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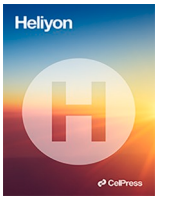

Review article

Malinzi, a traditional medicinal plants: Comprehensive review of botany, medical application, chemical composition, and pharmacology

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ABSTRACT

Malinzi is the dry ripe seed of *Iris Lactea* Pall. var. *chinensis* (Fisch.) Koidz and is a tradtional medicinal plant with significant development and utilization value. A total of 31 compounds from Malinzi have been reported, including flavonoids, quinones, oligostilbenes, and other constituents. Modern pharmacological studies have shown that Malinzi has good activities in anti-tumor, radio-sensitization, boost immunity, anti-oxidation, anti-fertility, and glucolipid metabolism. In this paper, by reviewing the domestic and foreign research literatures of Malinzi and summarizing its traditional uses, chemical constituents, and pharmacological activities, it is expected to provide theoretical reference for the subsequent in-depth research and application of Malinzi.

1. Introduction

Traditional Chinese medicine (TCM) has a long history of medical use for thousands of years and has been more widely used in modern times.

Iris Lactea Pall. var. *chinensis* (Fisch.) Koidz is a traditional medicinal plant resource and herbaceous perennial belonging to the Iridaceae family [1]. It is widely distributed in northwest, north, east, and northeast China and central and western Asia, Russia, Mongolia, and Korea [2]. It grows in the wasteland, roadside, and hillside grassland, especially on overgrazed saline-alkali grassland. It is widely distributed in coastal areas, mainly including the coastal areas of China and Korea. Because of its good salt tolerance and strong reproductive ability, it is distributed along the roadside in the shade and even planted in gardens by the sea [3].

Malinzi, the dry ripe seed of *Iris Lactea* Pall. var. *chinensis* (Fisch.) Koidz, is an irregular polyhedron, mostly reddish-brown and slightly glossy. Malinzi, formerly known as Lishi, was first recorded in *Shennong Ben Cao Jing* [4], and it is called Malinzi in *Tang Materia Medica* [5]. Malinzi is pungent and sweet in flavour, calm in nature, and widely used in TCM. It belongs to the lung, spleen,

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stomach, and liver meridians. Its effects are to clear heat and dampness, detoxify and disperse knots, stop bleeding, and kill worms. The symptoms primarily used to treat include jaundice, dribbling urination, inhibited urination, intestinal abscess, worm accumulation, malaria, wind-dampness, throat impediment, toothache, hematemesis, epistaxis, diarrhea, blood in the stool, flooding and spotting, scrofula, genital disease, hemorrhoid, scald, snakebite and other feature diagnosed by Chinese medicine. Malinzi has been researched as a medicinal plant resource in recent years, mainly focusing on its chemical composition and pharmacological activity. Irisquinone capsules taken from the seed coat of Malinzi are utilized as a radiosensitizer and included in the Chinese New Drug Conversion Standard.

In this paper, we reviewed the research progress of Malinzi in recent years in terms of its botany, traditional uses, medical application, chemical composition, and pharmacological activity to provide a reference for further study, development, and utilization of Malinzi.

1.1. Botany

Iris Lactea Pall. var. *chinensis* (Fisch.) Koidz is a perennial herb, 40–60 cm tall. Rhizome lignified, thick and robust, obliquely ascending. Fibril thick and long, yellowish white. Leaf tenacious, fasciate, nearly upright; lamina strip-like, 40–50 cm long, 4–6 mm wide, tip gradually pointed, entire, basal section mantle folded; flower blue, bluish purple, flower 5–6 cm in diameter, perianth lobes 6 in 2 whorls. Capsule long cylindrical, 4–6.3 cm long, 1–1.3 cm in diameter, with 6-separate longitudinal ridges, tip with rostrums (Fig. 1A). Seed irregularly polyhedral, blackish brown [6] (Fig. 1B).

