture of roots, leaves and stems demonstrated that the extract from fruits is the most active against *Helicobacter pylori* (including antibiotic-resistant strains) with MIC and MBC values in the ranges of 1.25-5 and 1.25-2.5 μg/mL, respectively. Comparative analysis of the antibacterial activity of extracts made from fruits using water, acetone, ethyl acetate or *n*-hexane against the same strains shows that acetone and ethyl acetate are the most active extracts with MIC and MBC values ranging from 0.625 to 2.5 μg/mL.[46,213-215]

Ethanol extract from *I. balsamina* aerial parts has anti-quorum sensing activity on *Chromobacterium violaceum*.[216] The acetone extract from *I. balsamina* leaves can inhibit the quorum sensing system on *C. violaceum* at concentration of 0.5 and 1 mg/mL. This extract has antibacterial activity against *P. aeruginosa* with a MIC of 3.125 mg/mL. At concentration of 1.56 mg/mL, the extract can inhibit Las A protease and chitinase activities of *P.aeruginosa* by 100% and 78.42%, respectively. It also can reduce the production of pyocyanin and biofilm formation on *P. aeruginosa* cultures by 93.33% and 30.75%, respectively. This extract is positive for the presence of 5,3'-dihydroxy flavone, 3-*O*-glucoside-6"-*O*-*p*-coumaroyl, luteolin 4'-*O*-glucoside, isorhamnetin 3-*O*-galactoside-6"-rhamnoside, quercetin 3-*O*-rutinoside (rutin) (2), kaempferol (3), and quercetin (4) according to High Performance Liquid Chromatography Coupled to Mass Spectrometry (HPLC-MS) analysis.[217]

Aritonang *et al.*, indicates that aqueous extract obtained from *I. balsamina* fresh leaves shows antibacterial activity against *S. aureus* and *E. coli* under agar diffusion assay. The antibacterial activity of the extract is enhanced by its formulation with $AgNO_3$ nanoparticles. Formulations of the extract with 5 mM of $AgNO_3$ have activity against *S. aureus* without difference in comparison with the activity of ciprofloxacin used as a positive control.[218] Carbon dots made with *I. balsamina* stems powder have antibacterial activity against Gram-positive bacteria with MIC values in the range of 0.08-0.02 mg/mL against *S. aureus, Enterococcus faecium* and *B. subtilis*, this preparate was inactive on Gram-negative bacteria (*Salmonella* sp, *E. coli*, and *P. aeruginosa*). The carbon dots act by promoting oxidative stress in bacterial cells.[219]

The essential oil from *I. balsamina* aerial parts has antibacterial activity against *S. aureus, E. coli, Citrobacter* sp., *Acinetobacter* sp., and *Klebsiella* sp., when tested with a dilution factor of 1/250 on agar dilution assay. According to Gas Chromatography Coupled to Mass Spectrometry (GC-MS) analysis, β-thujone is the most abundant compound in the essential oil.[220]

The comparative determination of the antimicrobial activity of the ethanol extracts from *I. glandulifera* roots, leaves, flowers and seeds and their low molecular weight peptide fractions (LMWPF, < 30 kDa) showed that LMWPF derived from leaves extract has the highest antimicrobial activity against *S. aureus* (MIC: 4200 μg/mL), *Staphylococcus epidermidis* (MIC: 1050 μg/mL) and *E. coli* (MIC: 525 μg/mL). LMWPF from root extract is the most potent preparate against *Streptococcus sanguinis* and *Streptococcus mutans* with MIC of 62.5 μg/mL in both cases. The comparative evaluation of the cytotoxic activity of LMWPFs on human fibroblasts (BJ) indicates that evaluated LMWPFs, despite their antimicrobial activity, have low cytotoxicity against normal cells (half-maximal Inhibitory Concentration (IC_{50}) values higher than 1000 μg/mL).[221]

The study of the antibacterial activity of the methanol and chloroform extracts from *I. walleriana* leaves on *Enterococcus* faecalis, *Enterococcus* sp., *B. subtilis, S. aureus, P. aeruginosa, E. coli, Salmonella* sp., and *K. pneumoniae* indicates that methanol extract is the most active with IZD values in the range of 10-16 mm when applying 20 μL at concentration of 125 mg/mL on agar diffusion assay.[222] The evaluation of the antimicrobial activity of the ethanol (80% v/v, acidified with trifluoro acetic acid 0.5% v/v) extracts from *I. walleriana* orange and pink flowers against *B. cereus, S. aureus, L. monocytogenes, E. coli, P. aeruginosa, S. typhimurium, A. fumigatus, A. versicolor, A. niger, P. funiculosum, P. ochrachloron,* and *P. verrucosum* var. *cyclopium* demonstrated MIC and MBC/MFC values in the ranges of 0.025-0.20 and 0.05-0.4 mg/mL, respectively.[223]

The comparative determination of the antimicrobial properties of ethanol (35 and 50%) and aqueous extracts from *I. noli-tangere* whole plants showed that aqueous extract is the most active against *E. coli, S. aureus, B. subtilis, Proteus* sp., and *C. albicans*.[224] The ethanol (50%) extracts from *I. noli-tangere*, obtained by microfiltration and ultrafiltration, have values of Total Phenolic Content (TPC) and Total Flavonoid Content (TFC) in the ranges of 590.2-983.7 mg of Gallic Acid Equivalents (GAE)/L and 184.8-449.5mg of Quercetin Equivalents (QE)/L, respectively. The combination of this extracts with the ethanol extract (70%) from *Symphytum officinale* gave an antibacterial mixture with IZD values from 4 to 21 mm in agar diffusion assays using *S. aureus, S. epidermis, B. cereus, Proteus mirabilis*, and *E. coli* as test bacteria.[225]

The analysis of the antibacterial activity of the aqueous, ethanol and ethyl acetate extracts from *I. tinctoria* roots against *S. aureus, S. epidermidis, S. pyogenes, Streptococcus agalactiae, E. faecalis, E. coli, S. typhimurium, S. flexneri, S. sonnei, P. aeruginosa, K. pneumoniae* and *P. mirabilis* indicates that ethyl acetate extract is the most active with MIC and MBC values in the ranges of 0.7-16 and 8-32 mg/mL, respectively.[187] The evaluation of the antifungal activity of the aqueous, ethanol and ethyl acetate extracts from *I. tinctoria* roots against *C. albicans*, *Trichophyton*

rubrum, Trichophyton mentagrophytes, A. niger, and *A. flavus* showed that the ethyl acetate extract is the most active with MIC and MFC values within the ranges of 0.7-32 and 1-64 mg/mL, respectively.[188]

The study of the antibacterial activity of *n*-hexane, chloroform, ethyl acetate, and methanol extracts from aerial parts of *I. bicolor* showed that methanol extract has the best activity profile with IZD values ranging from 7 to 11 mm.[226] In other study, the *n*-butanol fraction rich in saponins obtained from the methanol (50%) extract of the leaves of *I. capensis* was inactive against *S. epidermidis, S, aureus, B. subtilis, P. aeruginosa, E. coli* and *C. albicans*.[120] The comparative study of the antimicrobial activity of the petroleum ether, ethyl acetate and methanol extracts obtained from the aerial parts of *I. sulcata* against *E. coli, S. aureus, S. typhimurium, K. pneumoniae*, *Trichoderma viride, A. niger*, and *A. fumigatus* demonstrated that ethyl acetate extract has the widest antimicrobial spectrum with IDZ values ranging from 10 mm to 22 mm.[180]

Szewczyk *et al.* reported results for the comparative study of the antimicrobial activity of the methanol/acetone/water (3/1/1 v/v/v) extracts obtained from the aerial parts of six *Impatiens* species corresponding to *I. balfourii, I. balsamina, I. glandulifera, I. noli-tangere, I. parviflora* and *I. walleriana*. All extracts are active with MIC values ranging from to 125 µg/mL to 1000 µg/mL. However, *I. noli-tangere* extract is active against a higher number of test pathogens including *S. aureus, S. epidermidis, M. luteus, B. subtilis, B. cereus, S. pneumoniae* and *C. albicans*. The Ultra-High Performance Liquid Chromatography Coupled to Diode Array and Mass Spectrometry Detectors (UHPLC-DAD-MS) analysis identified quercetin 3-*O*-galactoside, quercetin 3-*O*-glucoside (isoquercetin) (5), and kaempferol 3-*O*-glucoside (astragalin) (6) as specific components present in *I. noli-tangere* extract, other compounds, including phenolic acids and glycosides derived from kaempferol, eriodictyol and quercetin were also detected without specific or absolute designation of their sugar moiety.[227]

The comparative evaluation of the antimicrobial activity of the ethanol (80%) extracts from *I. balsamina, I. walleriana* and *I. hawkeri* whole plants against *S. aureus, S. epidermidis, S. pyogenes, Streptococcus pneumoniae, P. aeruginosa, E. coli, C. albicans,* and *A. niger* indicates that *I. balsamina* extract, has the best antimicrobial activity profile. It is active against all Gram-positive bacteria and *C. albicans* with MIC values ranging from 2.5 to 10 mg/mL. This extract has bactericidal effect against *S. aureus, S. pyogenes, S. pneumoniae* with an MBC value of 10 mg/mL.[8]

The ethanol extract from *I. balsamina* flowers has shown antimicrobial activity against *Monilinia fructicola, Colletotrichum lindemuthianum, A. niger, Penicillium notatum, Pythium debaryanum, Rhodotorula glutinis* and *S. aureus* with IZD values ranging from 16 to 37.7 mm in agar diffusion assay. Compound 1 was isolated as the active antifungal principle. This compound has antifungal activity against *Rhodotorula glutinis* with IZD value of 24.7 mm when tested at concentration of 960 µg/mL in agar diffusion assay. The same substance has shown IC_{50} of 3.65 µg/mL on *M. fructicola* without phytotoxicity actions on tomato and beans shootings.[228] Similarly, Yang *et al.* has reported the isolation of 1 from the dichloromethane fraction of *I. balsamina* aerial parts ethanol extract by its bioguided fractionation using *Artemia salina* toxicity assay. This compound shows antibacterial activity against *S. aureus, B. cereus, Bacillus megaterium, B. subtilis, Aeromonas salmonicida* and *Aquaspirillum serpens* with MIC values ranging from 2 to 64 µg/mL. The isolated compound also has antifungal activity against *C. albicans, Fusarium oxysporum, A. fumigatus, Microsporum gypsum* and *T. mentagrophytes* with MIC values from 0.31 to 2.5 µg/mL. *I. balsamina* aerial parts tea contains 16.5 µg/mL of 1 according to High Performance Liquid Chromatography Coupled to Diode Array Detector (HPLC-DAD) analysis.[10,40] The fractionation of methanol extract from *I. balsamina* whole plants guided by broth dilution assay also allowed the isolation of 1. This compound is active on *A. niger* (MIC: 10 µg/mL), *C. neoformans* (MIC: 10 µg/mL), *Epidermophyton floccosum* (MIC: 5 µg/mL), *B. subtilis* (MIC: 5 µg/mL) and *S. typhimuriun* (MIC: 20 µg/mL).[229]

Compound 1 showed antibacterial activity against Methicillin-Resistant *S. aureus* (MRSA) strains (MIC range of 61.5-125 µg/mL). It also shows synergic antibacterial activity against MRSA strains in combination with α-mangostin rich extract (95% w/w) obtained from *Garcinia mangostana* pericarp according to checkerboard dilution assay. Crystal violet absorption assay indicates that 1 induces cell wall disruption at concentration of 31.25 µg/mL in MRSA. Compound 1 has MRSA antibiofilm formation activity at concentration range from 1/16 to 1/2 of MIC.[230]

Compound 1 and spinasterol (7) have been isolated from the acetone extract of *I. balsamina* fruits and the ethanol extract of a mixture made of *I. balsamina* roots, leaves, and stems. Both compounds have antibacterial activity against antibiotic resistant *H. pylori* strains, 1 has MIC and MBC values in the ranges of 0.156-0.625 and 0.313-0.625 µg/mL, respectively, while 7 demonstrates MIC and MBC values within the interval of 20-80 µg/mL. The activity of 1 is not influenced by pH values within 4-8. Measuring of the quantity of 1 among different anatomical sections of *I. balsamina* by HPLC-DAD analysis indicates that fruit is the organ with the highest level of this active substance (43.92 mg/g). It is proposed that 1 can act by promoting Reactive Oxygen Species (ROS) production that compromises bacterial cell viability.[10,74,213-215,231]

Docking experiments suggest that 7 can potentially binds to cytotoxin-associated gene A (CagA), an oncogenic protein factor expressed by *H. pylori*. In this way, 7 may inhibit the interaction between CagA and phosphatidylserine of gastric epithelial cells, a process implicated in the activation of prooncogenic proteins

and the inactivation of tumor suppressors proteins in gastric cells. This *in silico* evidence shows that 7 can potentially be a starting point for the development of molecules useful to prevent gastric cancer related with *H. pylori* infections.[232]

In other studies, compound 1 has demonstrated antibacterial activity against MRSA with a MIC of 15.6 µg/mL. It has antifungal activity on *C. albicans* and *T. rubrum* with MIC values of 7.8 and 3.9 µg/mL, respectively. According to checkerboard assay, this metabolite exerts additive activity with ampicillin against MRSA. Likewise, 1 has synergic antifungal effect with clotrimazole against *C. albicans* and *T. rubrum*.[233]

A mouthwash containing 1 at concentration 0.025% has demonstrated protective activity against *Candida* growth in oral cavity of HIV-infected patients or denture wearers.[234,235] The use of mouthwash with 1 at 0.025% can reduce the count of *Candida* sp. colonies in the oral cavity of HIV-infected subjects and denture wearers with minimum changes in the genotype of isolated *Candida* species. This result suggests that mouthwash with 1 as active principle can be effective as a prophylactic agent against oral candidiasis in HIV-infected patients and denture wearers with low risk of antifungal resistance induction.[12]

Oral sprays containing α-mangostin (5 mg/mL), 1 (250 µg/mL) or a combination of both (at concentration of 5 mg/mL and 250 µg/mL, respectively) were effective to inhibit the growth of *S. mutants, Porphyromonas gingivalis* and *C. albicans*. Among the assayed formulations, the one that only has 1 (250 µg/mL) as active principle was the most effective against *C. albicans* with MIC and MFC of 6,25% v/v, however, against *S. mutans*, the formulation that combines α-mangostin (5 mg/mL) and 1 (250 µg/mL) was the most effective with MIC and MBC of 6.25% (v/v) and 25% (v/v), respectively. All spray formulations shown MIC and MFC values of 25% (v/v) against *P. gingivalis*. The spray formulation that combines both components have the highest inhibitory activity against biofilm formation by all microorganisms tested.[236]

There is interest in the application of 1 as a low toxicity antifungal agent for crops protection. This compound has shown inhibitory effects against *P. digitatum* growth, a fungi pathogen of citrus, with a MIC of 5.0 µg/mL in broth dilution assay. Changes in mycelia morphology have been observed after treatment of *P. digitatum* with 1, twisting and swelling are the main reported changes. Based on transcriptomic, proteomic and metabolomic analyses of the effects of 1, it has been observed that this molecule exerts its inhibitory action against *P. digitatum* by affecting the synthesis of amino acids and cell wall components.[237] Compound 1 reduce *P. italicum* mycelial growth by 97.54% at concentration of 6.0 µg/mL. The proteomic profile of treated cultures indicates a remarkable disruption in the expression of fundamental proteins for energy metabolism and stimulus response.[238]

Compound 2-hydroxy-1,4-naphthoquinone (lawsone) (8), another naphthoquinone isolated from *Impatiens balsamina*,[239] is recognized by its antiparasitic activity against *Plasmodium falciparum* (IC_{50} = 1.9x10^{-4} M) and nematodes. This compound acts by inhibition of dihydroorotate dehydrogenase enzyme. The ethanol extract from *I. balsamina* stems has decreased the motility of *Caenorhabditis elegans* by about 30% at concentration of 10 mg/mL.[54]

The determination of the antimicrobial activity of the main naphthoquinones presents in *I. balsamina* leaves corresponding to 1, 8 and 2,2′-methylenebis(3-hydroxy-1,4-naphthoquinone) (9), against *S. aureus, S. epidermidis, B. subtilis, E. coli, P. acnes, H. pylori*, and *S. mutans,* showed that 1 is the most active substance with MIC and MBC values in the range of 3.5-125 µg/mL and 7.8-125 µg/mL, respectively. This compound demonstrated bactericidal effect on all assayed bacteria except *P. acnes*.[239]

Compounds 3 and 4 have shown activity against *P. acnes*, including clindamycin-resistant strains, with MIC and MBC in the ranges of 32-64 µg/mL and 64-256 µg/mL, respectively. Both compounds can show synergism in combination with clindamycin with fractional inhibitory concentration indexes ranging from 0.187 to 0.562.[77,240]

I. balsamina is recognized as an important source of antimicrobial peptides. Four antimicrobial peptides (Ib-AMP1 (10), Ib-AMP2 (11), Ib-AMP3 (12), and Ib-AMP4 (13)) have been isolated from *I. balsamina* seeds. They showed activity against several fungi and bacterial strains with low *in vitro* toxicity on human cells.[241-245] Ib-AMP peptides are constituted by 20 amino acids in length and they are encoded as part of the same transcript. It is known that 10 associates with cell membranes and induces death of fungus by unknown process different than pore formation and cell lysis induction.[242] Results from circular dichroism spectroscopy and proton nuclear magnetic resonance spectroscopy show that 10 has two hydrophilic zones at opposite ends that are separated by a large hydrophobic zone. Data indicates the existence of three β-turns located at residues 9-12, 10-13, and 12-15.[246]

Ib-AMP peptides activity is 2-20 times higher on filamentous fungi than yeast. It is proposed that this difference is a consequence of the higher content of chitin in cellular wall of filamentous fungi that enhance Ib-AMP peptides binding.[247] Compound 10 has antifungal activity with MIC values against *C. albicans* and *A. flavus* ranging from 2.5 to 5 µM, for oxidized peptide, or between 10 and 20 µM for the reduced form. The study of mechanism of antifungal activity of 10 showed that the oxidized peptide disrupts liposomal membranes composed of phosphatidylcholine and phosphatidylserine. Moreover, it is known that 10 can enter *C. albicans* cytoplasm, few is known about this internalization process and fungi death mechanism triggered by 10 inside the cell, but it has been observed that 10 associates with cell membrane and intracellular organelles of *C. albicans*.[247,248]

Compound 10 shows activity against pathogenic bacteria that includes *E. coli* O157:H7, *P. aeruginosa, S. aureus* and *B. cereus* with MIC values ranging from 50 to 200 µg/mL according to broth microdilution assay. This peptide exerts bactericidal activity on *E. coli* O157:H7, *P. aeruginosa* and *S. aureus* with MBC values within the range of 50 to 400 µg/mL. Compound 10 does not have antibacterial residual activity.[249] This compound promotes an increase in the number of *E. coli* O157:H7 permeable cells (56.18%) compared to control (untreated cells), additionally, peptide 10 promotes potassium and Adenosine Triphosphate (ATP) efflux from cells. Other effects include dissipation of membrane potential and reduction of Deoxyribonucleic Acid (DNA), Ribonucleic Acid (RNA) and protein synthesis in *E. coli* O157:H7 cells.[250]

Compound 12 reduces *A. flavus* germinated conidia growth by 41.2% at concentration of 25 µM according to broth dilution assay. This peptide does not show activity against non-germinated conidia of *A. flavus*. In contrast, 12 has strong activity against non-germinated and germinated conidia of *Fosarium moniliforme*, it reduces their viability by 95,3% and 99,5% at concentration of 25 µM, respectively. According to binding affinity assays, 12 has high affinity for chitin. This binding is viewed as a critical process for 12 antifungal activity.[251]