Iris Lactea Pall. var. *chinensis* (Fisch.) Koidz is widely distributed in northwest, north, east, and northeast China and in central and western Asia, Russia, Mongolia, and Korea [2,7]. *Iris Lactea* Pall. var. *chinensis* (Fisch.) Koidz is more common in grassland areas and less distributed in forest and desert areas. It is resistant to barren soil and often grows in the wasteland, roadside, natural grassland, and seaside saline-alkali land [8]. The salinized meadow is composed of *Iris Lactea* Pall. var. *chinensis* (Fisch.) Koidz, about 398 700 hm^2 in the country [8]. The root system of *Iris Lactea* Pall. var. *chinensis* (Fisch.) Koidz is well-developed, with a wide adaptation area, long green period, cold resistance, drought resistance, pest resistance, and salinity resistance, and can grow on arid hillsides, alpine grasslands, wasteland, and wetlands [9–11]. Therefore, it is also widely used in the greening transformation, soil and water conservation, and vegetation greening of saline-alkali land in the soil salinization, desertification, and dry climate areas in northern China and has become a building grass species in salinized meadows. Shi indicated it protects against soil erosion, shallow landslides, and other geological disaster phenomena in the study area [12]. Sun screened out the effects of different low-temperature treatment cycles of Malinzi and the different number of ramets of rhizomes on reproductive ability [13].

1.2. Herbal medicine identification

There are many kinds of plants in nature, and the appearance and shape of Iridaceae plants are similar. The sources of Malinzi are vast, the specifications are various, and numerous counterfeit products are easily confusing. The identification of its authenticity is the key. Currently, the research on the identification of Malinzi mainly includes chemical and microscopic identification. The two identification methods have their characteristics and advantages, and they can be used alone or in combination to identify effectively. The continuous improvement of the identification method has ensured the accuracy of the origin of the medicinal material of Malinzi and laid the foundation for further research and development.

1.2.1. Microscopic identification

The epidermis of the seed coat is a row of neatly arranged rectangular cells with thick walls, reddish-brown lumps, and a cuticle on the outer wall. There are 5–7 rows of shrunken decadent parenchyma cells below it, and the innermost layer is 3–4 rows of neatly arranged brown flat cells. Endosperm cells are round and oblong, with thick walls and aleurone grains in the cell cavity.

Malinzi powder is tan. Seed-coat epidermal cells are oblong, round, or polygonal, with thick walls and brown-red lumps. The cells in the seed coat are irregularly shaped and yellow, and the cell wall is tumor-like thickening. Endosperm cells are round, oblong, with

Fig. 1. (A) *Iris Lactea* Pall. var. *chinensis* (Fisch.) Koidz, (B) Malinzi
(Photographs from Plant Photo Bank of China, PPBC, http://ppbc.iplant.cn/).

thick walls, containing aleurone grains and fatty oil.

1.2.2. Chemical identification

Take 0.5g of Malinzi powder, add 25 mL of ether, sonicate for 20min, filter, and then evaporate the filtrate to dryness. Add 1 mL of ether to the residue to dissolve it, and use it as the test solution. Another medicinal reference material was taken, and the reference medicinal material solution was prepared by the same method. According to the thin-layer chromatography test, draw 2 μL of the above two resolutions, point them on the same silica gel thin-layer plate, use petroleum ether (60–90 °C)-diethyl ether (3:1) as the developing solvent, develop, take out, and dry. Viewed under sunlight and UV light (365 nm). In the chromatogram of the test substance, there are spots or fluorescent spots of the same color at the positions corresponding to the chromatograms of the reference medicinal materials.

1.3. Medical applications

1.3.1. Traditional uses

Malinzi has been used as TCM in China for more than 2000 years. Malinzi is pungent and sweet in flavour and calm in nature. It belongs to the lung, spleen, stomach, and liver meridians. Its effects are to clear heat and dampness, detoxify and disperse knots, stop bleeding, and kill worms. Malinzi was recorded initially in *Shennong Bencao Jing* [4], which stated Malinzi controls cold and heat in the skin, hot qi in the stomach, wind-cold-dampness, strong muscles, and bones, makes people addicted to food, lose weight in long-term

Table 1
The main traditional uses of Malinzi in China.

Preparation/Single medicine	Compositions	Clinic uses	Monograph
Single medicine	Malinzi 9g, decoction with water	Jaundice, yellow and scanty urine	*Handbook of Ningxia Chinese Herbal Medicine*
Preparation	Malinzi 9g, Inula 15g, decoction in water	Jaundice, yellow and scanty urine	*Hubei Chinese Herbal Medicine*
Preparation	Malinzi 60g, rock sugar 15g, stewing	gonorrhea	*Folk Practical Herbal Medicine*
Preparation	Malinzi 6g, Plantago ovata 9g, decoction in water	Poor urination	*Handbook of Shandong Chinese Herbal Medicine*
Preparation	Malinzi 25g, knotgrass 10g, mucuna pruriens 10g, decoction in water	Poor urination	*Jilin Chinese Herbal Medicine*
Preparation	Malinzi 9g, knotgrass 9g, plantain 9g, decoction in water	Poor urination	*Handbook of Ningxia Chinese Herbal Medicine*
Preparation	Malinzi 9g, Huangra Bark 9g, decoction in water	Early stage of dysentery	*Xining Chinese Herbal Medicine*
Single medicine	Malinzi 49 grains, pounded and taken with water	Laryngeal paralysis	*Taiping Holy Prescriptions for Universal Relief*
Preparation	Malinzi 2.4g, Burdock 1.8g, pounded and powdered, to be taken with water	Swelling and pain in the throat	*Guang Ji Fang*
Preparation	Chuan Sheng Ma 50g, Malinzi 100g, poured and dispersed, 3.75g each time	Swelling and pain in the throat	*Taiping Holy Prescriptions for Universal Relief*
Preparation	Malinzi 6g, White Fescue Root 30g, Xianhecao 15g, decoction with water	Bleeding from nostrils, vomiting blood	*Handbook of Shandong Chinese Herbal Medicine*
Single medicine	Malinzi 30g, fried black, ground, 6g each time	Bleeding from the nose	*Jilin Chinese Herbal Medicine*
Preparation	Malinzi 9g, cumin 6g, neem 9g, decoction in water	painful hernia	*Handbook of Liaoning Chinese Herbal Medicine*
Single medicine	Malinzi 9g, fried in vinegar, decoction	Cold hernia	*Anhui Chinese Herbal Medicine*
Preparation	Malinzi 18g, Douluo 24g, decoction in water	Uterine cancer	*Tianjin Chinese Herbal Medicine*
Preparation	Malinzi 9g, Douluo 15g, Bei Chonglou 15g, grinded, 9g each time	Uterine cancer	*Handbook of Plateau Chinese Herbal Medicine Treatment*
Preparation	Malinzi 6g, Amaranthus officinalis 30g, Dandelion 30g, decoction in water	Canker sores and boils	*Handbook of Qingdao Chinese Herbal Medicine*
Single medicine	Malinzi in appropriate quantity, roasted, ground, fragrant oil	Canker sores and boils	*Tianjin Chinese Herbal Medicine*
Single medicine	Malinzi fried and dried, powdered, 5–7g at a time	Bone Tuberculosis	*National Chinese Herbal Medicine*
Single medicine	Malinzi boiled with flour and taken with hollow rice	Dysentery	*Zhang Wenzhong Formulary for Emergency*
Preparation	Malinzi, dried ginger, and Huang Lian, boiled in soup	Dysentery	*Zhang Wenzhong Formulary for Emergency*
Preparation	Malinzi 500g, ground, soaked in wine and realgar and orpiment dried in the sun 200g each, made into pills	Intestinal bleeding	*Prescriptions for Universal Relief*
Preparation	Chuan Sheng Ma 50g, Malinzi 100g, poured and dispersed, 3.75g each time	Throat paralysis and swelling pain	*Taiping Holy Prescriptions for Universal Relief*
Preparation	Malinzi 9g, Malus officinalis 9g, Pomegranate peel 12g, grinded	Excessive menstruation	*Handbook of Xinjiang Chinese Herbal Medicine*
Single medicine	Malinzi 10g, boiled with flour	Cold hernia with inability to eat	*Yao Sengyuan Ji Yan Fang*
Single medicine	Malinzi 3–9g, decoction in water	Painful hernia	*National Chinese Herbal Medicine*