The comparison of the antifungal activity of Ib-AMP peptides indicates that 13 is the most active peptide. This compound exerts inhibitory activity on plant pathogenic fungi strains corresponding to *Alternaria longipes, Botrytis cinerea, Cladosporium sphaerospermum, Fusarium culmorum, P. digitatum, Trichoderma viride, Verticillium alboatrum, Gloeosporium solani, Nectria galligena, Phialophora malorum* and *Sclerotinia sclerotiorum*. The IC_{50} of 13 varies between 1 to 150 µg/mL in broth dilution assay and is significantly increased when culture media is supplemented with calcium. Compound 13 is also the most active Ib-AMP against human pathogenic Gram-positive bacteria (*B. subtilis, Micrococcus luteus, S. aureus,* and *E. faecalis*) and plant pathogenic Gram-negative bacteria (*Xanthomonas campestris* pathovar *pelargonii* and *Xanthomonas oryzae*). This peptide shows IC_{50} values ranging from 5 to 20 µg/mL against these microorganisms.[251-254]

In other study, Fan *et al.* reports that 13 has shown antibacterial activity in broth microdilution assay against *B. megaterium* (MIC: 0.49 µM), *B. subtilis* (MIC: 0.98 µM), *M. luteus* (MIC: 1.97 µM), *Enterococcus casseliflavus* (MIC: 1.57 µM), *E. faecalis* (MIC: 15.74 µM), Vancomycin-resistant Enterococci (MIC: 31.48 µM), *S. aureus* (MIC: 3.15 µM), MRSA (MIC: 9.84 µM), *S. epidermidis* (MIC: 31.48 µM), *Streptococcus oralis* (MIC: 31.48 µM), *Staphylococcus saprophyticus* (MIC: 0.98 µM), *S. agalactiae* (MIC: 62.97 µM), *S. pneumoniae* (MIC: 7.87 µM), *S. pyogenes* (MIC: 3.15 µM), *Klebsiella oxytoca* (MIC: 15.74 µM), *K. pneumoniae* (MIC: 47.23 µM), *E. coli* (MIC: 3.15 µM), *P. aeruginosa* (MIC: 62.97 µM). Compound 13 has demonstrated synergic effect when is combined with thymol against *K. pneumonia* and *E. faecalis*. Furthermore, it has synergic activity against *E. faecalis* when combined with silver nitrate.[255]

The antibacterial activity of 13 also varies according to growth media conditions used in inhibition assays. This peptide exerts antibacterial activity against the following Gram-positive bacteria: *B. megaterium, B. subtilis, M. luteus, S. agalactiae, E. faecalis, S. oralis, S. epidermidis, S. aureus, S. pneumoniae, S. pyogenes* and *Enterococcus casseliflavus*. It also shows activity against Gram-negative bacteria, including *K. oxytoca, K. pneumoniae, E. coli* and *P. aeruginosa*. The MIC obtained for this peptide in broth microdilution assay on mentioned bacteria range from 1.25 to 160 µg/mL in calcium-free media, however, in culture media containing calcium, the MIC varies between 10 and 160 µg/mL on all bacteria excepting *S. oralis, S. epidermidis, K. oxytoca* and *P. aeruginosa* whose growth is not completely inhibited within that concentration range.[256]

According to Quartz Crystal Microbalance with Dissipation (QCM–D) experiments, 13 at test concentration of 200 µg/mL, can penetrate unilamellar liposomes made of 1,2-dioleoyl-sn -glycero-3-phosphocholine (DOPC) used as a model of cellular membranes. Studies with QCM-D also showed the existence of resealing phase after 13 insertions on liposomes surface. Experiments on DOPC liposomes with encapsulated calcein, a fluorescent probe, have demonstrated that 13 induces calcein release with maximal response at concentration of 100 µg/mL. Bactericidal kinetics evaluation of 13 showed that it can kill 98% of *S. aureus* cells in 10 min at concentration of 40 µg/mL. Observation of *E. coli* cells after treatment with 500 µg/mL of 13 for 20 min revealed leaking of part of their cytoplasm without loss of their characteristic rod shape. This result indicates that 13 does not produce lyses of cell wall. Instead, integration of the evidence obtained from these studies suggests that 13 exerts its bactericidal action in an insertion–poration–resealing pattern that occurs repeatedly on bacterial cell surface.[257]

Compound 13 can be produced successfully by biotechnology strategies. It was expressed in *E. coli* BL21 and its bactericidal activity evaluated against *Acinetobacter calcoaceticus, P. vulgaris, P. mirabilis, Enterobacter cloacae, S. marcescens, Pseudomonas stutzeri, P. aeruginosa, K. oxytoca, Klebsiella aerogenes, Citrobacter freundii, E. coli, E. faecium, S. pneumoniae, Staphylococcus haemolyticus, S. epidermidis,* and *S. aureus* (including MRSA strains) resulted in MIC values in the range of 1.5-128 µg/mL on susceptible strains. Only *A. calcoaceticus, P. aeruginosa, C. freundii* are not susceptible at maximum test concentration of 128 µg/mL.[245,258] According to data obtained from models of MRSA induced wound infection and septicemia on Syrian mice, 13 expressed in *E. coli* BL21 are effective to promote wound healing and to span survival time on treated animals.[245]

Several research works have been done to improve the antimicrobial activity of Ib-AMP peptides through structure modifications. One of them has allowed to discover that 10 with oxidized cysteine residues in the form of disulfide bridges is 4-fold more potent than the reduced form of the peptide against *in vitro* cultures of *C. albicans* and *A. flavus*.[242]

Wang *et al.* reported the optimization of 10 antibacterial activity by modifying its amino acid sequence. Four analog peptides were synthetized without disulfide bonds of 10. In analogue 1, one amino acid from both, N-terminal and C-terminal extremes, was removed in comparison to 10. Analogues 2, 3 and 4 have the same modifications than analogue 1 but they include a substitution of L-proline at eighth position. In analogue 2, 3 and 4, L-proline was substituted by D-proline, alanine peptoid residue, and lysine peptoid residue, respectively. The analogues are more active against *E. coli, P. aeruginosa, S. typhimurium, B. subtilis, S. epidermidis, S. aureus* than 10. Analogue 4 has the lower MIC values (2-16 μM) according to broth microdilution assays. All analogues and 10 have minimal hemolytic concentration higher than 400 μM. These analogue peptides promote a higher increase in *S. aureus* membrane permeability and depolarization than 10. According to circular dichroism spectroscopy, peptides acquire a β-sheet conformation in negative charged micelles that function as a bacterial membrane-mimetic environment. It is suggested that this conformation is important to compromise the bacterial membrane integrity.[259]

The antibacterial and hemolytic profile of 13 have been optimized according to experimental results obtained for synthetic analogues of this peptide. It is possible to get a peptide with more than 100-fold potency of 13 (reducing the IC_{50} against *E. coli* from > 100 to 1 μM) without hemolytic activity at concentration equivalent to its antibacterial IC_{50} value. This peptide can be obtained by the elimination of disulfide bonds and the replacement of amino acid residues: cysteine at sixth, seventh and sixteenth positions by methionine, proline at position eleventh by arginine, tyrosine at position fifteenth by methionine, and cysteine at twentieth position by tryptophane.[260] Peptides Ib-M1, Ib-M2, and Ib-M6 are analogues of 13 that have shown antibacterial activity against *E. coli*. From them, Ib-M2 is the most active with MIC and MBC values of 3.1 and 7.6 μM, respectively.[261] Other synthetic peptides derived from 10 and 13 have improved antifungal activity against *B. cinerea, F. culmorum, S. cerevisiae,* and *Pichia pastoris*.[262]

It has been proposed that *Impatiens* species can host endophyte microorganisms that produce antimicrobial products. Co-culture experiments have demonstrated that actinomycetes isolated from *I. chinensis* can inhibit the growth of plant pathogenic fungi that includes *Verticillium dahlia, F. oxysporum, Colletotrichum orbiculare, Fusarium graminearum, Exserohilum turcicum, Curvularia lunata* and *B. cinerea*. This actinomycetes also show activity against *S aureus*.[263]

Antineoplastic activity

Comparison of the cytotoxic activity of petroleum ether, ethyl acetate, and butanol extracts from *I. balsamina* seeds indicates that ethyl acetate extract has the strongest inhibitory effect on proliferation of human prostate adenocarcinoma (PC-3), human prostate epithelial carcinoma (RV1), and human androgen-sensitive prostate adenocarcinoma (LNCaP) cell lines with IC_{50} values of 32, 69 and 85 μg/mL, respectively. This extract, at concentrations of 40 and 80 μg/mL, can inhibit Matrix Metalloproteinase 2 (MMP-2) expression and reduce the cell migration of PC-3 and RV1 cells according to transwell matrigel migration assay. At the same concentrations, the extract induces cell cycle arrest at the G0/G1 phase and apoptosis in PC-3 and LNCaP cells. Apoptosis is triggered by the activation of caspase 3 and the increase of B-cell lymphoma 2 associated X protein (Bax) activation and decrease in the activity of B-cell lymphoma 2 (Bcl-2) protein. The extract can reduce the phosphorylation of protein kinase B (Akt) and Extracellular Signal-Regulated Kinases (ERK) proteins, this promotes a reduction in cell growth and proliferation.[52]

The methanol extract from *I. balsamina* herb can promote cytotoxic effects against Human Oral Squamous Cell Carcinoma (HSC-4) cell line in a dose-depending pattern at concentrations in the range of 10-40 μg/mL. This extract promotes activation of caspase 3, cleavage of poly-adenosine diphosphate-ribose polymerase, DNA fragmentation, nuclei condensation and apoptosis. The extract reduces the phosphorylation of Akt and promotes its degradation. It also reduces survivin protein and messenger RNA (mRNA) expression and promotes Bax activation and its translocation to mitochondria. Similar effects are observed against Human Oral Squamous Cell Carcinoma (OSC-20) cell line when the extract is tested at concentration of 100 μg/mL.[264]

The methanol extract from *I. balsamina* can reduce the cell viability of Human Oral Squamous Carcinoma (HSC-2) cell line by 30% approximately. This extract induces the activation of 5'-Adenosine Monophosphate-Activated Protein Kinase (AMPK) pathway and attenuates mammalian Target of Rapamycin (mTOR) signaling. The extract promotes the expression of BH3-interacting domain death agonist (Bid), Bcl-2 homologous antagonist/killer (Bak) and Bcl-2-associated agonist of cell death (Bad) proteins, as consequence, it induces cell apoptosis in HSC-2 cells.[265]

The evaluation of the cytotoxicity of the ethanol (80:20 v/v, acidified with trifluoro acetic acid 0.5% v/v) extracts from the orange and the pink flowers of *I. balsamina* against human breast adenocarcinoma (MCF-7), human non-small cell lung cancer (NCI-H460), human cervical carcinoma (HeLa), human hepatocellular carcinoma (HepG2), and normal porcine liver (PLP2) cell lines demonstrated that all cancer cells are susceptible to extracts. The extract from pink flowers is the most potent with

IC_{50} values ranging from 90 to 167 μg/mL. None of the extracts are active at a concentration of 400 μg/mL against PLP2 used as normal cells.[212]

The ethanol extract (80%) from whole plants of *I. balsamina* is cytotoxic against normal mouse embryonic fibroblast (NIH 3T3) and HeLa cells (IC_{50} of 49.6 and 33.7 μg/mL, respectively). Results from xenograft model in Swiss albino mice using Dalton's Lymphoma ascites (DLA) cell line indicates that extract prolongs life span, reduces blood count of tumor cells, attenuates weight gain, and partially counteracts changes in hematological parameters (counts of white blood cells count, red blood cells, and platelets; packed cell volume; hemoglobin) when is given at daily oral dose of 200 mg/kg or 400 mg/kg.[10,82]

Ding *et al.* reported the isolation 1 from the chloroform extract of *I. balsamina* leaves through chromatographic fractionation guided by the results of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cell viability assay on HepG2 cells. The crude extract and the isolated compound showed IC_{50} values of 41.5 and 6.08 μg/mL, respectively.[10,266]

Compounds 1, balsamitril (14), balsamitril-3-*O*-β-D-glucoside (15), (3*S*,4*R*)-3,4-dihydroxy-3,4-dihydronaphthalen-1(2*H*)-one (16), *trans*-(3*S*,4*S*)-3,4-dihydroxy-1-tetralone (17), hydroquinone (18), *p*-hydroxybenzoic acid (19), *p*-hydroxybenzoic acid methyl ester (20), protocatechuic acid (21), vanillic acid (22), tyrosol (23), *trans*-*p*-coumaric acid (24), and *trans*-ferulic acid (25) were isolated from *I. balsamina* white flowers methanol (80%) extract. The evaluation of their cytotoxicity against human lung adenocarcinoma (A-549), human ovarian adenocarcinoma (SK-OV-3), human malignant melanoma (SK-MEL-2), and human colorectal cancer (HCT-15) cell lines showed that 1 has the best antineoplastic profile with IC_{50} values of 25.51 and 1.03 μM against A-549 and SK-MEL-2 cells. The IC_{50} values against SK-OV-3 and HCT-15 cells are > 30 μM.[267]

The bioassay-guided fractionation of methanol extract from aerial parts of *I. balsamina* using luciferase test on Human Embryonic Kidney cell line (HEK293) allowed the isolation of 1 as a compound that downregulates T Cell Factor protein (TCF)/β-catenin complex transcriptional activity (IC_{50} of 2.9 μM). This cellular process is necessary for protein expression when Wnt signaling pathway is active. The activation of Wnt pathway can induce carcinogenesis, therefore, compounds that inhibits these signaling events are considered as potential agents to suppress cell growth.[268]

Compound 1 exerts cytotoxicity against A-549 cell line according to cell viability assays (IC_{50} of 7.5 μM). The compound induces apoptosis in A-549 cells at concentration of 10 μM without distinction of cell cycle phase. *In vitro* assay using fluorogenic probe 2′,7′-dichlorodihydrofluorescein diacetate (DCFDA) reveals that 1 promotes ROS generation in A-549 cell cultures. This ROS generation triggers damage in DNA and activation of c-Jun N-terminal Kinase (JNK) and p38 Mitogen-Activated Protein Kinase (MAPK) proteins, these processes are responsible of apoptosis induction in A-549 cells exposed to 1.[269,270] Moreover, 1 induces cytotoxicity on human stomach adenocarcinoma (MKN45) cells with IC_{50} of 24.01 μM. This substance promotes S and G2/M phases cell cycle arrest, disrupts cell membrane potential, increases the production of ROS, and triggers apoptosis via Bax expression and cytochrome c release from mitochondria.[271]

Daud *et al.* reported that 1 and apigenin (26), a flavonoid present in several *Impatiens* species,[182,212,225,272-275] can reduce the viability of human breast triple-negative adenocarcinoma (MDA-MB-231) cells (IC_{50} of 29 μM). Compounds 1 and 26 reduce the glucose up-take (approximated reduction of 40%) at concentrations of 29 and 100 μM, respectively. On the other hand, 1 reduces lactate production and the expression of Akt and glucose transporter 1 (GLUT-1) mRNAs.[276] According to Liew *et al.*, 1 reduces the cell viability of MDA-MB-231 cells by approximately 60% at concentration of 20 μM. This compound can decrease the cell migration and invasion according to results of wound-healing migration and Matrigel invasion assays when evaluated at concentration range of 2.5-7.5 μM. Compound 1 reduces the activity of Matrix Metallopeptidase 9 (MMP-9) in cell secreted protein fraction by 75% at concentration of 7.5 μM.[277]

The exposition of MDA-MB-231 cells to 1, at concentration of 7.5 μM, promotes changes in the proteome including a reduction in the expression of nineteen proteins implicated in cytoskeleton organization, protein synthesis and folding, protein covalent modification, ribosome processing, cell adhesion, epithelial-mesenchymal transition, Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation, cell cycle DNA transcription, DNA repair, DNA methylation, nucleotide synthesis, immune response, mRNA processing and membrane trafficking. Furthermore, the expression of seven proteins implicated in oxidative stress response and protein tyrosine phosphatase activity is increased. Among those proteins which expression is reduced, S100-A4 and laminin-binding protein (RPSA) are highlighted due their roll in metastasis promotion while the increase in E-cadherin expression is also remarkable considering its role in preventing epithelial-mesenchymal transition. Another change observed in treated cells is the reduction in NF-κB and ERK1/2 phosphorylation.[278]

The treatment of human Burkitt lymphoma (Raji) cells with 1 at concentration of 40 μM induces changes in the expression of genes implicated in MAPK, Phosphoinositide 3-kinase (PI3K), and NF-κB signaling pathways. Up-regulated genes participate in cell cycle, apoptosis, and tumor suppressor while down-regulated genes are involved in apoptosis inhibition, angiogenesis, and cell cycle, they mainly correspond to transcription factors and proto-oncogenes.[279]

Balsaminone A (27), B (28) and C (29) have been isolated from *I. balsamina* seed ethanol extract. Cytotoxic activity of these compounds has been evaluated on human liver cancer (Bel-7402), A-549, and HeLa cell lines. According to results, 27 is the most active compound with IC_{50} of 9.36, 11.25 and 9.73 μM on A-549, Bel-7402 and HeLa cells, respectively. The other two compounds have IC_{50} values ranging from 19.05 to 64.69 μM against the same cell lines.[10,50] Compounds 1, 28, balsaminone D (30), and balsaminone E (31), were isolated from the ethanol (75%) of *I. balsamina* flowers. The cell viability assay against tumor necrosis factor α (TNF-α) stimulated rat hepatic stellate (t-HSC/Cl-6) cells showed that 30 is the most potent compound (IC_{50} of 30.54 μM).[280]

Compounds 2, 3, 4, 6, kaempferol 3-*O*-rutinoside (nicotiflorin) (32), kaempferol 3-*O*-α-rhamnoside-7,4-di-*O*-β-galactoside (33), 6-methoxykaempferol 3-*O*-β-D-glucosyl(1‴→2″)-β-D-glucopyranosyl-(6‴-(*E*)-caffeoyl)-7-*O*-β-D-glucopyranoside (34), dihydromyricetin (35), myricetin (36), 1,2-*O*-(4-dihydroxybenzoyl)-2,4,6-trihydroxyphenylacetic acid (37), methyl 2-*O*-(4-hydroxybenzoyl)-2,4,6-trihydroxyphenylacetate (38), 2-*O*-(4-hydroxybenzoyl)-4-*O*-β-D-glucopyranosyl-6-hydroxyphenylacetic (39), methyl 2-*O*-(4-hydroxybenzoyl)-4-*O*-β-D-glucopyranosyl-6-hydroxyphenylacetate (40), ethyl 2-*O*-(4-hydroxybenzoyl)-4-*O*-β-D-glucopyranosyl-6-hydroxyphenylacetate (41), butoxy 2-*O*-(4-hydroxybenzoyl)-4-*O*-β-D-glucopyranosyl-6-hydroxyphenylacetate (42), butoxy 2-*O*-(4-hydroxybenzoyl)-4,6-dihydroxyphenylacetate (43), (6-*O*-*p*-coumaroyl)-β-D-glucopyranosyl-2-*O*-(4-hydroxybenzoyl)-4-*O*-β-D-glucopyranosyl-6-hydroxyphenylacetate acid (44), and 4-*O*-β-D-glucopyranosyl-2,6-dihydroxyphenylacetic acid (45) were isolated from the ethanol (75%) extract of *I. balsamina* flowers. The evaluation of their cytotoxicity against t-HSC/Cl-6 cells indicates that 36 is the most active compound with a IC_{50} value of 15.91μg/mL.[281]

Aromatase enzyme is considered as a molecular target in metastatic estrogen-dependent breast cancer. Aromatase inhibition *in vitro* assay indicates a IC_{50} value of 10 μM for 36. FlexX docking studies, have shown that binding complexes between 36 and human aromatase have energies ranging from -23 to kJ/mol to -13 kJ/mol for the best 20 poses.[282]

Imbalosides A (46), B (47) and C (48) are oleanane-type triterpenoidal glycosides isolated from the white flowers of *I. balsamina.* The cytotoxicity of the compounds was tested *in vitro* on A-549, SK-MEL-2, SK-OV-3, and human invasive breast carcinoma (BT549) cell lines. No compound is cytotoxic against SK-OV-3 and SK-MEL-2 cell lines at concentration of 30 μM. Only 48 exhibited low cytotoxic on A-549 cell line (IC_{50} = 29.8 μM) while 47 and 48 are cytotoxic on BT549 cell line (IC_{50} of 26.4 μM and 29.2 μM, respectively).[283,284]