use. *Mingyi Bielu* [14]has also presented that Malinzi could stop upset, urination, and grow skin hypertrophy. In addition, this herb could treat sore blood inflow, and abscesses, has been stated in *Tang Materia Medica* [5]. Moverover, a detailed record of indication was kept in *Rihuazi Bencao* [15], which described Malinzi could treat women's blood qi and depression, postpartum blood dizziness, metrorrhagia, leukorrhagia, eliminate sores, furuncles, and swollen toxins, prevent nosebleed and vomiting blood, clear the small intestine, eliminate alcohol toxin, cure jaundice, snake bites, and polyp toxin. Moreover, the *Compendium of Maleria Medica* [16] has recorded this herb for treating abdominal hernia pain, intra-abdominal cold accumulation, dysentery, and other diseases. Malinzi has been used to soften hardness and break blood, recorded in *Medical and Forestry Compilation* [17]. So far, 24 pieces of literature on TCM have recorded the traditional uses of Malinzi (Table 1).

1.3.2. Chinese patent medicine

Shiliuweimalinziwan pill is Tibetan medicine, mainly composed of 16 medicines such as Malinzi, *Przewalskia tangutica* Maxim., cardamom, etc [18]. It has the effects of astringent, anti-inflammatory, promoting mucosal healing, clearing heat and benefiting lung, relieving cough, and reducing phlegm. Pharmacological test studies have shown that gallic acid is the medicine's main ingredient [19].

Shisanwei Malin San is composed of 13 herbs: Malinzi, R.tibetica Hook.f., Secretion of *Ficus benghalensis* L., *Symplocos caudata* Wall. ex G.Don, crab, *Przewalskia tangutica*, *Veronica eriogyne* H.J.P.Winkl., *Canavalia gladiata* (Jacq.) DC., the seed of *Mangifera indica* L., *Syzygium jambos* (L.) Alston, *Caesalpinia bonduc* (L.) Roxb, Lapis micae aureus, Sal Ammoniac [20]. It is a purple powder with a slightly fragrant smell, spicy and bitter taste, and is mainly used for anti-inflammatory and diuretic, and testicular enlargement [21].

Nine-Flavored Ciwujianhua Powder is a traditional Chinese medicine formula composed of nine herbal ingredients, including Cistanche deserticola, *Salviae Miltiorrhizae* Radix et Rhizoma, Chinese wolfberries, Chinese date fruit, Chinese yam, black sorghum, cabbage, and *Silvianthus bracteatus* Hook. f. It is mainly used to treat kidney yin deficiency, impotence, nocturnal emission, and other conditions. It has a strong nourishing effect on kidney yin, can tonify the kidney and strengthen its essence and marrow, and can regulate the body's internal environment [22–24]. It is suitable for people who are weak after illness, have consumption of the body's essence and marrow, and are unable to have sexual intercourse due to impotence or nocturnal emission [25,26].

Anka (Irisquinone capsules) is used as a radiation sensitizer. The research results show that Anka has a sensitizing effect on the radiotherapy of lung cancer, esophageal cancer, and other visceral tumors, which can speed up the shrinkage of lesions and significantly increase the rate of complete disappearance of lesions [27,28]. Its main component is irisquinone which has been detected by RP-HPLC and single-sweep oscillopolarography in existing quality standard studies, and its reasonable range has been investigated [29,30]. Zhang found that to improve the solubility and stability of irisquinone, hydroxypropyl-β-cyclodextrin (HP-β-CD) with good water solubility and low toxicity was used as the inclusion material to prepare irisquinone-HP-β-CD. The research on physical and chemical properties shows that the inclusion compound can significantly enhance intestinal uptake of the drug and improve its

Table 2
The parts of compounds isolated from Malinzi.