Compounds balsaminsides A (49), B (50), C (51) and D (52) were isolated from the ethyl acetate fraction obtained from the ethanol (75%) extract of *I. balsamina* flowers. These compounds demonstrated anti-hepatic fibrosis activity on t-HSC/Cl-6 cells with IC_{50} range of 13.9-98.91 μM. Compound 49 is the most potent compound.[13,33] Honsenkol A-3-*O*-β-D-glucopyranosyl-26-*O*-β-D-glucopyranosyl-28-*O*-β-D-glucopyranosyl-*O*-β-D-glucopyranose (53) and (3*S*,4*R*,17*R*,20*S*)-17-hydroxy-3-*O*-β-D-xylopyranose(12)-β-D-glucopyranosyl-26-*O*-β-D-glucopyranosyl-28-*O*-β-D-glucopyranosyl-21,24-epoxybaccharane (54) were isolated from ethanol extract (80%) of *I. balsamina* seeds. Compound 54 has demonstrated cytotoxic activity on human melanoma (A375) cells with IC_{50} of 114.96 μM.[51]

Model of tumorigenesis induction in Swiss Webster albino mice by topic exposition to dimethylbenzanthracene and croton oil demonstrated that the external application of the ethanol extract from leaves of *I. balsamina* and 1, in the area where the skin tumorigenesis has been promoted, can protect internal organs (stomach, pancreas, duodenum, and spleen) against the development of histological alterations observed in non-treated animals.[285]

The comparative study of the cytotoxicity of the *n*-hexane, ethyl acetate and methanol extracts from stems, leaves and roots of *I. glandulifera* against A-549, human glioma (U373) and human melanoma (SMEL-28) cell lines indicates that ethyl acetate extract from stems is the most active with a median IC_{50} of 33 μg/mL. The compounds 1 and 7 were isolated from the ethyl acetate extract from the stems, leaves and roots, while glanduliferin A (55) and glanduliferin B (56) were obtained from the ethyl acetate extract from stems. The evaluation of the cytotoxicity of these isolated compounds against the after mentioned cell lines showed that 1 is the most active compound with IC_{50} values in the range of 2-3 μg/mL.[286]

Seeds from several *Impatiens* species, including *I. balsamina, I. bracteata, I. campanulata, I. chinensis, I. cuspidata, I. gardneriana, I. jurpia, I. latiflora, I. latifolia, I.pulchra, I. oppositifolia, I. pulcherrima, I. racemosa, I. racemulosa, I. stenantha, I. talbotii, I. tomentosa*, and *I. viscida* have α-parinaric acid (57) in quantities in the range of 3.18-34.15%. Seeds from *I. racemulosa* have the highest content of this unsaturated fatty acid.[287] Compound 57 is also the mayor fatty acid present in the oil of *I. edgeworthii* seeds.[288] Cytotoxicity of 57 was evaluated using *in vitro* cell viability assays with fetal rat astrocytes (36B10), rat glioma (C6), human glioma (A172), and human monocytic leukemia (U-937) cell lines. The test compound induces a cell death percentage of 20% in fetal rat astrocytes at concentration of 40 μM. At 4 μM, 57 promotes a cell death percentage of 70% in 36B10 line. In C6 and A172 glioma lines, cell mortality is 70% and 82% when they are exposed to 57 at concentration of 12 μM, respectively. In U-937 cell line, the cell mortality induced by 57 is 90% at concentration

of 4 μM. Isoprostane is increased in cell cultures treated with 57 and cytotoxicity of this compound is attenuated when culture media is supplemented with α-tocopherol, this observation suggest that 57 acts via oxidative stress induction.[289] Moreover, it has been demonstrated that 57 induces cell death in 36B10 line via JNK upregulation and p38 MAPK downregulation according to western blotting and Reverse Transcription-Polymerase Chain Reaction (RT-PCR) analyses of cell cultures treated with 57.[290]

IPS-1 (58) and IPS-2 (59) were isolated from the *n*-butanol fraction of methanol extract form the leaves of *I. parviflora*. According to the *Vibrio harveyi* mutagenicity assay, both compounds are no mutagenic at concentration of 40 ng/mL. Compound 58 is cytotoxic on A375 and human melanoma (HTB140) cell lines inducing a reduction in cell viability of 69.51% and 39.81% at concentration of 50 μg/mL, respectively. Compound 58 also reduces the viability in prostate cancer Du145 and PC-3 cell lines by 49.61% and 17.32%, at the same test concentration, respectively. However, 58 is inactive against human melanoma (WM793), BJ and normal human prostate epithelium (PNT2) cells at concentration of 50 μg/mL.[161]

Compounds monogalactosyl diacylglycerol 1 (MGDG-1) (60) and digalactosyl diacylglicerol 1 (DGDG-1) (61) have been isolated from the methanol extract of *I. parviflora*. The cytotoxicity of these compounds has been tested against WM793, HTB140, A-375, and human keratinocyte (HaCaT) cell lines. Compound 60 is more active than 61 with IC_{50} of 15.14 μg/mL against A375. However, this value is > 50 μg/mL on the remaining cell lines. Compound 60 shows synergic cytotoxicity in combination with doxorubicin on A-375 cell line. It also inhibits around 40% of tyrosinase enzyme activity at concentration of 500 μg/mL while 61 is inactive. Lactate dehydrogenase viability assay performed on HepG2 cell indicates that 60 and 61 have not hepatotoxicity activity at concentration of 100 μg/mL.[291]

Impatienoside G (62) was isolated from the *n*-butanol fraction of the ethanol-water (7:3) extract obtained from *I. siculifera* whole herb. This compound showed cytotoxic activity against human acute myeloid leukemia (HL-60), human stomach adenocarcinoma (KATO-III), and A-549 cells with IC_{50} values of 21.8, 36.7, and 24.8 μM, respectively.[177]

Impatiprins A (63), B (64), and C (65) were isolated from *n*-butanol fraction from the methanol extract of *I. pritzelii* Hook. f. var. *hupehensis* rhyzomes. According to cytotoxicity assays, 63 has IC_{50} values of 106.5, 134.57, and 157.83 μM against Balb/c mice sarcoma tumor (S-180), HeLa and HepG2 cell lines, respectively. Compound 64 has IC_{50} values of 37.40, 44.93, and 55.78 μM against S-180, HeLa and HepG2, respectively. Compound 65 is inactive on the same cell lines.[163]

Compounds 62, scaberoside A_2 (66), 3-*O*-β-D-glucuronopyranosyl-echinocystic acid-28-*O*-β-D-apiofuranosyl-(1→3)[*O*-β-D-xylopyranoseyl)(1→4)]-*O*-α-L-rhamnopyranosyl-(1→2)-β-L-arabinopyaranoside (67), and 3-*O*-β-D-glucuronopyranosyl-echinocystic acid 28-*O*-β-D-apiofuranosyl-(1→3)[*O*-β-D-xylopyranosyl-(1→4)]-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-xylopyranoside (68), were isolated from *I. pritzelii* var. *hupehensis* rhizome ethanol (50%) extract. Compound 62 is the most potent in reducing the cell viability of Balb/c mice lymphocytes. It reduced the cell viability by 38.9% at concentration of 80 μg/mL.[167]

The evaluation of the cytotoxicity of the esterified triterpenoid and fatty acid fractions derived from the petroleum ether (45-60°C) extracts of *I. glandulifera* and *I. noli-tangere* seeds, leaves and roots revealed that triterpenoid fractions from the seeds of *I. noli-tangere* and *I. glandulifera* are the most active against human myeloblastic leukemia cell lines (HL-60 and HL-60/MX2) with IC_{50} values in the interval of 11.69-88.07 μg/mL. According to GC-MS and Gas Chromatography Coupled to Flame Ionization Detector (GC-FID) analyses, α-spinasterol acetate is the most abundant compound in the *I. glandulifera* triterpenoid fraction (21.63%) while 5α-lup-20(29)-en-3β-ol acetate is the mayor component of *I. noli-tangere* triterpenoid fraction (13.08%).[292]

The cytotoxicity of the methanol extract from *I. textorii* aerial parts was evaluated on the following cell lines: HeLa, human gastric adenocarcinoma (MK-1), murine melanoma (B16F10), and human T-cell lymphotropic virus type1-infected T cells (MT-1 and MT-2 cell lines). In the case of MT-1 and MT-2, it is remarkable that lymphotropic virus type 1 can induce adult T-cell leukemia/lymphoma. The extract is active against B16F10 cells with IC_{50} in the range of 50–100 μg/mL. It is also active on MT-1 and MT-2 with IC_{50} in the range of 10–100 μg/mL.[293,294]

The study of the cytotoxicity of the methanol extract from *I. textorii* whole plants and its *n*-hexane, ethyl acetate, *n*-butanol, and water fractions against human gastric adenocarcinoma (AGS), human colorectal adenocarcinoma (HT-29), HeLa, and A-549 cell lines shows that the ethyl acetate is the most active, promoting a reduction on cell viability higher than 90% at concentration of 500 μg/mL against all tested cell lines.[295]

The ethanol fraction from *I. textorii* flower *n*-hexane extract reduces the cell viability (approximately 40% reduction) of mouse melanoma (B16BL6) cells at concentration of 400 μg/mL. In comparison to non-treated control cultures, the extract, at test concentration of 200 μg/mL, counteracts cell proliferation (17%), melanin production (57.48%), tyrosinase enzymatic activity (36.90%), and protein expression of melanocyte inducing transcription factor (MITF) (50.7%) and tyrosinase (59.54%) on B16BL6 cells stimulated with α-melanocyte-stimulating hormone (α-MSH).[183]

The *n*-butanol fraction, rich in saponins, obtained from the methanol (50%) extract of the leaves of *I. capensis* has cytotoxic effects against MCF-7 cell line completely suppressing its proliferation at concentration of 100 μg/mL. The fraction has

only cytostatic activity against HT-29 cell line inhibiting its proliferation by 35% approximately. The fraction is inactive on A375 cell line.[120]

The leaves from *I. walleriana* have anthocyanins and carotenoids with reported approximated amounts of 8.577 µmol of cyaniding 3-O-glucoside equivalents (C3GE)/g and 1 mg/g, respectively. The aqueous extract from *I. walleriana* leaves shows cytotoxicity against AGS and SK-OV-3 with IC_{50} of 2.5 and 1.6 mg/mL, respectively. This extract can induce apoptosis on test cells according to flow cytometry analysis.[296] Similarly, it is reported that aqueous extract from the aerial parts of *I. walleriana* has IC_{50} of 2.87 mg/mL against AGS cell line.[297]

The ethanol (80% v/v, acidified with trifluoro acetic acid 0.5% v/v) extract from *I. walleriana* orange flowers its more cytotoxic against HeLa, HepG2, MCF-7, and NCI-H460 cell lines (IC_{50} in the range of 177.3-333.4 µg/mL) than extract from *I. walleriana* pink flowers. None of these extracts are cytotoxic at concentration 400 µg/mL against PLP2 cells.[223]

Anti-inflammatory and analgesic activities

The evaluation of the anti-inflammatory activity of the water and ethanol extracts from the stems and roots of *I. balsamina* using the carrageenan induced paw edema model in Wistar rats demonstrated that ethanol extracts from stems and roots, at oral dose of 50 mg/kg, have the best anti-inflammatory profile.[298] The aqueous extract from the leaves of *I. balsamina* has shown anti-inflammatory activity in cotton pellet implantation, granuloma pouch sub-acute inflammation, and formaldehyde arthritis chronic inflammation model using Wistar rats. The oral dose of 2000 mg/g shows the highest anti-inflammatory properties on the experimental models. According to toxicity assays, the extract does not induce toxicity signs at oral dose of 3000 mg/kg.[299] Furthermore, the aqueous extract from leaves of *I. balsamina* has shown anti-inflammatory activity in albino rat model of carrageenan induced paw edema and analgesic effects on tail flick model when given at oral dose in the range of 500-1000 mg/kg.[300] Other extracts from leaves can be active too, the oral administration of the ethanol extract from leaves and stems of *I. balsamina* at dose of 500 mg/kg significantly reduces paw edema and joints inflammation on Wistar rats model of arthritis induced by intraplantar injection of complete Freund's adjuvant. A reduction in TNF-α in plasma of treated animals is also reported.[301] Aqueous and ethanol extracts from *I. balsamina* seeds have analgesic and anti-inflammatory effects in models of xylene ear edema in mice and egg-white induced foot swelling and granuloma.[302]

The methanol extract from *I. balsamina* petals has TPC and TFC values of 103.26 mg GAE/g and 64.69 mg QE /g, respectively. The antinociceptive activity of the extract has been studied through animal models using Swiss albino mice. The extract reduces acetic acid-induced writhing response when given at oral dose of 50 mg/kg. Similar results are observed in formalin-induced paw licking test, the extract reduces the licking response in mice at oral dose of 50 mg/kg. The extract increases the latency time in hot plate test, specially at oral dose of 400 mg/kg, this effect is antagonized by naloxone. According to tail immersion test, the extract increases the latency time at oral dose of 100 mg/kg, response that is also antagonized by naloxone. Results from hole cross and open field tests have shown that extract promotes depression of central nervous system 30 min after the treatment of mice with oral doses of 400 mg/kg and 100 mg/kg, respectively.[303]

The ethanol (80% v/v, acidified with trifluoro acetic acid 0.5% v/v) extract from pink flowers of *I. balsamina* can reduce the production of Nitric Oxide (NO) on Lipopolysaccharide (LPS) stimulated murine macrophage (RAW 264.7) cell line with IC_{50} of 164 µg/mL. This extract is more potent than extract obtained from orange flowers (IC_{50} of 281 µg/mL).[212]

Several studies on anti-inflammatory mechanism of *Impatiens* plants extracts and metabolites have been carried out. Protein denaturation is a common process in inflammatory events, the ethanol extract from *I. balsamina* seeds shows inhibitory activity against bovine serum thermal denaturation with IC_{50} of 210 µg/mL.[304] According to the *in vitro* evaluation of chemiotaxis inhibitory activity through Boydan chamber assay, using human Polymorphonuclear leukocytes (PMN) and monocytes as test cells and formyl-Methionyl-Leucyl-Phenylalanine (fMLP) as a chemoattractant, compound 1 can reduce chemiotaxis with IC_{50} of 7.63 µg/mL. Compound 1 can also inhibit myeloperoxidase enzyme from PMN stimulated with phorbol 12-myristate 13-acetate (PMA) (IC_{50} of 24.6 µg/mL). Luminol assay indicates that 1 reduces the production of ROS in human whole blood cells, PMN and monocytes with IC_{50} values of 8.51, 9.43 and 6.49 µg/mL, respectively.[305]

Oral sprays containing α-mangostin (5 mg/mL), 1 (250 µg/mL) or a combination of both (at concentration of 5 mg/mL and 250 µg/mL, respectively) are effective to reduce NO production on RAW 264.7 cells stimulated with LPS with low cytotoxicity. The formulation that combines α-mangostin (5 mg/mL) and 1 (250 µg/mL) does not show cytotoxicity at concentrations equal or lower than 6.25 µg/mL but shows the best NO production inhibitory activity (reduction of 200% on NO production) on RAW 264.7 cell cultures at concentration of 0.78 µg/mL.[236]

Beauty-salt™ is a food additive used in Korea as remedy for inflammatory illnesses. The ingredients of this product include solar salt and *I. balsamina* extracts. Beauty-salt™ treatment of Human Mast (HMC-1) cells stimulated with a mixture of PMA and the Calcium Inophore A23187 (PMACI) significantly reduces the production of Thymic Stromal Lymphopoietin (TSLP), Interleukin (IL) 1β and IL-8 mRNAs and their expression at concentration of 1 mg/mL without a significant reduction of cell viability in comparison to control cells. This product inhibits

caspase 1 enzymatic activity and its expression. Moreover, Beauty-salt™ can reduce the activation of receptor-interacting-serine/threonine-protein kinase 2 (RIP2) and NF-κB. It also inhibits the phosphorylation of ERK and JNK, thus, it is proposed that Beauty-salt™ attenuates the expression of pro-inflammatory cytokines through the inhibition of caspase 1/NF-κB/RIP2/MAP kinase pathway.[16]

Compound 3, a flavonoid present in Beauty-salt™, at concentrations of 0.2 μg/mL and 2 μg/mL, inhibits in a dose-response manner the expression of clusters of differentiation 11, 14 and 44 induced in human leukemia monocytic (THP-1) cell cultures by their stimulation with IL-32. Compound 3, at concentrations of 0.02, 0.2, and 2 μg/mL, reduces the enzymatic activity of caspase 1 and the production of TSLP, IL-1β, IL-18 and TNF-α on THP-1 cells exposed to IL-32. Results from western-blotting analysis suggest that 3 reduces the production of proinflammatory cytokines by inhibiting the p38-MAPK/NF-κB/caspase 1 pathway. Compound 3, at doses of 0.02, 0.2, and 2 μg/mL, reduces the production of NO, IL-6, IL-8, TSLP and TNF-α in THP-1 cells stimulated with LPS. Compound 3 is not cytotoxic on THP-1 cells at assayed concentrations.[81]

Compounds 46, 47 and 48 were isolated from white flowers of *I. balsamina.* They showed inhibitory action on NO production on cultures of murine microglia (BV-2) cell line stimulated with LPS with (IC_{50} values of 41.0, 33.8, and 34.8 μM, respectively). These results suggest that tested compounds could serve as anti-neuroinflammatory agents.[283] Similar results are reported by Kim *et al.*, the ethyl acetate fraction from the methanol extract of *I. balsamina* white petals reduces NO production in BV-2 cells stimulated with LPS (IC_{50} of 5.3 μg/mL). Compounds 2, 3, 4, 5, 6, 32, 35, kaempferol 3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside (69), and kaempferol 3-*O*-β-D-allopyranoside (70), were isolated from the active ethyl acetate fraction. These compounds reduce the NO production on BV-2 microglial cells treated with LPS. From them, compound 3 is the most active (IC_{50} of 8.86 μM).[306]

Impatienol (71), isolated from ethanol (35%) extract of *I. balasamina* aerial parts; balsaquinone (72), isolated from ethanol (50%) extract of *I. balasamina* pericarp; and its sodium salts, obtained from the ethanol (35%) extract of *I. balasamina* fresh corollas (impatienolate (73) and balsaminolate (74), respectively) can inhibit Cyclooxygenase 1 (COX-1) and 2 (COX-2). The analysis of their effects indicates that 73 is the most active compound with IC_{50} of 101.0 and 0.2 μM against COX-1 and COX-2, respectively. It is remarkable the high selectivity of 74 on COX-2 (IC_{50} values of > 100 μM against COX-1 and 9.4 μM against COX-2).[307]

Kim *et al.* reported the isolation of thirteen phenolic compounds from *I. balsamina* white flowers methanol (80%) extract. The evaluation of their ability to reduce the production of NO on BV-2 cells stimulated with LPS showed that 18 is the most potent compound (IC_{50} of 20.73 μM). The cell viability was higher than 77% at determined IC_{50} values for these compounds.[267] Compounds 6, 7, 19, 32, 1β,2α,4β-triol-1,2,3,4-tetrahydronaphthalene (75), 1β,2β,4β-triol-1,2,3,4-tetrahydronaphthalene (76), (7*R*,8*S*)-dihydrodehydrodiconiferyl alcohol-9-*O*-β-D-glucopyranoside (77), β-amyrin (78), erythrodiol (79), 29-nor-20-oxolupeol (80), lupenone (81), and lupeol (82) have been isolated from the methanol (80%) extract of *I. balsamina* stems. From them, 78 is the most potent compound in reducing the production of NO in BV-2 cells stimulated with LPS (IC_{50} of 25.59 μM). Test compounds showed low cytotoxicity at determined IC_{50} (cell viability > 82%).[308]

Ethanol extract made of *I. noli-tangere* leaves and stems was subjected to micro and nanofiltration. Retentate obtained by nanofiltration has the highest *in vitro* anti-inflammatory activity according to results of inhibition assays on Lipoxygenase (LOX) (IC_{50} = 2.46 μg/mL), COX-1 (IC_{50} = 18.4 μg/mL) and COX-2 (IC_{50} = 1.9 μg/mL) enzymes. The anti-inflammatory activity of retentate obtained through nanofiltration was tasted *in vivo* on paw edema induction models with dextran and kaolin. The extract showed a weak anti-inflammatory effect at dose of 5 mL equivalent to 14 mg of phenolic compounds. Chemical analyses of this bioactive extract through HPLC-MS revealed the presence of 2, 4, 5, ursolic acid, phenolic acids, peonidin 3-*O*-glucoside and malvidin as components.[153]

The anti-inflammatory activity evaluation of the polysaccharides isolated from aerial parts and roots of *I. balsamina, I. glandulifera, I. noli-tangere* and *I. parviflora* showed that only polysaccharides from *I. glandulifera* aerial parts, at a concentration of 50 μg/mL, could significantly reduce the expression of IL-8 in human neutrophils stimulated with LPS under *in vitro* assay (expression reduction percentage of 32.7%). None of the polysaccharides are cytotoxic on human neutrophils at a concentration of 50 μg/mL according to *in vitro* cell viability assay.[309]

The methanol extract from the fresh leaves of *I. parviflora* can inhibit the thermal denaturation of serum albumin, showing an inhibition percentage of 79.05% at concentration of 500 μg/mL. In contrast, methanol and chloroform extracts from dry leaves are inactive when tested at the same concentration. Compound 60 isolated from the leaves of *I. parviflora* has inhibitory activity of 17.67% at 500 μg/mL while 61, other galactolipid isolated from the same plant material, is inactive in the same assay conditions. The comparison of anti-hyaluronidase activity of the mentioned extracts demonstrates that methanol extract from fresh leaves is the most potent, reaching an inhibition percentage of 27.62% at test concentration of 127.90 μg/mL. Compound 60 is more active than 61, showing an inhibition percentage of 100% at test concentration of 127.90 μg/mL.[310]

Aqueous extract from *I. parviflora* stimulates prostaglandins production on bovine seminal gland microsomes (increase of 12%) and Platelet-Activating Factor (PAF) mediated neutrophil exocytosis (increase of 7%).[311] However, 58 and 59, isolated from the methanol extract of *I. parviflora* roots, show significant *in vitro* anti-inflammatory activity. These compounds inhibit bovine albumin thermal denaturation (IC_{50} of 86.7 and 109.76 μg/mL, respectively). Additionally, 59 demonstrates significant anti-hyaluronidase activity (IC_{50} = 286.7 μg/mL).[312]

The methanol extract from whole herb of *I. textorii* does not compromise the viability of Bone Marrow Derived Macrophages (BMDM) from C57BL/6 mice at concentration of 100 μg/mL. The extract reduces the *in vitro* production of IL-1β on BMDM exposed to LPS by reducing the oligomerization of apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and caspase 1 maturation that are necessary for NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasomes activation. Results from *in vivo* model of LPS-induced acute lung injury in C57BL/6 mice indicate that methanol extract from whole herb of *I. textorii* reduces cellular broncho-alveolar infiltration, IL-1β production and NLRP3 expression when given at dose 40 mg/kg 12 hr and 2 hr before mice exposition to LPS.[181]

Results from collagen-induced arthritis model in BABL/c mice indicates that methanol extract of *I. pritzelii var. hupehensis* roots and its *n*-butanol fraction attenuate the erythema and swelling related to arthritis-like inflammation, with best results obtained at oral doses of 1.12 mg/kg and 0.53 mg/kg, respectively. Thymus and spleen indexes are also significantly reduced by both treatments. The extract and the fraction reduce the serum levels of Ig G immunoglobulins, IL-18 and Interferon-*γ* (IFN-γ). Both, extract and fraction, increment IL-10 serum levels. The extract and its *n*-butanol fraction have acute lethal dose higher than 50 mg/kg.[166]

IL-8 is an important cytokine considered as a target in several immune diseases including rheumatoid arthritis. Soya-cerebrosides I (83) and II (84) have been isolated as an isomeric mixture from rhizomes of *I. pritzelii*. This mixture, at concentration of 1 μM, significantly reduces *in vitro* production of IL-18 in Peripheral Blood Mononuclear Cells (PBMC) stimulated with LPS without cytotoxicity.[313]

Compounds 64, 65, echinocystic acid (85), 3-*O*-β-D-glucuronopyranosyl echinocystic acid (86), 3-*O*-[(6-*O*-methyl)-β-D-glucuronopyranosyl] echinocystic acid (87), and 3-*O*-[(6-*O*-ethyl)-β-D-glucuronopyranosyl] echinocystic acid (88) were isolated from the *n*-butanol extract of *I. pritzelii* var. *hupehensis* rhizomes. The ability of these compounds to reduce the production of IL-18 on PBMC stimulated with LPS has been evaluated under *in vitro* experiments. All compounds are active but 85 is the most potent, reducing the production of IL-18 from 0.620 ng/mL of the control to 0.105 ng/mL at test concentration of 100 μM.[314]

Compounds 3, 4, 5, 7, 20, (*S*)-naringenin (89), (*S*)-pinocembrin (90), (±)-3′,5′,5,7-tetrahydroxyflavanone (91), phlorizin (92), 2,4-dihydroxydihydrochalcone-6-*O*-*β*-D-glucoside (93), dehydrovomifoliol (94), methyl 2,4,6-trihydroxybenzoate (95), isotachioside (96), polybotrin (97), isofraxidin (98), and 7*R*,8*S* isomer of yemuoside YM1 (99) have been isolated from the methanol (95%) extract of *Impatiens chapaensis* whole plants. From them, 20 has the best inhibitory activity (IC_{50} of 107.15 μg/mL) against the production NO on RAW 264.7 cells stimulated with LPS.[315]

The ethanol (80% v/v, acidified with trifluoro acetic acid 0.5% v/v) extract from *I. walleriana* orange flowers can reduce the production of NO on RAW 264.7 cells stimulated with LPS (IC_{50} of 312.1 μg/mL). This extract is more potent than pink flowers extract (IC_{50} of 349.21 μg/mL).[223]

Another compound with anti-inflammatory activity ubiquitously detected in *Impatiens* plants seeds is 57. This molecule is an inhibitor of LOX-1 enzyme with IC_{50} and inhibition constant (Ki) of 18. 8 and 9.8 μM, respectively. According to enzyme kinetic and molecular docking studies, this molecule acts as a competitive inhibitor of LOX-1.[316]

Anti-anaphylactic and antipruritic activities

PAF mediated blood pressure reduction is a process observed in anaphylaxis and inflammation. The pretreatment of ddY mice with ethanol extract (35%) from *I. balsamina* white petals, at intravenous dose of 0.01 mg/kg, inhibits the decrease in blood pressure induced by PAF intravenous administration. The activity of 1, 2, 4, 5, 6, 8, 32, and kaempferol 3-*O*-rhamnosyldiglucoside (100), isolated from *I. balsamina,* was also evaluated at intravenous dose of 10 μg/kg. Only 4, 6, 5, 8, 32, 100 are effective to counteract the blood pressure reduction observed after PAF administration.[317]

The ethanol extract (35%) of *I. balsamina* flowers, given at intravenous dose ranging from 0.01 to 256 mg/kg, significantly reduces the mortality and anaphylaxis symptoms in Hen Egg-white Lysozyme (HEL) sensitized ddY mice after their re-exposition to HEL. The pretreatment with the extract before HEL antigen administration to sensitized mice prevents the fall in blood pressure commonly observed in anaphylactic reactions.[75,318-320] Compounds 8, 32, 100 have been isolated from the ethanol extract of *I. balsamina* white petals. When 8 and 100 are intravenously administered at dose of 0,1 mg/kg before HEL challenge, they demonstrate antianaphylaxis activity under the previously described model. Compounds 8 and 32 show similar results when they are oral administrated at dose of 10 mg/kg in mice before HEL exposure.[321,322]

Ethanol (35%) and *n*-butanol extracts from *I. balsamina* flowers, given at oral or intravenous dose of 100 mg/kg before HEL challenge, reduce the mortality of sensitized ddY mice when they are re-exposed to antigen. The pretreatment with aqueous and ethyl acetate extracts from *I. balsamina* flowers can also reduce the mortality on mice when they are given at the same dose but only through oral and intravenous routes of administration, respectively. Likewise, compounds 1, 8, and 32 isolated from *I. balsamina* flowers reduce mice mortality when they are intraperitoneal administered at dose of 10 mg/kg. Compounds 8 and 32 also reduce mice mortality when they are given at oral dose of 10 mg/kg.[323]

According to *in vivo* model of heterologous passive cutaneous anaphylaxis reactions using Wistar/ST rats as receptors of HEL-sensitized ddY mice serum, the pretreatment of mice with compound 3, isolated from *I. balsamina* flowers, at oral dose of 10 mg/kg before HEL sensitization reduces the vascular extravasation triggered by HEL exposition in rats that previously received an intradermal injection (50 µL) of sensitized mice serum. The mixture of serum from HEL sensitized ddY mice with 10 µg of ethanol (35%) or ethyl acetate extracts from *I. balsamina* flowers before serum intradermal administration to rats attenuates the vascular extravasation response observed in rats after HEL challenge. Similar results are observed when serum from sensitized mice is mixed with 1 µg of 8 or 32. These data suggest that 3 prevents the sensitization (production of Ig E antibodies) process in mice while 8 and 32 reduce the anaphylactic response mediated by the serum of ddY mice sensible to HEL. Additionally, results obtained from model of rat skin intradermal histamine-induced vasodilation indicates that intradermal administration of 10 µg of *I. balsamina* ethanol, ethyl acetate extracts or 1 µg of 8 reduces the vascular extravasation induced by histamine.[323]

The oral administration of ethyl acetate fraction from the ethanol extract of leaves and stems of *I. balsamina* has immunomodulatory effects in Balb/C mice at dose of 125 and 250 mg/kg. According to delayed type hypersensitivity model using sheep red blood cells as antigen, the treatment with the fraction significantly reduces the paw edema developed by sensitized animals challenged by footpad injection of the antigen. The fraction administration reduces plasma antibody levels in challenged animals and results from carbon clearance assay shows a decrease in phagocytic activity in blood from test animals. The fraction attenuated spleen growth observed in animals whose immune system has been challenge by the re-exposition to the test antigen.[324]

Determination of the ability of the ethanol (35%) extract from the white petals of *I. balsamina* and its components 8 and 32 to control chronic scratching behavior and dermatitis on NC mice used in atopic dermatitis model indicates that extract is effective to reduce the development of both symptoms in mice when it is given at dose 100 mg/kg, intravenously or orally. Compounds 8 and 32 can attenuate the scratching frequency in mice at intravenous dose of 10 µg/kg.[325,326]

Compounds 1, 27, and 28 were isolated from the methanol extract of *I. balsamina* pericarps and their antipruritic activity assayed on ddY mice model of pruritus induced with compound 48/80. The pretreatment with 1 and 28 significantly reduces scratching behavior of mice induced by compound 48/80 when they are given orally at dose of 10 mg/kg.[327] Other compounds, including 8, 9, 19, 24, 25, 71, 72, and scopoletin (101), were also isolated from the *I. balsamina* and their antipruritic effect were evaluated on the same *in vivo* model. Compounds 8, 9, 25, and 71 can significantly reduce the scratching frequency of mice induced by compound 48/80 when they are given orally at dose of 10 mg/kg.[328]

Ishiguro *et al.* studied the ability of the ethanol (35%) extract from the white petals of *I. balsamina* and its compounds 1, 2, 3, 4, 6, 8, 32, and 100 to reduce the pruritus induced on ddY mice with dextran T40 and compound 48/80. The pretreatment with extract, 2, 4, 6, 8, 32, or 100, reduces the scratching behavior of mice treated with dextran T40 when they are administered at intravenous dose of 10 mg/kg (extract) or 10 µg/kg (for pure compounds). The extract, 1, 3, 4, and 8 can reduce the scratching frequency of mice treated with compound 48/80 when they are given at oral dose of 100 mg/kg (extract) or 10 mg/kg (for pure compounds).[329]

The pretreatment of ddY mice with the ethanol (35%) extract of *I. textorii* flowers and its water, *n*-butanol and ethyl acetate fractions, at oral dose of 100 mg/kg, significantly reduces the magnitude of blood pressure decline observed after PAF intravenous administration. Compounds 26, apigenin 7-*O*-glucoside (102) and luteolin (103) were isolated from *I. textorii* flowers. From them, 26 and 103 counteract the blood pressure decrease induced by PAF administration.[182]

Iwaoka *et al.* reported results from the evaluation of anaphylaxis-preventive effects of the ethanol (35%) extract of *I. textorii* flowers using ddY mice sensitized to HEL. According to results, the oral administration of *I. textorii* flowers extract at dose of 200 mg/kg in mice inhibits the decrease in blood flow observed after HEL sensitization. Compounds 26, 102, 103, and luteolin 7-*O*-glucoside (104) are flavonoids isolated from *I. textorii* flowers that can also inhibit the decrease in blood flow of mice after HEL sensitization when they are given at oral dose of 20 mg/kg.[273]

According to Ueda *et al.*, the ethanol (35%) extract from *I. textorii* flowers administered at oral dose of 200 mg/kg counteracts the blood pressure reduction induced in ddY mice through the intravenous administration of compound 48/80, a recognized anaphylaxis inductor agent. Similarly, compounds 26, 102, and 103 exert the same effect when they are administered at oral dose of 20 mg/kg. According to results obtained from HEL sensitized ddY mice model, 26, 102, and 103, given at oral dose of 20 mg/

kg, inhibit the blood pressure and blood flow decline observed after ddY mice re-exposition to HEL. The ethanol extract of *I. textorii* flowers has similar effect on blood flow at oral dose of 200 mg/kg. Only the ethanol (35%) extract of *I. textorii* flowers (intravenous dose of 100 mg/kg) and 26 (oral dose of 10 mg/kg) are capable to reduce the scratching behavior in ddY mice exposed to compound 48/80, serotonin or PAF.[274,330]

I. capensis and *I. pallida* concentrated juices and their oxidase enzymes fractions have reduced the skin rash induced with poison ivy exposure in human subjects. It has been proposed that oxidative enzymes present in the juice of *I. capensis* and *I. pallida* are responsible of their antidermatitic effect through oxidation of poison ivy toxic components.[331]

Data from a double-blinded assay carried out on 10 adult participants with documented history of sensitivity to poison ivy/oak indicates that aqueous extract from *I. capensis* stems is not effective to reduce the inflammatory reaction due to contact dermatitis induced by poison ivy/oak. However, all participants indicated a reduction in pruritus associated with extract treatment.[119] The efficacy of fresh mashes, infusions, and soaps made from whole plants of *I. capensis* or *I. balsamina* to preventing poison ivy dermatitis was evaluated on 40 volunteer subjects. Mash from *I. balsamina* and soaps from both plants, were significantly effective in reduce the rash associated with poison ivy dermatitis. The magnitude of the effect was no associated with compound 8 content determined by HPLC-DAD analysis in tested materials.[11,332]

The *n*-butanol fraction, rich in saponins, obtained from the methanol (50%) extract of the leaves of *I. capensis* can significantly reduce the severe rash induced after the topic exposure of forearm of volunteer subjects to poison ivy leaves. On the other hand, the mashes made from *I. capensis* leaves promote a decrease in rash observed in volunteers who developed mild poison ivy dermatitis. Soaps with or without the saponin rich fraction can reduce rash in severe and mild cases.[120,332]

Antidepressant and anxiolytic activities

Compounds 21 and hyperoside (105) isolated from ethanolic extract of *I. glandulifera* have shown antidepressant activity in male Albino Swiss mice. According to Forced Swimming Test (FST) and Tail Suspension Test (TST), 21 and 105 significantly reduce the immobility time of animals at an intraperitoneal dose of 1.875 mg/kg. Animals from TST treated with 21 (3.75 mg/kg, intraperitoneal) or 105 (7.5 mg/kg, intraperitoneal) have shown significantly higher levels of Brain-Derived Neurotrophic Factor (BDNF) in the hippocampus. This increase of BDNF can be a mode of action responsible of the antidepressant effect observe for 21 and 105 in mice.[333]

Additional experiments were made to get information about the role of serotonin and catecholamines in the mode of action of 21 and 105. Mice were pretreated with *p*-chlorophenylalanine methyl ester (PCPA) (100 mg/kg, intraperitoneal, once a day for 4 days, 24 hr before the administration of 21 or 105), α-methyl-DL-tyrosine (AMPT) (100 mg/kg, intraperitoneal, 4 hr before the administration of 21 or 105) or sulpiride (50 mg/kg, intraperitoneal, 30 min before the administration of 21 or 105). After different pretreatments, mice were subjected to acute administration of 21 or 105 at intraperitoneal dose of 3.75 mg/kg, and the behavior of animals was observed under FST. Results obtained indicates that PCPA (a serotonin synthesis inhibitor) pretreatment significantly reduces the effect of 21 on immobility time. AMPT (a catecholamine synthesis inhibitor) pretreatment significantly minimizes the reduction of the immobility time observed after administration of 21 and 105 alone. Sulpiride (a dopamine D_2-receptor antagonist) pretreatment also attenuates the antidepressant response induced by 21 and 105.[333]

The described results suggest that availability of serotonin in synaptic cleft is a requisite for the antidepressant effect of 21 observed in FST. This is supported by the synergic effect observed for the coadministration of fluoxetine (5 mg/kg, intraperitoneal) and 21 (0,94 mg/kg, intraperitoneal) on the reduction of immobility time of mice in FST. On the other hand, results obtained with mice pretreated with AMPT suggest that the presence of norepinephrine in synaptic cleft also contributes to the observed antidepressant activity of 21 and 105 in FST, hypothesis that is supported by the synergic antidepressant effect observed for simultaneous administration of reboxetine (5 mg/kg, intraperitoneal) and 21 or 105 (0,94 mg/kg, intraperitoneal). The reduction on antidepressant activity of 21 and 105 when they are administrated in combination with sulpiride supports the implication of dopamine receptors in 21 and 105 antidepressant activity.[333]

Neuroprotective activity

The methanol extract from *I. balsamina* obtained Korean Plant Extract Bank can significantly reduce the secretion of β-amyloid peptides and rise the production of secreted amyloid precursor protein-alpha (sAPPα) in swedish mutant amyloid precursor protein overexpressing mouse neuroblastoma cells (SweAPP N2a) at concentrations of 1 and 10 μg/mL. The extract, at the same concentrations, can also inhibit the activity of β-secretase enzyme.[334]

Compound 1 enhances ATP production when mitochondrial complex I is inhibited with rotenone according to results obtained under *in vitro* assays on HepG2 cells and mitochondrial fraction isolated from liver cells of mice (mixed 129Sv and C57Bl/6 background) using a concentration of 10 μM. Compound 1 acts as an electron acceptor in Nicotinamide Adenine Dinucleotide (NADH) oxidation catalyzed by diaphorase enzymes located in mitochondrial matrix, process that is critical for mitochondrial substrate-level phosphorylation which facilities ATP synthesis

in response to mitochondrial complex I inhibition. Due to this mechanism, 1 is considered as a "complex I bypass factor" that can be potentially investigated as a therapy for illnesses characterized by mitochondrial complex I dysfunction, including Alzheimer disease and Leber's hereditary optic neuropathy.[335,336]

Olfactory Ensheathing Cells (OEC) are implicated in the regeneration of the primary olfactory nervous system during life. Transplantation of this kind of cell has viewed as a potential therapy for nervous system injuries. Compound 1 can increase metabolic rate, phagocytic activity, expression of p75 Neurotrophin Receptor (p75NTR), and replication rate in OEC. This compound promotes changes in cell cycle progression of OEC, most cells are maintained in S phase and more cells are held in early stages of mitosis when they are treated with 1 in comparison with non-treated cells. It is suggested that 1 promotes these changes due its ability to activate nuclear factor erythroid 2-related factor 2 (NRF2). These results support the hypothesis that 1 can enhance further therapies with OEC through stimulating them before transplants.[337,338]

The ethyl acetate fraction from the methanol extract of *I. balsamina* promotes Nerve Growth Factor (NGF) secretion in C6 cells (152.64% at test concentration of 50 µg/mL). Compounds 2, 3, 4, 5, 6, 32, 35, 69, 70, balsamiside A (106), B (107), C (108) and D (109) have been isolated from the ethyl acetate fraction of the methanol extract of *I. balsamina* white petals. They have anti-neuroinflammatory effects according to *in vitro* model of BV-2 cells stimulated with LPS. They promote the secretion of NGF in C6 cells. Compound 35 is the most active inducing NGF production of 172.04% at test concentration of 20 µM. None of test compounds are cytotoxic against A-549, SK-OV-3, SK-MEL-2, BT549, BV-2, or C6 cell lines.[306]

Kim *et al.*, reported the isolation of twelve compounds from the methanol (80%) extract of *I. balsamina* stems, 7 was the most effective compound to promote NGF secretion on rat glioma C6 cells (157.34% of secretion at concentration of 20 µM). None compounds reduce the cell viability more than 17% at test concentration.[308] On the other hand, among thirteen phenolic compounds isolated from *I. balsamina* white flower methanol (80%) extract, 21 is the best promoter of NGF secretion on C6 cells (160.46% of secretion at concentration of 20 µM). No compound is cytotoxic at test concentration.[267]

Antioxidant activity

The aqueous extract from *I. balsamina* red flowers showed antioxidant activity on 2,2-diphenyl-1-picrilhidrazil (DPPH) radical scavenging activity (IC_{50} of 1140.36 µg/mL) and phosphomolybdenum reduction (13.04 mg of Ascorbic Acid Equivalents (AAE)/g) assays.[65] *I. balsamina* infusion has TPC, Ferric Reducing Antioxidant Power (FRAP), and 2,2'-azi no-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical scavenging activity values of 4.47 mg GAE/g dry plant, 49.23 µmol Fe^{2+} equivalents/g dry plant and 47.36 µmol of trolox equivalents (TE)/g dry plant, respectively.[339] The comparative study of the antioxidant activities of ethanol, methanol, and acetone extracts of *I. balsamina* leaves, flowers, and stems showed that acetone extract from flowers has the highest levels for TPC and TFC values (1692.46 mg GAE/g and 1139.97 mg QE/g, respectively). Flower ethanol, methanol and acetone extracts also demonstrated the highest DPPH scavenging radical activity, reaching almost 100% of activity at concentration of 1.67 mg/mL.[68]

The ethanol extract from *I. balsamina* seeds has antioxidant activity with IC_{50} of 320 µg/mL in DPPH radical scavenging assay. In FRAP and phosphomolybdenum reduction assays, it can reach percentages of antioxidant activity of 4.33 and 71.43%, respectively, when assayed at concentration of 500 µg/mL.[304] The comparative analysis of the antioxidant activity of the petroleum ether (60-90°C), diethyl ether, chloroform, methanol, and water extracts from *I. balsamina* stems showed that diethyl ether extract is the most active in DPPH radical scavenging activity (IC_{50} of 11.26 mg/mL) and FRAP assays (half maximal effective concentration (EC_{50}) of 2.94 mg/mL). This extract has TPC and TFC values of 13.63 mg GAE/g and 6.73 mg QE/g, respectively.[29,320]

The study of the antioxidant activity of the ethanol (70% v/v) extracts from stems or leaves of *I. balsamina* recollected at different harvest times showed that extracts from leaves have the highest DPPH radical scavenging activity with scavenging percentage within the range of 44,84-54.05% at test concentration of 0.1 mg/mL. The hydroxyl radical scavenging activity of the extracts does not show clear differences among the extracts of stems and leaves (hydroxyl radical scavenging percentage varying from 5-15% at test concentration of 0.1 µg/mL). The TPC and TFC values for leaves extracts are in the ranges of 79.55-103.94 mg GAE/g and 57.43-104.28 mg QE/g, respectively. There are significant differences in the results obtained for the same kind of extract made from plant material obtained at different harvest times.[211]

High Performance Liquid Chromatography Coupled to Diode Array Detector and Tandem Mass Spectrometry (HPLC-DAD-MS/MS) analysis of the methanol (50%) and aqueous extracts from leaves and stems of *I. balsamina* indicates the presence of 3, 4, 8, quercetin glucoside, kaempferol rutinoside, and caffeic acid in leaves of *I. balsamina*. This analysis also indicates the presence of 8 and scopoletin diacylpentoside in the stems of the same plant. The methanol extract from leaves has TPC and TFC values of 4.96 mg GAE/g and 6.58 mg of Rutin Equivalents (RE)/g, respectively. This extract has IC_{50} values of 0.282, 0.284, 0.604, and 0,705 mg/mL according to DPPH radical scavenging activity, ABTS radical scavenging activity, iron chelating activity, and FRAP assays, respectively. On the other hand, methanol extract from the stems has TPC and TFC values of 2.85 mg GAE/g and 2.83 mg RE/g, respectively. This extract has IC_{50} values of 0.380, 0.358, 0.994,

and 0,856 mg/mL for DPPH radical scavenging activity, ABTS radical scavenging activity, iron chelating activity, and FRAP assays, respectively.[340]

The comparative study of the ethanol (80:20 v/v, acidified with trifluoro acetic acid 0.5% v/v) extracts from orange and pink flowers of *I. balsamina* showed that the extract from pink flowers is the most potent according to Oxidative Hemolysis Inhibition Assay (OxHLIA) (IC_{50} of 29.2 µg/mL). This extract has TPC, TFC, Total Non-Anthocyanidin Phenolic (TNAPC), and Total Anthocyanin (TAC) contents of 2.36, 14.843, 17.19, and 19 mg/g, respectively. Ultra-High Performance Liquid Chromatography Coupled to Mass Spectrometry (UHPLC-MS) analyses of extract indicates the presence of glycosides derived from pelargonidin, malvidin, peonidin, coumaric acid, apigenin, kaempferol and quercetin.[212]

The ethanol extract from *I. balsamina* whole plant, at oral dose of 200 mg/kg, has protective effect against the oxidative stress induced in Wistar rats by the administration of potassium dichromate. The extract counteracts the diminution of catalase and reduced glutathione in liver homogenates and the rise of its lipid peroxidation inducted by oxidative stress. The extract also attenuates the serum increment of aspartate and alanine transaminases promoted by oxidative stress.[83]

Szewczyk and Olech have studied the phenolic acid composition and antioxidant activity of the methanol extracts obtained from flowers, roots, or leaves of *I. glandulifera* using different extraction methods corresponding to Soxhlet extraction, ultrasound assisted extraction and accelerated solvent extraction. For the last method, the authors used methanol or aqueous methanol (80% v/v) as solvents and three different extraction temperature ranges corresponding to 80, 100 and 120°C at the same pressure 100 bar. The flower extract obtained using Soxhlet apparatus has the best DPPH radical scavenging activity (IC_{50} around 0.06 mg/mL) while the flower extract obtained using ultrasound method has the highest reducing power (IC_{50} around 0.5 µg QE/mL). On the other hand, the extract of roots prepared with Soxhlet apparatus has the best iron chelating activity (IC_{50} around 2 mg/mL). According to High Performance Liquid Chromatography Coupled to Electrospray Ionization and Tandem Mass Spectrometry (HPLC-ESI–MS/MS) analysis of the three extracts mentioned, compound 21 is the most abundant phenolic acid, with contents of 113.44, 84.03, and 94.53 µg/g, respectively. Other phenolic acids detected in the three extracts were 19, 22, gentilic acid, *trans*-caffeic acid, syringic acid, *p*-coumaric acid, salicylic acid and *cis*-ferulic acid. Gallic acid and *cis*-caffeic acid were detected only in the extracts obtained from flowers while 3-hydroxy cinnamic acid was identified only in the extract of roots prepared with Soxhlet apparatus. The Total Phenolic Acid Content (TPAC) of the three extracts, in the order mentioned above, are 188.07, 216.03, and 281.82 µg/mL, respectively.[341]

The phenolic compounds 1, 5, 6, 19, 21, 32, 100, 105, kaempferol 3-*O*-galactoside (trifolin) (110), eriodictyol (111), and eriodictyol 7-*O*-β-D-glucoside (112) were isolated from methanol extract of *I. glandulifera* aerial parts. The antioxidant activity of these compounds was evaluated under DPPH and ATBS radical scavenging assays. According to results, 5 is the most potent compound with IC_{50} of 0.11 and 0.01 mg/mL in DPPH and ATBS assays, respectively.[342]

The aqueous extract from the aerial parts of *I. walleriana* have FRAP values of 1.30 mM of Fe^{2+} equivalents.[297] The evaluation of the antioxidant activity of the chloroform, methanol, and hexane extracts from *I. walleriana* leaves demonstrated that methanol extract is the most active on DPPH radical scavenging assay, reaching an inhibition percentage of 80.4% when tested at concentration of 0.5 mL/mL. It shows a TPC value of 67.57 g GAE/kg.[222]

The fresh flowers of *I. walleriana* have DPPH radical scavenging activity of 6.89 g AAE/kg. They have TPC and TFC values of 4.85 g GAE/kg and 1.93 g RE/kg, respectively.[15,343] Flowers from *I. walleriana* were subjected to extraction with tetrahydrofuran to get a fat-soluble fraction, the material was subsequently extracted with a mixture of methanol–acetic acid–water (50:3.7:46.3, v/v/v) to get a water-soluble fraction, finally, the residue was hydrolyzed with 10 mL of 2 M sodium hydroxide, acidified to pH 2 with 6 M HCl and extracted with hexane to remove fatty acids, a fraction with the insoluble-bound phenolic compounds was obtained by extraction with diethyl ether and ethyl acetate (1:1, v/v). From these fractions, water-soluble has the highest value for TPC and the best results for FRAP and ABTS radical scavenging activity assays. It has values of 6.83 mg GAE/mL wet weight of flowers, 64.94 µmol Fe^{2+} equivalents /g wet weight of flowers, and 30.71 µmol TE/g wet weight of flowers, respectively. According to HPLC-DAD analysis, *I. walleriana* flowers have values of 96.11, 183.45 and 83.97 mg/100 g for epicatechin, gallic acid and 21 contents, respectively.[344]

The comparative evaluation of the antioxidant activity of the ethanol (80:20 v/v, acidified with trifluoro acetic acid 0.5% v/v) extracts from pink and orange flowers of *I. walleriana* using OxHLIA assay showed that extract from pink flower is the most active (IC_{50} of 34 µg/mL). According to HPLC-MS analysis, anthocyanin glycosides derived from peonidin, malvidin and pelargonodin; phenolic acid glycosides from caffeic and *p*-coumaric acids; and eryodictiol-*O*-hexoside can be differently detected among the extracts (concentrations range of 0.52-11.5 mg/g). Values for TPAC, TFC, TNAPC and TAC are higher in pink flowers extracts (15.9, 2.57, 18.6, and 17.4 mg/g, respectively).[223]

Ethanol extract from *I. noli-tangere* leaves and stems was subjected to micro and nanofiltration. The analysis of microfiltrate and retentate obtained by nanofiltration indicates that last preparation has higher TPC (2786.9 mg GAE/L) and TFC (1983.1 mg QE/L)

values. This extract also shows higher antioxidant activity in DPPH radical scavenging assay (IC_{50} = 19.3 µg/ml).[153]

Microfiltration fraction of ethanol (50%) extract of *I. noli-tangere* herb has TPC and TFC values of 749.9 mg GAE/mL and 221.9 mg QE/mL, respectively. Permeate obtained from ultrafiltration of the same ethanol extract has values of TPC and TFC of 351.0 GAE mg/L and 114.1 mg QE/mL, respectively. Retentate from the same process has values of 1395.3 mg GAE/mL and 432.5 mg QE/mL for TPC and TFC, respectively. Phenolics determined by HPLC-MS in microfiltration fraction and ultrafiltration retentate of the extract were 2, 3, 4, 5, 26, 103, chlorogenic acid (113), rosmarinic acid (114), caffeic acid, and ellagic acid. In these fractions, 5 is the most abundant quantified phenolic with concentrations of 65.20 and 122.17 µg/mL, respectively. Microfiltration fraction and retentate from ultrafiltration have DPPH radical scavenging activity with IC_{50} values of 709.2 µg/mL and 174.3 µg/mL, respectively. Both fractions show EC_{50} in FRAP assay of 1.972 µg/mL and 0.830 µg/mL, respectively.[275]

The analysis of the antioxidant activity of the esterified triterpenoid and fatty acid fractions derived from the petroleum ether (45-60°C) extracts of *I. glandulifera* and *I. noli-tangere* seeds, leaves and roots showed that the fatty acid fraction of *I. glandulifera* leaves has the best DPPH radical scavenging activity (IC_{50} of 11.69 µg/mL) and metal chelating capacity (IC_{50} of 5.49 µg/mL). The most abundant compound of this fraction is α-linolenic acid (40.5%) according to GC-MS and GC-FID analysis.[292]

The evaluation of the antioxidant properties of the methanol extract from *I. textorii* whole plants and its *n*-hexane, ethyl-acetate, *n*-butanol, and water fractions indicates that the ethyl acetate fraction has the highest DPPH radical scavenging (IC_{50} of 9.80 µg/mL) and FRAP activities. This fraction has TPC and TFC values of 141.39 mg GAE/g and 125.93 mg QE/g, respectively.[295] Acetone extracts of *I. noli-tangere* and *I. textorii* ground parts have DPPH radical scavenging activity equivalent to 0.34 and 0.63 µmol of α-tocopherol/g, respectively. They have TPC values of 50 and 74 mg of (+)-catechin equivalents/g, respectively.[345] Antioxidant activity of dry seeds, leaves, stems, roots, and flowers of *I. chinensis* was evaluated using *in vitro* assays. According to results, flowers are the most active plant section with 7462 and 910.8 µmol TE/g in ABTS and DPPH radical scavenging assays, respectively. This anatomic section of the plant also has the highest TPC value (5046 µmol GAE/g).[124]

The antioxidant activity determination of the *n*-hexane, dichloromethane, ethyl acetate, *n*-butanol, aqueous fractions from the methanol extract of *I. bicolor* whole plants showed that the dichloromethane fraction is the most active reaching a DPPH scavenging activity of 82% at concentration of 0.05 mL/mL. This fraction contents methyl-4-hydroxyl cinnamate, stigmasterol, stigmasterol 3-*O*-β-glucoside, and β-sitosterol among their components.[346] In contrast, the analysis of the antioxidant activity of *n*-hexane, chloroform, ethyl acetate, and methanol extract from aerial parts of *I. bicolor* demonstrated that the ethyl acetate extract has the highest DPPH radical scavenging assay, reaching an inhibition percentage of 92.2% when tested at concentration of 400 µg/mL. The TPC values of these extracts are in the range of 104-532 mg GAE /g.[226] Compound 25 isolated from the ethyl acetate extract of *I. bicolor* whole plant has antioxidant activity according to DPPH radical scavenging activity (activity of 94.32% at test concentration of 200 µg/mL) and FRAP (reducing power equivalent to 145.6 µM of $FeSO_4 \cdot 7H_2O$ at 200 µg/mL at test concentration of) assays.[347]

Nisar *et al.* reports the antioxidant activity evaluation of the subfractions obtained by gradient silica gel column chromatography fractionation of the *n*-hexane fraction derived from the methanol extract of *I. bicolor* whole plant. The first subfraction obtained using *n*-hexane as eluent is the most active in the DPPH radical scavenging assay (IC_{50} of 23.22 µg/mL). According to GC-MS analysis, the main components of this subtraction are methyl hexadecanoate (12.35%), methyl octadecenoate (9,63%), methyl eicosanoate (5.45%), methyl docosanoate (8.95%) and methyl tetracosanoate (8.35%).[348]

The evaluation of the antioxidant activity of the petroleum ether, ethyl acetate and methanol extracts from the arial parts of *I. sulcata* has shown that they have DPPH radical scavenging capacity (IC_{50}), phosphomolybdenum reducing capacity, ABTS radical scavenging activity and FRAP activity in the ranges of 95.3-138.37 µg/mL, 76.08-93.06 mg AAE/g, and 3424.56-10142.23 µmol TE/g, respectively. These extracts have TPC and TFC values in the ranges of 111-137 mg GAE/g and 102-236 mg RE/g, respectively.[180]

Comparative evaluation of the methanol/acetone/water (3/1/1 v/v/v) extracts from the aerial parts of *I. balfourii, I. balsamina, I. glandulifera, I. noli-tangere, I. parviflora* and *I. walleriana* indicates that the extract from *I. balfourii* has the best DPPH radical scavenging capacity with IC_{50} near to 0.05 mg/mL. The extract from *I. glandulifera* has the highest iron chelating activity showing IC_{50} around 6 mg/mL while the extract from *I. noli-tangere* shows the best reducing power with IC_{50} around 4 µg QE/mL. According to UHPLC-DAD-MS analysis, compounds 5, 6, and 105 are flavonoids present in *I. balfourii, I. glandulifera* and *I. noli-tangere*. However, 3 and 111 are only identified in *I. glandulifera* extracts. Other compounds, including phenolic acids, kaempferol, eriodictyol and quercetin glycosides were also detected through UHPLC-DAD-MS analysis without specific designation of their sugar moiety identity.[227]

The analysis of the antioxidant activity of the essential oils obtained by hydrodistillation of roots or aerial parts of *I. glandulifera, I. noli-tangere, I. balsamina* and *I. parviflora* indicates that essential oil from *I. glandulifera* aerial parts is the most active on DPPH radical scavenging activity and linoleic

acid peroxidation inhibition assays with IC_{50} values of 3.96 µg/mL and 102.08 µg/mL, respectively. The yield reported for this essential oil was 0,22% w/w. According to the GC-MS analysis, the main components in essential oil of *I. glandulifera* aerial parts are β-phellandrene (7.4%), cryptone (5.7%), α-terpinyl acetate (16.6%), (Z)-butylidenphthalide (8.5%), and (Z)-ligustilide (11.0%), this extract has the highest proportion of aromatic volatile compounds (23%).[349]

Szewczyk *et al.* reports the extraction of polysaccharides from aerial parts and roots of *I. balsamina, I. glandulifera, I. noli-tangere* and *I. parviflora* using hydroalcoholic maceration and ultrasound assisted extraction. The polysaccharides yield ranged between 1,97% for *I. parviflora* roots and 18.63% for *I. balsamina* aerial parts with a molecular weight up to 2.31 MDa according to size exclusion chromatography. Characterization of the polysaccharides through GC-FID revealed that galacturonic acid is the main monosaccharide in the polysaccharides obtained for all botanical material except for *I. parviflora* roots and *I. noli-tangere* roots and aerial parts. Polysaccharides from roots of *I. parviflora* and *I. noli-tangere* have glucose as the principal monosaccharides while aerial parts of *I. noli-tangere* has galactose as a major monosaccharide. According to the *in vitro* evaluation of the antioxidant activity of polysaccharides obtained from *I. balsamina, I. glandulifera, I. noli-tangere* and *I. parviflora*, the most potent polysaccharides are those obtained from *I. balsamina* aerial parts with EC_{50} of 0.24 and 0.32 mg/mL in DPPH and ABTS radical scavenging activity assays, respectively.[309] Compounds 60 and 61 isolated from *I. parviflora* showed low antioxidant activity in DPPH radical scavenging activity assay (IC_{50} > 200 µg/mL).[291]

The comparison of the antioxidant activity of the ethanol (80%) extracts from *I. balsamina, I. walleriana* and *I. hawkeri* whole herbs indicates that *I. hawkeri* extract has the higher antioxidant potential according to Oxygen Radical Absorbance Capacity (ORAC) (ORAC value of 1528,13 µmol TE/g), FRAP (FRAP value of 98.49 µmol TE/g), and DPPH radical scavenging activity (IC_{50} of 100 µg/mL) assays. This extract has TPC and TFC of 44.04 mg GAE/g and 55.02 mg QE/g, respectively.[8]

Antidiabetic activity

The ethanol extract from *I. balsamina* roots can inhibit the activity of α-amylase (IC_{50} of 0.316 mg/mL).[350] From the nineteen compounds isolated from the ethanol (75%) extract of *I. balsamina* flowers, 43 is the most active substance in α-glucosidase inhibitory assay with IC_{50} of 0.72 µg/mL.[281] The evaluation of the α-glucosidase inhibition activity of the methanol extract from *I. textorii* whole plants and its *n*-hexane, ethyl-acetate, *n*-butanol, and water fractions indicates that ethyl acetate extract has the highest inhibitory activity (IC_{50} = 8.56 µg/mL).[295] Compounds 5, 32, 82, 92, 102, ginsenoside Rg1 (115), iparvisepala-1 (116), tocopherylquinone (117), phytol (118), glycerol 1-(9Z,12Z)-nonadecadienoate (119), and uracil (120) have been isolated from the methanol (95%) extract from *Impatiens parvisepela* whole plant. Compound 102 has the highest inhibitory activity against α-glucosidase enzyme (IC_{50} value of 12.53 µM).[351] Compound 91 is one of the sixteen components isolated from the methanol (95%) extract of *I. chapaensis* whole plant. It has the highest potency in α-glucosidase inhibition assay with IC_{50} of 28.91 µg/mL.[315]

Microfiltration fraction from the ethanol (50%) extract of *I. noli-tangere* herb and retentate obtained by extract ultrafiltration can inhibit α-amylase with IC_{50} values of 4.39 and 4.01 mg/mL, respectively. Compounds 3, 4, 113, and 114 were isolated from *I. noli-tangere*, they have IC_{50} values of 0.40, 0.35, 0.19, and 0.09 mg/mL in the same assay, respectively. Microfiltration fraction, retentate from ultrafiltration, 3, 4, 113, and 114 inhibit α-glucosidase with IC_{50} values of 0.72, 0.47, 0.06, 0.07, 0.05, and 0.02 mg/mL, respectively.[276]

The ethanol extract from *I. niamniamensis* seeds and its compound hypaphorine (121) have antihyperglycemic activity according to streptozotocin-induced diabetes model in Wistar/Sprague-Dawley rats at doses of 200 mg/kg and 50 mg/kg, respectively.[352]

Wound healing properties

The external treatment of surgical wounds induced in Wistar rats with the ethanol extract from *I. balsamina* leaves promoted their healing. The histological analysis of skin from wound area treated with 10.5 or 21 mg of the extract demonstrated a reduction in inflammatory cells and a rise in collagen production.[353] It is reported that herbal baths made from the combination of nine plants used in Chinese Traditional Medicine, that includes *I. balsamina* whole plant, are effective adjuvants to reduce the lesion area and progression of psoriasis in human patients.[354] Gold nanoparticles with *I. balsamina* leaves aqueous extract showed wound and burn healing activity in Swiss albino rat models of skin lesion healing.[355]

Chitosan patches with a mixture of the ethanol extract (70%) from *Symphytum officinale* and the ethanol (50%) extracts from *I. noli-tangere* can promote skin healing in Wistar rats according to burn wound model. The analysis of wound biopsies indicates that patches with the extract combination can promote collagen synthesis while the blood analysis of the test animals indicates a reduction in proinflammatory cytokines IL-6 and TNF-α. The HPLC-MS analysis of *I. noli-tangere* extracts indicates the presence of 2, 4, 5, 26, 103, 113, 114, ellagic acid, and ursolic acid. From them, 114 are the most abundant (49.86 µg/mL).[225]

The characterization of the ethanol fraction from *I. textorii* flower *n*-hexane extract through GC-MS analysis showed that palmitoleic acid is the mayor compound. This extract promotes cell viability (263.52% at test concentration of 200 µg/mL) and proliferation (265.19% at test concentration of 100 µg/mL) on

keratinocytes (HaCaT cell line). It can also promote cellular migration on the same cell line according to Boyden chamber assay (177.75% at test concentration of 100 μg/mL) and collagen sprout test (352.21% at test concentration of 100 μg/mL). The extract increases the synthesis of type I (163.24%) and IV (220.47%) collagen at test concentration of 200 μg/mL. It acts by promoting phosphorylation of ERK 1/2, p38 MAPK, Akt, and JNK on HaCaT cells.[183]

Insecticidal activity

The ethanol extract from *I. balsamina* roots can promote the paralysis and death on mature *P. posthuma* worms at test concentration of 50 mg/mL, showing paralysis and death times of 8 and 11 min, respectively.[350] The comparative analysis of the larvicidal activity of the benzene, chloroform, ethyl acetate and methanol extracts from leaves of *I. balsamina* against *Anopheles stephensi, Aedes aegypti* and *Culex quinquefasciatus*, recognized malaria, dengue, and filariasis vector mosquitoes, indicate that the methanol extract is the most potent, with IC_{50} in the range of 98.04-220.60 mg/mL.[356]

Methanol extract of *I. stuhlmannii* leaves have shown weak acaricidal activity against *Rhipicephalus appendiculatus* reducing by 50% its oviposition at concentration of 50 mg/mL.[357] Acetone-methanol (2:1 v/v) extract from *I. parviflora* aerial parts induces a mortality rate of 10% and 5% in *Oncopeltus fasciatus* nymphs at their last instar and during their first 10 days of adult life, respectively.[358] *I. balsamina* seed oil has mild toxic activity against earthworms (*Pheretima posthuma*), at concentration of 100 mg/mL, it induces worm paralysis and death after 13 and 62 min of contact.[359]

The evaluation of the repellency and toxicity activities of the methanol extracts from *I. glandulifera, I. noli-tangere*, and *I. parviflora* leaves against green peach aphid (*Myzus persicae*) showed that *I. glandulifera* extract at concentration of 0.5% is the most potent with repellency rate of 82.9-100% (exposure period of 5-40 hr), and mortality rate of 6.2-99.7% (exposure time 8-54 hr). This extract also has the highest amount of 1 (3.01 mg/g) and flavanols (86.62 mg/g) according to HPLC-DAD analysis.[360]

Compound 1, isolated from the methanol extract of *I. glandulifera* leaves, flowers, and stems, and two synthetic analogues (2-propoxy-1,4-naphthoquinone and 2-isopropoxy-1,4-naphthoquinone) can reduce the activity ecdysone 20-monooxygenase, a clue enzyme in insect postembryonic development, in organ homogenates from *A. aegypti, Drosophila melanogaster*, and *Manduca sexta* with IC_{50} in the range of 3×10^{-5} to 7×10^{-4} M.[361]

Allelopathy

Naphthoquinones have allelochemical actions due several mechanism, including ROS production and mitochondrial respiratory chain disruption on plant cells.[362] Leaves from *I. balsamina*, a source of naphthoquinones, can reduce the growth and development of lettuce seeds according to the results of sandwich and disk pack assays used to determined allopathic effects of plant material.[363] Two naphthoquinones corresponding to 1 and 8 are recognized allelopathic metabolites that are also available in the flowers of *I. glandulifera*. According to Block *et al.*, these metabolites could protect the nectar of *I. glandulifera* against fungus growth. This observation is supported by results of agar diffusion inhibition assays using the common nectar microbes *Metschnikowia reukaufii* and *Aureobasidium pullulans* as test microorganisms.[364,365] Compound 8 is an allelochemical that delays the germination of some few plant species: *Lolium perenne, Poa pratensis* and *Solanum melongena*.[366]

I. glandulifera plant patches have lower hyphal mass than nearby areas in decidual forest of Switzerland due the allelopathic properties of 1 secreted by roots and leaves of the plant.[367] Additionally, *I. glandulifera* plants reduce the bacterial activity of soil around them due the allelopathic properties of secreted naphthoquinones in temperate forests of Europe where the plant is invasive.[368]

The quantities of 1, 8, and 1,4-naphthoquinone in *I. glandulifera* and *I. noli-tangere* herbs were determined by UHPLC-MS analysis at different stages of plant development. In the case of *I. glandulifera*, leaves are the main producer organ of 1 (around 0,6% w/w in seedlings). Compound 8 was only detected in roots when plants were at senescent stage. On the other hand, 8 is present at higher quantity in leaves of fruiting *I. glandulifera* plants (0,082% w/w).[369]

Evaluation of the ability of *I. glandulifera* to exude 1,4-naphthoquinones was carried out by measuring them in plant surrounding soil and rainwater obtained from leaves. The amount of this kind of compound in aqueous extracts made just by soaking plants in water was also determined. According to results, soil around senescent plants has the highest amount of 1 while soil near to seedlings and juvenile plants has the highest quantity of 1,4-naphthoquinone. Compound 1 can be detected in rainwater too. Analysis of aqueous extracts obtained by soaking *I. glandulifera* plants in water indicates that seedlings and juvenile plants produce the higher amount of 1 (14.64 μg/mL).[369]

The aqueous extract from *I. glandulifera* shoots of juvenile plants can significantly inhibit the germination of *Hieracium murorum* and *Scrophularia nodosa* according to *in vitro* experiments. It was determined a significant correlation between 1 content in the extracts and their phytotoxic effect. In addition, the extracts from shoots and roots can significantly reduce the growth of *Laccaria bicolore, Lactarius subdulci* and *Pisolithus tinctorius* mycelia. The magnitude of the inhibitory effect is correlated with the quantity of 1 present in the extracts. Antifungal activity was also observed when mycelia of test fungi were treated with pure 1 reaching inhibitory effects of 100%, 60% and 100% on *L. bicolore, L. subdulci* and *P. tinctorius,* respectively.[369]

The essential oil from the aerial parts of *I. parviflora*, obtained by hydrodistillation, has significant phytotoxic effect over seeds of *Lactuca sativa* at concentration equal or higher than 0.065 µg/mL according to *in vitro* germination assay. The same essential oil reduces the radical elongation of *Triticum aestivum* under *in vitro* conditions. Phytol, *p*-cymene, terpinolene, nonanal, linalool, decanal, carvacrol, dehydro-β-ionone, β-ionone epoxide, β-ionone, germacrene D, caryophyllene oxide, benzyl benzoate, hexahydrofarnesyl acetone, hexadecanoic acid, tricosane, pentacosane, heptacosane, nonacosane and hentriacontane are among the major constituents of essential oil based on results of GC-FID and GC-MS analyses. However, there is wide variability in qualitative and quantitative composition within essential oils from plants obtained in different recollection areas. These results suggest that essential oil of *I. parviflora* can contribute for its spreading to new areas.[370]

Skin hyperpigmentation treatments

Tyrosinase and xanthine oxidase are enzymes implicated in skin hyperpigmentation. Koodkaew and Sukonkhajorn reported results for the study of anti-tyrosinase activities of ethanol, methanol, and acetone extracts of *I. balsamina* leaves, flowers, and stems. The three extracts derived from flowers have the highest anti-tyrosinase activity with an inhibition percentage near to 50% at concentration of 0.5 mg/mL.[68] The ethanol extract from *Impatiens sirindhorniae* has shown tyrosinase and xanthine oxidase inhibitory activity with IC_{50} values of 12.01 and 24.16 µg/mL, respectively. The TPC and TFC values reported for this extract are 752.94 mg GAE/g and 1468.84 mg QE/g, respectively.[371]

Compounds 3 and 4 can competitively inhibit tyrosinase enzymatic activity with Ki of 0.008 and 0.011 mM, respectively, when L-tyrosine is the substrate. The methanol extracts from *I. balsamina* flowers can inhibit the melanin production in *Streptomyces bikiniensis*, the main active compound of the extract is 3. This molecule also reduces the production of melanin on *S. bikiniensis* cultures.[372] Similarly, compound 1 can reduce the production of melanin in mouse melanocyte (Melan-a) cell line by almost 70% at test concentration of 0.2 µg/mL with low cytotoxicity.[373]

Other effects

Results obtained through C57BL/6 mice model of androgenic alopecia indicate that paste made of *I. balsamina* herb can promote hair growth when is topically applied once a day for 35 days in shaved areas of experimental animals previously treated with testosterone. The analysis of the skin in contact with *I. balsamina* paste indicates a reduction in testosterone and dihydrotestosterone that may explain the observed hair growth effect.[374] There is a case report of a patient treated with a lotion that includes the aqueous extract from *I. balsamina* leaves and flowers mixed with triamcinolone acetonide (40 mg/mL) (50:50), pilocarpine (1%) and nicotinic acid (2%). The formula was successful to treat alopecia areata in the patient.[375]

Ethanol extract from *I. balsamina* aerial parts shows inhibitory activity against steroid 5α-reductase enzyme obtained from LNCaP cell culture (IC_{50} of 5.4 µg/mL).[375] Similarly, Ishiguro *et al*. reports that ethanol (35%) extract from *I. balsamina* aerial parts can inhibit steroid 5α-reductase enzyme isolated from Wistar rat prostate with IC_{50} of 52.9 µg/mL. The bio-guided fractionation of the extract led the isolation of 71 that has enzymatic inhibitory activity on steroid 5α-reductase with IC_{50} of 99.4 µg/mL. Compounds that inhibit steroid 5α-reductase may be potential treatments to androgen-related skin disorders (as acne and male alopecia) and benign prostate hypertrophy.[376,377]

The methanol extract from *I. balsamina* leaves reduces the levels of blood cholesterol and Low-Density Lipoproteins (LDL) in Sprague-Dawley rats fed with cholesterol rich diet when given at oral dose of 400 mg/kg. In contrast, the treated rats have higher levels of High-Density Lipoproteins (HDL). Histopathological analysis of liver sections from treated animals demonstrates a decrease in steatosis and inflammation in comparison to none treated animals.[378]

The syrup made with *I. balsamina* seeds promotes contraction in isolated mouse uterus. The aqueous extract from *I. balsamina* seeds promotes uterine contractions in rabbits at intramuscular and intravenous doses of 0.05-0.3 mg/kg. The decoction from *I. balsamina* seeds reduce the fertility in female mice when given at daily oral dose of 3 mg/kg during 5 days before and 5 days after sexual intercourse with male mice. The extract inhibits ovulation and atrophies uterus and ovaries. The infusion form *I. balsamina* does not show labor induction in pregnant guinea pigs.[22]

The aqueous extract from *I. balsamina* flowers, when given at daily oral dose of 100 and 400 mg/mL during 6 weeks, can reduce proteinuria in mice with membranous nephropathy induced by cationic bovine serum albumin intraperitoneal injection. The treated mice also showed a reduction of serum triglyceride, blood urea nitrogen, immunoglobulin G, TNF-α, and IL-1β levels. Histological examination of kidney tissue has demonstrated that extract treatment can reduce the thickening of the glomerular basement membrane observed after membranous nephropathy induction with cationic bovine serum albumin.[379]

The peptide fraction obtained from *I. balsamina* seeds has positive immunomodulatory effects. It can promote the production of NO on RAW 264.7 macrophage cell line at concentrations of 12 and 25 µg/mL without cytotoxicity. It also induces the production TNF-α, IL-1β, IL-6, and IL-10 on the same cell line. The peptide fraction stimulates T-lymphocyte proliferation at test concentration of 25 µg/mL.[380] Compound 1 can cooperate with monocyte chemoattractant protein-1 (MCP-1) to promote migration of THP-1 cells in transwell migration assay. The combination of MCP-1 and 1 reduces the intracellular level

of adenosine monophosphate (cAMP) and promotes the phosphorylation of ERK 1/2.[381]

A protein with average mass of 310 kDa has been isolated from *I. balsamina* fruit pericarp. This protein of four 75 kDa subunits promotes a significant reduction in rabbit muscle actin polymerization at concentration of 15.5 µg/mL. Further research must be done to complete the structural characterization of this protein and to define a potential application for it.[382]

Compound 25, isolated from *I. bicolor* ethyl acetate extract, showed *in vitro* inhibitory effects on catalytic activity of trypsin (IC_{50} = 0,96 mM). This result can support further research of the inhibitory activity of 25 in other serine proteases implicated in diseases including cancer, arthritis, and pancreatitis.[383] Compound 25 also has acetyl cholinesterase inhibitory activity (inhibition of 42.86% at concentration of 200 µg/mL).[347]

Aryl hydrocarbon receptor (AhR) activation is implicated in toxic response to halogenated and polycyclic aromatic hydrocarbons. This cellular event can trigger harmful effects as carcinogenesis, teratogenesis and vascular inflammation. Acetone extracts of *I. noli-tangere* and *I. textorii* ground parts, at concentration of 0.5 mg/mL, reduce the activation of AhR induced with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on cytosolic fraction isolated from rat hepatocytes by 28.9% and 71.4%, respectively.[345]

The *n*-butanol fraction, rich in saponins, obtained from the methanol (50%) extract of *I. capensis* leaves increases (30,5% increment) the heart rate in black worms (*Lumbriculus variegatus*) suggesting the induction of chronotropic effects.[120]

Flowers from *I. glandulifera* are part of Bach floral remedies used to treat stress and anxiety. The efficacy and use of this therapies is controversial. Results from some small clinical studies support their uses but other refuse them.[384-389] Thus, more studies with better design are needed to confirm or definitively discard the efficacy of this alternative therapy.

Figure 2 summarizes the structure of compounds isolated from *Impatiens* that have demonstrated biological effects when they are tested individually in different biological assays.

TOXICOLOGICAL STUDIES

According to *Caenorhabditis elegans* model, a method used for fast screening of medicinal herbs toxicity, ethanol (55%) extract of *I. balsamina* stems reduce the viability of nematodes by 24% at concentration of 10 mg/mL. Compounds 1 and 8 are the main toxic compounds present in this extract, they reduce the nematodes survival by around 20% and 80%, respectively at concentration of 0.5 mg/mL. These compounds significantly reduce *C. elegans* nematodes mobility and body size at the same concentration. Compound 8 shows more marked effects than 1.[390] The seeds of *I. balsamina* were extracted successively with hexane, a mixture of dichloromethane-methanol (1:1) and water. The water and dichloromethane-methanol fractions were no toxic on brine shrimp (*Artemia salina*) (lethal concentration that kills 50% of test organisms (LC_{50}) > 1000 µg/mL).[391] Compound 1 can be an aquatic toxicant; it has toxic effects against *Daphia* sp. with a median LC_{50} of 2.84 mg/L. This compound can reduce the defensive responses of *Daphia magna* to kairomones obtained from predatory species as *Triops cancriformis* and *Notonecta* sp.[392]

The methanol extract from *I. balsamina* leaves does not induce acute toxicity or mortality in rats at oral doses of 500, 1000 and 2000 mg/kg.[378] The ethanol extract (80%) from whole plants of *I. balsamina* does not show toxicity symptoms or mortality when given at dose of 2000 mg/kg in acute oral toxicity assay carried out on Swiss albino mice according to Organization for Economic Co-operation and Development (OECD) 423 guidelines.[82] The evaluation of the acute toxicity of the *n*-hexane fraction derived from the methanol extract of *I. balsamina* stems and leaves on Sprague-Dawley rats according to the OECD 425 guidelines demonstrated that fraction, at oral dose of 5000 mg/kg, does not promote any sign of toxicity or histological changes on liver and kidneys.[393] The ethanol extract from *I. balsamina* has not shown significant toxicity signs or mortality in sub-chronic oral toxicity assay on F344/DuCrj rats. The No-Observed-Adverse-Effect-Level (NOAEL) was determined as 3997 mg/kg/day for male and 4577 mg/kg/day for female rats.[394] The aqueous extract from *I. tinctoria*, at dose of 9600 mg/kg, does not promote mortality or toxicity symptoms in albino mice used in acute toxicity assay carried out according to OECD 420 guidelines.[187]

The allergenic potential of 1 and 8 was evaluated using an *in vivo* model of male albino guinea pigs previously sensitized with deoxylapachol. Animals have not shown hypersensitivity reaction after topical exposure with 8 at concentration of 20 mM. In the case of 1, it induced weak or moderated erythema in almost 75% of experimental animals after its topical application at concentration of 100 mM.[395]

The evaluation of the oral toxicity of several 1,4-naphthoquinones in female rats of the Ruakura colony of Sprague-Dawley-derived animals, at oral dose of 750 µmoles/kg/day during 6 days indicates that 8 can produce important signs of toxicity that includes increase in splenic, renal and hepatic mass, reduction of blood packed cell volumes and hemoglobin levels, formation of Heinz bodies, elevation of urea and creatinine levels in plasma, splenic sinusoidal engorgement associated with iron hepatic and splenic deposition, necrosis in distal portion of the proximal convoluted tubules and presence of eosinophilic debris in distal convoluted and collecting tubules.[396]

Safety studies showed that 10 and 13 do not cause erythrocyte lysis. They neither show cytotoxicity in tumor cells, including A-549, human immortalized myelogenous leukemia (K-562), and human breast adenocarcinoma (MDA-MB-361), and mouse

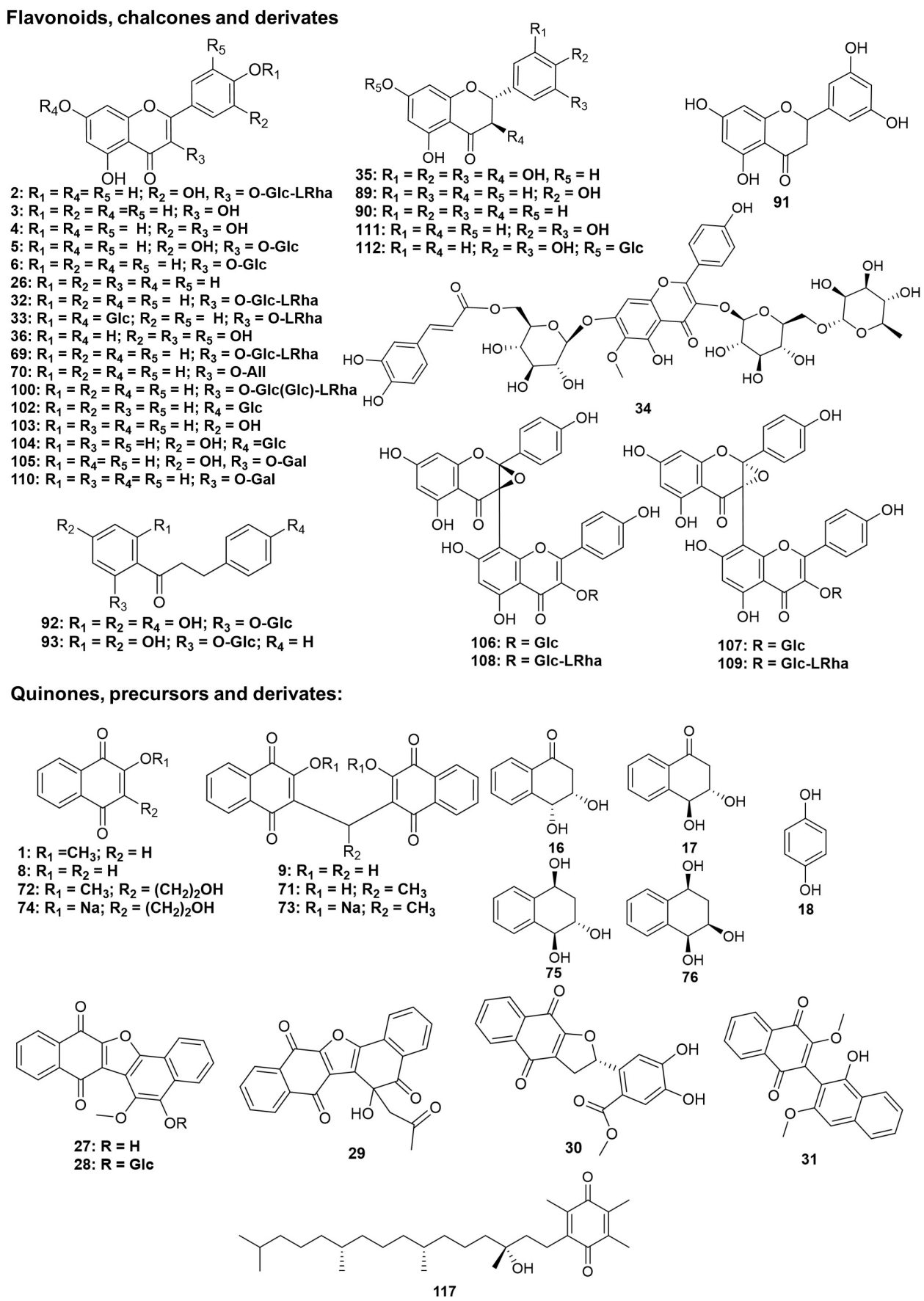


Figure 2: Structure of isolated compounds from *Impatiens* plants evaluated in biological assays.

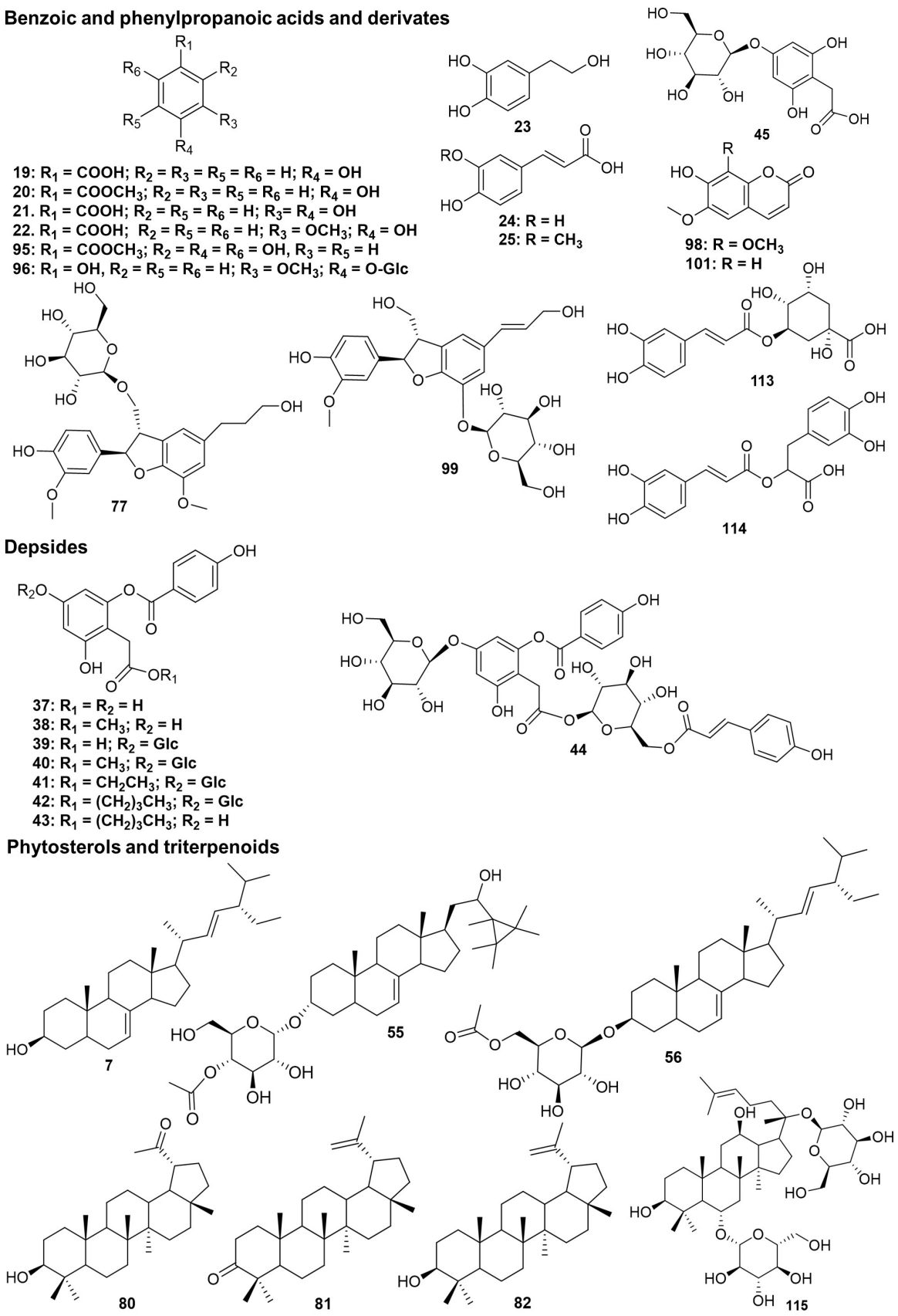
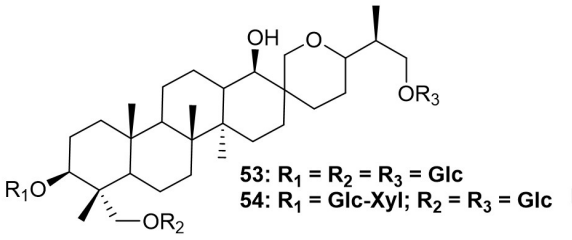
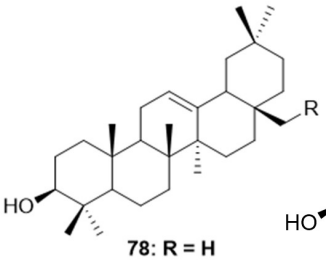


Figure 2 (continued).

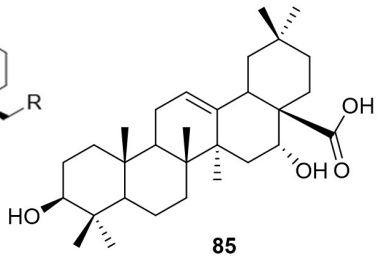
Phytosterols and triterpenoids (continuation)



53: $R_1 = R_2 = R_3 =$ Glc
54: R_1 = Glc-Xyl; $R_2 = R_3$ = Glc



78: R = H
79: R = OH



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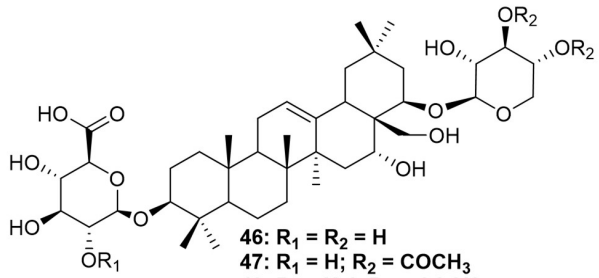
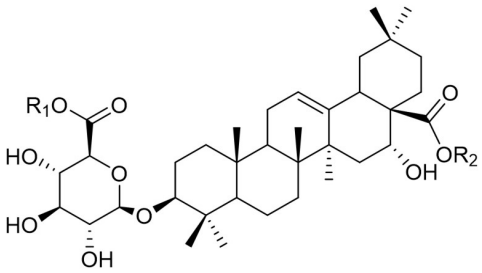
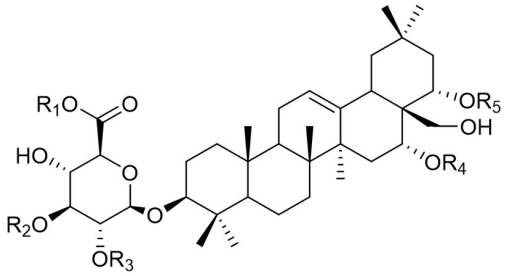


46: $R_1 = R_2$ = H
47: R_1 = H; $R_2 = COCH_3$
48: R_1 = Xyl; $R_2 = COCH_3$

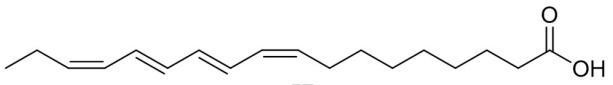


62: R_1 = H; R_2 = Xyl-LRha-LAra
63: $R_1 = CH_2CH_3$; R_2 = H
64: $R_1 = (CH_2)_3CH_3$; R_2 = H
65: $R_1 = (CH_2)_3CH_3$; R_2 = Xyl-LRha-Xyl
66: $R_1 = CH_3$; R_2 = Xyl-LRha-Xyl
67: R_1 = H; R_2 = LAra-LRha(Api)-Xyl
68: R_1 = H; R_2 = Xyl-LRha(Api)-Xyl
86: $R_1 = R_2$ = H
87: $R_1 = CH_3$; R_2 = H
88: $R_1 = CH_2CH_3$; R_2 = H



49: $R_1 = (CH_2)_3CH_3$; $R_2 = R_3 = R_4$ = H; R_5 =LAra
50: $R_1 = (CH_2)_3CH_3$; $R_2 = R_4$ = H; R_3 = Xyl; R_5 = LAra
51: $R_1 = R_2 = R_3 = R_4$ = H; R_5 = LAra
52: $R_1 = R_2 = R_4$ = H; R_3 =Xyl; R_5 = LAra
58. $R_1 = R_5$ = H; $R_2 = R_3$ = Glc; $R_4 = COCH_3$
59: $R_1 = R_4 = R_5$ = H; $R_2 = R_3$ = Glc
116: $R_1 = R_5$ = H; R_2 = LAra; R_3 = Glc; $R_4 = COCH_3$

Fatty acids and derivates:



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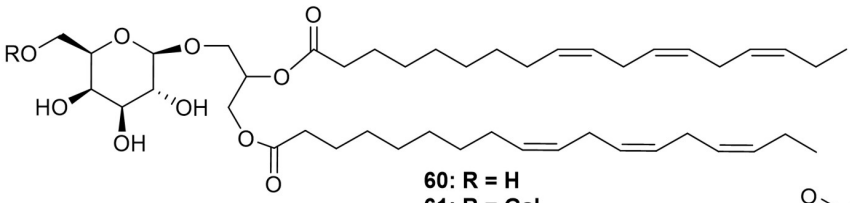
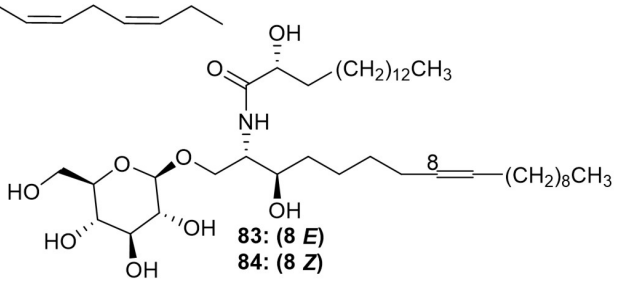


60: R = H
61: R = Gal



83: (8 *E*)
84: (8 *Z*)

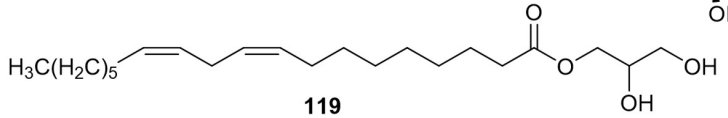


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Figure 2 (continued).

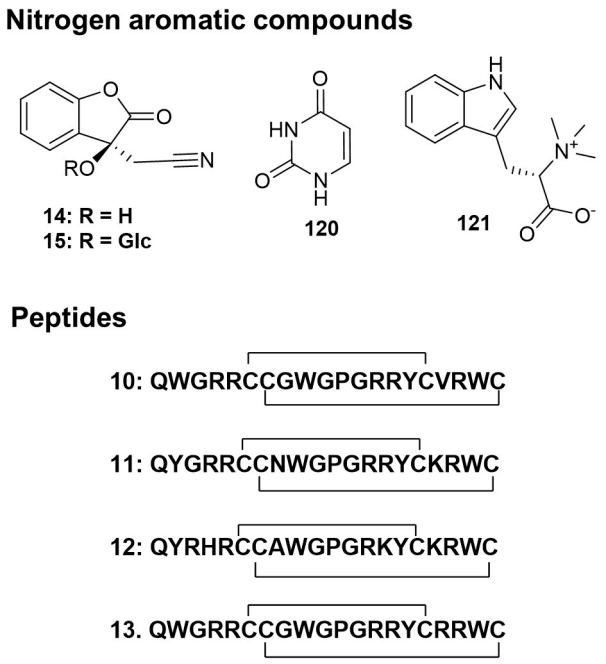

Figure 2 (continued).

myeloma cells.[248,262] Moreover, 10 has low cytotoxicity on HT-29, HepG2, and human fetal small intestine (FHs 74 Int) cell lines (IC_{50} ranging from 200 to 500 µg/mL).[249]

OTHER APPLICATIONS

Edible material

Several *Impatiens* species are considered edible and potential sources of pigments for food industry applications.[212,397] Among this species are *I. arguta, I. aurella, I. balsamina, I. capensis, I. glandulifera, I. noli-tangere, I. pallida, I. parviflora, I. sulcata, I. textori*, and *I. walleriana.*[397] However, the nutritional properties of few species have been characterized. Flowers from *I. walleriana* are edible and some nutritional features have been studied. The fresh flowers have the following contents: dry matter: 14.75% w/w, crude protein content: 4.60 g/kg, phosphorus: 382.73 mg/kg, potassium: 2835.25 mg/kg, calcium: 405.62 mg/kg, magnesium: 203.34 mg/kg, sodium: 94.29 mg/kg, iron: 7.26 mg/kg, manganese: 6.05 mg/kg, cupper: 1.31 mg/kg, zinc: 8.72 mg/kg, molybdenum: 0.39 mg/kg.[15,343]

The comparison of the nutritional properties from fresh pink and orange flowers of *I. balsamina* demonstrated that each 100 g of orange flowers have ash, fat, protein, carbohydrates, total sugar and energy values of 26 g, 0.13 g, 0.33 g, 4.2 g, 1,2 g and 19.2 kcal, respectively. Whereas pink flowers have values of 26 g, 0.10 g, 0.315 g, 4.76 g, 1.34 g and 21.145 kcal for the same parameters. The most abundant sugar among *I. balsamina* fresh flowers is glucose with values in the interval of 1.23-1.34 g/100 g. The content of saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids in the flowers are in the ranges of 34.37-44.9, 12.9-14.13, and 40.9-52.7 g/100 g, respectively. The main fatty acids present are stearic acid and linoleic acid in orange and pink flowers, respectively. Succinic acid is the major organic acid present in both orange and pink flowers, with levels from 43.9 to 59.8 g/100 g.[212]

Honey from *I. glandulifera* pollen has fructose and glucose as the predominant monosaccharides, with average values of 39.34% and 31.91%, respectively. Maltose and (3.04%) and sucrose (0.08%) are the main disaccharides. On the other hand, trisaccharides melezitose (0.55%) and raffinose (0.13%) are the minor sugars. This honey has antioxidant activity in FRAP assay equivalent to 225.38 µM of $Fe2^{+}$. The average TPC value for the extract was 130.97 mg GAE/kg.[398]

Food and crude drugs preservatives

Covering cold-stored tangerines and oranges with carboxymethyl cellulose coating containing *I. balsamina* stems ethanol extract deaccelerates decay in fruits, reduces the loss of their nutritional properties and contributes to maintain the activity of their antioxidant enzymes.[399-401] Likewise, the methanol extract and 1 obtained from *I. balsamina* have antifungal activity against *Alternaria panax* growth in Ginseng.[402] Moreover, it is proposed that knowledge of the biosynthetic pathways and genes implicated in the synthesis of antimicrobial polyphenols from *Impatiens* can be useful to their expression in *Saccharomyces cerevisiae* and be potentially used as natural food preservatives.[403]

Biotechnological development of antimicrobial fusion proteins

Antimicrobial fusion proteins that include Ib-AMP peptide sequences as linker for fusion protein design are also interesting for agronomy due their potential use against plant pathogenic microorganisms. A fusion protein, corresponding to a hybrid of *Trigonella foenum-graecum* defensin 2 (Tfgd2) and *Raphanus sativus* Antifungal Protein 2 (RsAFP2), was synthetized using Ib-AMP protein precursor as a linker peptide and *E. coli* BL21 (DE3) pLysS cells as expression system. The obtained fusion

protein exerts antimicrobial activity against plant pathogenic fungi, including *B. cinerea, F. moniliforme, F. oxysporum* and *Phaeoisariopsis personata*, with growth inhibition percentages more than 95.45% at 40 µg/mL on tested microorganism according to broth dilution assays.[404]

Ib-AMP polyprotein sequence from *I. balsamina* seeds have been used as a linker to design chimeric polyprotein that includes sequences of two antimicrobial peptides, DmAMP1 originating from *Dahlia merckii* seeds and RsAFP2 originating from *R. sativus* seeds. The yield of individual antimicrobial peptides is higher in transgenic *Arabidopsis* plants with the chimeric construct than those plants with transgenes for single peptides.[405,406]

Through plasmid construction and its introduction in *E. coli* BL21, it was possible to produce a hybrid protein of beta-casein and 13 antimicrobial peptide. This protein has shown antibacterial activity against *E. coli* (MIC: 64 µg/mL; MBC: 256 µg/mL), *S. typhimurium* (MIC: 256 µg/mL; MBC: > 512), *S. aureus* (MIC: 8 µg/mL; MBC: 64 µg/mL) and *L. monocytogenes* (MIC: 256 µg/mL; MBC: > 512 µg/mL). It also has antifungal effect on *C. albicans* (MIC: 256 µg/mL; MFC: > 512) and *A. flavus* (MIC: 16 µg/mL; MFC: 128 µg/mL). The hybrid protein has synergy antibacterial and antifungal activity when it is combined with thymol.[407]

A recombinant peptide that integrates 13 and Thioredoxin (Trx) amino acid sequences has been expressed in *E. coli*. This peptide has antibacterial activity with MIC of 0.0875 mg/mL against *S. aureus*. Both peptides, 13 and Trx-Ib-AMP4 can reduce the bacterial load in wound infection model using Wistar rats. They promote a decline of immune cell infiltration during wound healing process. Trx-Ib-AMP4 showed synergic effects in these assays when it was combined with Trx-E50-52, a recombinant peptide derived from Trx and bacteriocin 50-52.[408]

Diagnostic and imaging applications

Carbon dots made with *I. balsamina* stem powder can function as a selective fluorescent probe to detect Gram-positive bacteria and differentiate them from Gram-negative cells. Additionally, they had low cytotoxicity against HepG2, HaCaT, and mice macrophage cells keeping an approximately cell viability of 80-100% when tested at concentration of 3 mg/mL. These dots can be useful for bio-imaging applications due their ability to probe eucaryotic cells with fluorescence.[219]

A fusion protein was synthetized using DNA recombination technology and *E. coli* as expression organism. It consists in the fusion of Green Fluorescent Protein (GFP) and 13 giving a peptide probe that anchors bacteria cell walls. It retains the antibacterial activity of 13 and the fluorescent feature GFP. This fusion protein can be used for the identification of pathogenic bacteria due their variability in fluorescence emitted depending on bacteria type at which it is anchored.[256]

Targeted drug release systems

Fan *et al.* reports the synthesis of a fusion protein of 13, Pc1 peptide and GFP through DNA recombination technology using *E. coli* as expression organism. This fusion protein can be anchored to red blood cells derived vesicles and DOPC liposomes charged with doxorubicin, allowing the generation of products with higher cytotoxicity and improved selectivity on cancer cells that highly express αvβ3 integrin, protein that binds with high affinity to Pc1 peptide. This application demonstrates a promissory role of 13 in the development of systems for the selective release of drugs in target tissues given its membrane anchoring characteristics. Additionally, the vesicles surrounded by the fusion protein could be useful for tumor imaging due GFP portion according to the results of murine xenograft model using A-549 cancer cells that express αvβ3 integrin.[409]

Cosmetic formulations

There are reports of cosmetics products formulated to its application based on pharmacological properties of *Impatiens* plants. For instance, it is proposed to use *I. balsamina* extracts for the development of cosmetics for skin rash relieving.[87]. Several cosmetics with *I. balsamina* extracts have been formulated, including patches, creams, shampoos, peel-off mask, nail polish, soaps, and gels. Their antimicrobial activity has been tested against *S. aureus, S. epidermidis, P. acnes*, and *C. albicans* using agar diffusion assay. These products have shown antimicrobial activity with IZD range of 5.66-22.2 mm.[410-412]

Industrial dyes

Flowers from *I. balsamina* and *I. glandulifera* are considered as source of dyes for their application in textile, paper, and food industry.[212,397,413,414]

PERSPECTIVES AND RESEARCH OPPORTUNITIES

Despite the studies related to the discover of bioactivities in extracts and metabolites from *Impatiens* species, there is a wide area of research that can be explored taking into consideration the vast variety of ethnobotanical applications reported for plants of this genus. It is important to notice that ethnopharmacological and chemotaxonomic approaches have been successful for the discover of active extracts and compounds from *Impatiens* species according to revisited information. Antimicrobial, anti-inflammatory, cytotoxic, anti-anaphylactic, and antioxidant effects are the major bioactivities discovered for *Impatiens* plants and their isolated metabolites.

According to our review, different kinds of bioactive compounds have been identified among *Impatiens* plants but most of these metabolites correspond to short peptides, phytosterols triterpenoids and phenolics. Therefore, the attention for bioactive compounds characterization can be addressed to these groups of

metabolites in further research of unexplored *Impatiens* species. The selection of botanical material for the development of further studies may be oriented by the available ethnobotanical information, especially for *Impatiens* plants that have been poorly studied.

Szewczyk summarized the reported results from studies of phytochemical characterization of 27 species from *Impatiens* genus. These studies have allowed the identification of more than 300 compounds including flavonoids, phenolic acids, coumarins, quinones, triterpenoids, alkaloids and peptides.[17] Despite the important number of compounds that have been isolated or identified among *Impatiens* genus plants, must be notice that only a low fraction of them has been recognized as biological active and, in consequence, only few can be related with the biological effects shown by the extracts of *Impatiens* plants or their reported ethnobotanical applications. Hence, further efforts must be done to understand the relative importance of each compound observed in bioactive material instead to only report its presence.

The nutritional properties and pharmacological activities of most ethnobotanically relevant *Impatiens* species have not been investigated yet. This fact demonstrates that there is an important research area that may be explored. However, there are many reports of ethnobotanical applications of *Impatiens* plants to treat illnesses or to improve health on humans or animals. Nevertheless, among this information is possible to identify reports without specific information related to plant sections used, their preparation, and administration routes. This situation can be an obstacle in the nutritional studies, ethnopharmacological validation of remedies and their toxicological evaluation. Furthermore, this could be a barrier to identify the major bioactive compounds and plant organs that are more useful for the development of phytomedicines and functional foods. Thus, further ethnobotanical data compilations may take these factors into account to have a more complete register of ethnobotanical applications of *Impatiens* plants.

In additional to studies mentioned in previous sections, there are several reports of the development of instrumental analytical procedures for the separation and determination of known bioactive compounds of specific *Impatiens* plants. These techniques include analytic methodologies for the quantification of *Impatiens* metabolites in biological fluids that can be useful for pharmacokinetic studies. Most of these tools are chromatographic techniques coupled to a wide variety of detectors that include mass spectrometers, ultraviolet-visible light detectors, and light scattering detectors.[35,45,48,49,70,415-419] These methods may be adapted for the analyses of unexplored species.

Studies on *Impatiens* naphthoquinones biosynthesis have revealed that they are derived from shikimic acid pathway. Other efforts have been done to discover and characterize *I. balsamina* genes involved in the biosynthesis of bioactive naphthoquinones.[420-423] Integration of these data can be used to improve the bioactive compounds production in the plant using genetic modification and biotechnology tools.[420,423]

I. balsamina in vitro root cultures experiments, using different growth regulators and biosynthesis precursors, have shown a significant increase in naphthoquinones production that are useful for commercial production of this metabolites.[424-427] Biotechnology techniques have been also applied for the production of antimicrobial peptides from *I. balsamina* and hybrids of them with other antimicrobial peptides of natural origin, this includes the development of transgenic organism, as *Arabidopsis thaliana* and *E. coli* strains, used as expression systems.[256,404-408]

Chemical synthesis techniques are other way to improve bioactive molecule production.[259-262,428,429] Additionally, chemical synthesis can be used to modify the structure of known *Impatiens* plants bioactive compounds aiming improvements of their activity, safety and pharmacokinetic features. Examples of this are the structure-activity relationship studies carried out with Ib-AMP peptides for the enhancement of their antimicrobial properties and safety profile.[259,260,262]

One limitation found in revisited literature is the use of agar diffusion assay in an important fraction of antimicrobial activity reports for metabolites and extracts obtained from *Impatiens* species. It is important to encourage the use of standard and recognized broth dilution assays protocols, like those from Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) to have more confident MIC and MBC values that can be used for comparative proposes. In this sense, it is important to emphasize that agar diffusion assays at one concentration level are commonly recognized only as a preliminary test and they have important limitations related to diffusion of non-polar antimicrobial compounds.

Another limitation is the fact that antioxidant activity research in *Impatiens* plants is limited to chemical *in vitro* antioxidant assays in most cases. Therefore, further efforts must be done for the evaluation of antioxidant activity using more biological relevant assays including cellular models. Antioxidants can have a wide spectrum of applications, including cancer prevention, cardiovascular diseases prophylaxis, and anti-inflammatory therapies, however, in the case of *Impatiens* plants extracts and their metabolites with antioxidant activities is not clear for which application are their antioxidant properties studied. Hence, a definition of a direction in this topic is a pending task.

Chemical constitution of extracts and their bioactivities varies significantly depending on plant phenotype, plant phenological stage, botanical material recollection date, extraction methodology and plant organ used to their preparation according with several studies reported for *I. balsamina* and *I. glandulifera*.[29,211,341,369]

Therefore, it is important to consider this kind of analysis for the future investigation of poor studied *Impatiens* species. This information is basic to standardize the production of bioactive extracts from these plants.

According to our review, the elucidation of the mechanism of action of the bioactive compounds and plant extracts from *Impatiens* species is another opportunity of research in most cases. Moreover, there are few reports of pharmacological studies of extracts and compounds isolated from *Impatiens* genus using *ex vivo* models and animal studies. Additionally, there are limitations in the information related to the toxicity for most of these substances. It is important to explore these approaches of research to get a better understanding of the potential applications of *Impatiens* extracts and its metabolites. No less important is the fact that these investigation approaches can give an approximated measure of the efficacy and safety of ethnobotanical uses of *Impatiens* plants for medicinal purposes.

CONCLUSION

In summary, *Impatiens* genus plants are promising sources of metabolites and extracts with biological activities. Among reported activities, antioxidant, antimicrobial, cytotoxic, anti-anaphylactic, and anti-inflammatory effects are the most frequent. Despite of the wide variety of compounds identified in different *Impatiens* species, phenolics, phytosterols, triterpenoids, peptides and plant extracts rich in this kind of metabolite seem to be the most promissory for the development of products with pharmacological applications and functional foods. Ethnobotanical information can guide the selection of more species from *Impatiens* genus for the evaluation of their biological effects and the identification of their active molecules. Further investigations, using biological models should be done to confirm the effectiveness and safety of bioactive plant extracts and secondary metabolites along to their mechanism of action to gain a better understanding of their future application in humans or animals.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

36B10: Fetal rat astrocytes cell line; **A172:** Human glioma cell line; **A-375:** Human melanoma cell line; **A-549:** Human lung adenocarcinoma cell line; **AAE:** Ascorbic acid equivalents; **ABTS:** 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); **AGS:** Human gastric adenocarcinoma cell line; **AhR:** Aryl hydrocarbon receptor; **Akt:** Protein kinase B; **AMPK:** 5'-adenosine monophosphate-activated protein kinase; **AMPT:** α-methyl-DL-tyrosine; **ASC:** Apoptosis-associated speck-like protein containing a caspase recruitment domain; **ATP:** Adenosine triphosphate; **B16BL6:** Mouse melanoma cell line; **B16F10:** Murine melanoma cell line; **Bad:** B-cell lymphoma 2 associated agonist of cell death; **Bak:** B-cell lymphoma 2 homologous antagonist/killer; **Bax:** B-cell lymphoma 2 associated X protein; **Bcl-2:** B-cell lymphoma 2; **BDNF:** Brain-derived neurotrophic factor; **Bel-7402:** Human liver cancer cell line; **Bid:** BH3-interacting domain death agonist; **BJ:** Human fibroblasts cell line; **BMDM:** Bone marrow derived macrophages; **BT549:** Human invasive breast carcinoma cell line; **BV-2:** Murine microglia cell line; **C3GE:** Cyaniding 3-*O*-glucoside equivalents; **C6:** Rat glioma cell line; **CagA:** Cytotoxin-associated gene A; **cAMP:** Cyclic adenosine monophosphate; **CLSI:** Clinical and Laboratory Standards Institute; **COX:** Cyclooxygenase; **DCFDA:** 2′,7′-dichlorodihydrofluorescein diacetate; **DGDG-1:** Digalactosyl diacylglicerol 1; **DLA:** Dalton's Lymphoma Ascites cell line; **DNA:** Deoxyribonucleic acid; **DOPC:** 1,2-dioleoyl-sn -glycero-3-phosphocholine;**DPPH:**2,2-diphenyl-1-picrilhidrazil; **Du145:** Prostate cancer cell line; **EC_{50}:** Half maximal effective concentration; **ERK:** Extracellular signal-regulated kinases; **EUCAST:** European Committee on Antimicrobial Susceptibility Testing; **FHs 74 Int:** Human fetal small intestine cell line; **fMLP:** Formyl-methionyl-leucyl-phenylalanine; **FRAP:** Ferric reducing antioxidant power; **FST:** Forced swimming test; **GAE:** Gallic acid equivalents; **GC-FID:** Gas chromatography coupled to flame ionization detector; **GC-MS:** Gas chromatography coupled to mass spectrometry; **GFP:** Green fluorescent protein; **GLUT-1:** Glucose transporter 1; **HaCaT:** Human keratinocyte cell line; **HCT-15:** Human colorectal cancer cell line; **HDL:** High-density lipoproteins; **HEK293:** Human embryonic kidney cell line; **HEL:** Hen egg-white lysozyme; **HeLa:** Human cervical carcinoma cell line; **HepG2:** Human hepatocellular carcinoma cell line; **HIV:** Human immunodeficiency virus; **HL-60:** Human acute myeloid leukemia cell line; **HL-60/MX2:** Human acute myeloid leukemia cell line; **HMC-1:** Human mast cell line; **HPLC-DAD:** High performance liquid chromatography coupled to diode array detector; **HPLC-DAD-MS/MS:** High performance liquid chromatography coupled to diode array detector and tandem mass spectrometry; **HPLC-ESI–MS/MS:** High performance liquid chromatography coupled to electrospray ionization and tandem mass spectrometry; **HPLC-MS:** High performance liquid chromatography coupled to mass spectrometry; **HSC-2:** Human oral squamous cell carcinoma cell line; **HSC-4:** Human oral squamous cell carcinoma cell line; **HT-29:** Human colorectal adenocarcinoma cell line; **HTB140:** Human melanoma cell line; **IC_{50}:** Half-maximal inhibitory concentration; **IFN-γ:** interferon-γ; **IL:** Interleukin; **IZD:** Inhibition zone diameter; **JNK:** c-Jun N-terminal kinase; **K-562:** Human immortalized myelogenous

leukemia; **KATO-III:** Human stomach adenocarcinoma; **LC_{50}:** Lethal concentration that kills 50% of test organisms; **LDL:** Low-density lipoproteins; **LMWPF:** Low molecular weight peptide fraction; **LNCaP:** Human androgen-sensitive prostate adenocarcinoma cell line; **LOX:** Lipoxygenase; **LPS:** Lipopolysaccharide; **MAPK:** Mitogen-activated protein kinase; **MBC:** Minimal bactericidal concentration; **MCF-7:** Human breast adenocarcinoma cell line; **MCP-1:** Monocyte chemoattractant protein-1; **MDA-MB-231:** Human breast triple-negative adenocarcinoma cell line; **MDA-MB-361:** Human breast adenocarcinoma cell line; **Melan-a:** Mouse melanocyte cell line; **MFC:** Minimal fungicidal concentration; **MGDG-1:** Monogalactosyl diacylglycerol 1; **MIC:** Minimal inhibitory concentration; **MITF:** Melanocyte inducing transcription factor; **MK-1:** Human gastric adenocarcinoma cell line; **MKN45:** Human stomach adenocarcinoma cell line; **MMP-2:** Matrix metalloproteinase 2; **MMP-9:** Matrix metallopeptidase 9; **mRNA:** Messenger RNA; **MRSA:** Methicillin-resistant *Staphylococcus aureus*; **MT-1:** Human T-cell lymphotropic virus type 1-infected T cell line; **MT-2:** Human T-cell lymphotropic virus type 1-infected T cell line; **mTOR:** Mammalian target of rapamycin; **MTT:** 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; **NADH:** Nicotinamide adenine dinucleotide; **NCI-H460:** Human non-small cell lung cancer cell line; **NF-κB:** Nuclear factor kappa-light-chain-enhancer of activated B cells; **NGF:** Nerve growth factor; **NIH 3T3:** Normal mouse embryonic fibroblast cell line; **NLRP3:** NACHT, LRR and PYD domains-containing protein 3; **NO:** Nitric oxide; **NOAEL:** No-observed-adverse-effect-level; **NRF2:** Nuclear factor erythroid 2-related factor 2; **OEC:** Olfactory ensheathing cells; **OECD:** Organization for Economic Co-operation and Development; **ORAC:** Oxygen radical absorbance capacity; **OSC-20:** Human squamous cell carcinoma cell line; **OxHLIA:** Oxidative hemolysis inhibition assay; **p75NTR:** p75 neurotrophin receptor; **PAF:** Platelet-activating factor; **PBMC:** Peripheral blood mononuclear cells; **PC-3:** Human prostate adenocarcinoma cell line; **PCPA:** *p*-chlorophenylalanine methyl ester; **PI3K:** Phosphoinositide 3-kinase; **PLP2:** Normal porcine liver cell line; **PMA:** Phorbol 12-myristate 13-acetate; **PMACI:** Mixture of PMA and the calcium inophore A23187; **PMN:** Human polymorphonuclear leukocytes; **PNT2:** Normal human prostate epithelium cell line; **QCM-D:** Quartz crystal microbalance with dissipation; **QE:** Quercetin equivalents; **Raji:** Human Burkitt lymphoma cell line; **RAW 264.7:** Murine macrophage cell line; **RE:** Rutin equivalents; **RIP2:** Receptor-interacting-serine/threonine-protein kinase 2; **RNA:** Ribonucleic acid; **RPSA:** Laminin-binding protein; **ROS:** Reactive oxygen species; **RsAFP2:** *Raphanus sativus* antifungal protein 2; **RT-PCR:** Reverse transcription-polymerase chain reaction; **RV1:** Human prostate epithelial carcinoma cell line; **S-180:** Balb/c mice sarcoma tumor cell line; **sAPPα:** Secreted amyloid precursor protein-alpha; **SK-MEL-2:** Human malignant melanoma cell line; **SK-OV-3:** Human ovarian adenocarcinoma cell line; **SMEL-28:** Human melanoma cell line; **SweAPP N2a:** Swedish mutant amyloid precursor protein overexpressing mouse neuroblastoma cell line; **TAC:** Total anthocyanin content; **TCF:** T cell factor; **TE:** Trolox equivalents; **TFC:** Total flavonoid content; **Tfgd2:** *Trigonella foenum-graecum* defensin 2; **t-HSC/Cl-6:** Rat hepatic stellate cell line; **THP-1:** Human leukemia monocytic cell line; **TNAPC:** Total non-anthocyanidin phenolic content; **TNF-α:** Tumor necrosis factor α; **TPAC:** Total phenolic acid content; **TPC:** Total phenolic content; **Trx:** thioredoxin; **TSLP:** Thymic stromal lymphopoietin; **TST:** Tail suspension test; **U373:** Human glioma cell line; **U-937:** Human monocytic leukemia cell line; **UHPLC-DAD-MS:** Ultra-high performance liquid chromatography coupled to diode array and mass spectrometry detectors; **UHPLC-MS:** Ultra-high performance liquid chromatography coupled to mass spectrometry; **WM793:** Human melanoma cell line; **α-MSH:** α-melanocyte-stimulating hormone.

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