Type	No.	Name	Source	References
Flavonoids	1	Catechin	Ethyl acetate	[32]
	2	(−)-catechin	95 % ethanol	[33]
	3	Procyanidin B1	Ethyl acetate	[32]
	4	Procyanidin B3	Ethyl acetate	[32]
	5	Procyanidin B7	Ethyl acetate	[32]
	6	Prodel-phinidin B3	Ethyl acetate	[34]
Quinones	7	2-methoxy-6-pentadecyl-1,4-benzoquinone	95 % ethanol	[33]
	8	3-hydroxyirisquinone	95 % ethanol	[33]
	9	Pallason A	Ether	[35]
	10	Pallason B	Ether	[36]
	11	Pallason C	Ether	[36]
Oligostilbenes	12	*Trans*-ε-viniferin	95 % ethanol	[37]
	13	r-2-viniferin	95 % ethanol	[37]
	14	ε-viniferin	85 % ethanol	[38]
	15	Vitisin A	85 % ethanol	[38]
	16	Vitisin B	85 % ethanol	[38]
	17	Vitisin C	85 % ethanol	[38]
	18	Vitisin D	NaOH aqueous solution	[39]
	19	*Cis*-vitisin A	NaOH aqueous solution	[39]
	20	Ampelopsin B	NaOH aqueous solution	[39]
Others	21	Betulin	Ether	[40]
	22	Lupene-3-one	Ether	[40]
	23	β-sitosterol	Ether	[40]
	24	Linoleic acid	Petroleum ether	[41]
	25	Stearic acid	Petroleum ether	[41]
	26	Oleic acid	Petroleum ether	[41]
	27	Myristic acid	Petroleum ether	[41]
	28	Palmitic acid	Petroleum ether	[41]
	29	Decanoic acid	Petroleum ether	[41]
	30	Lauric acid	Petroleum ether	[41]
	31	Vitisin A-13-*O*-β-*d*-glucoside	NaOH aqueous solution	[42]

Table 3
Statistical table of pharmacological activities of Malinzi.

Pharmacological effects	Component	Cells line/Model/Patients	Detail	Reference (s)
Anti-tumor	Pallasone A	H22-bearing mice	Improving immune function and reduceing the expression of VEGF and MVD in the tumor	[43]
Anti-tumor	Pallasone A	Cells SMMC-7721, LOVO, A549, BGC-823, and MCF-7	Influence of cell cycle regulation, and the induction of apoptosis	[44]
Anti-tumor	Pallasone A	COC1/DDP cell line	Interfering with the intracellular GSH/GST detoxification system	[45]
Anti-tumor	Pallasone A	Cells CNE2, SUNE1, and Fadu	Cytotoxic effects	[46]
Anti-tumor	Pallasone A	Cells K562	Cells with pallasone A in G0/G1 phase was more than that of control cells, but less in S phase significantly.	[47]
Anti-tumor	Pallasone A	Cells NCI–H1975	Connect with suppression of IAPs family proteins	[48]
Anti-tumor	Pallasone A	Cells PANC-1	Inhibit the proliferation, invasion, and migration	[49]
Anti-tumor	2-*r*-viniferin	Cells HepG2	Promoting apoptosis by blocking the G2/M phase and increasing the level of intracellular ROS	[33]
Anti-tumor	*Trans*-ε-viniferin	Cells HepG2	MTT assay found that the *trans*-ε-viniferin had an anti-proliferation effect on HepG2 cells of liver cancer	[37]
Anti-tumor	Viniferin	Cells HepG2	Blocking their progression in their cell cycle at the G2/M transition	[50]
Boost immunity	Pallasone A	KM mice and U14 cells	Increasing the delayed hypersensitivity reaction of tumor-bearing mice and improve the cellular immunity of the body	[51]
Radio-sensitization	Pallasone A	Patients with advanced esophageal cancer	The half-dose efficacy of radiotherapy and the complete elimination rate at the end of radiotherapy in the treatment group were significantly better than those in the control group	[52]
Radio-sensitization	Pallasone A	Patients with non-small cell lung cancer, esophagus, head and neck cancer, nasopharyngeal carcinmo	After 40 Gy, the tumor elimination rate in the treatment group was significantly higher than that in the control group.	[52]
Radio-sensitization	Pallasone A	Cells CHO	It increases the radiosensitivity of hypoxic cells by 59 %	[53]
Radio-sensitization	Pallasone A	58 patients with nasopharyngeal Cancer	There are significant differences between the treatment group and the control group in the treatment of nasopharyngeal carcinoma with the combination of Pallasone A and radiotherapy	[54]
Radio-sensitization	Pallasone A	34 patients with esophagus cancer	The rate of CR&PR were 88.24 % and 86.67 % in drug using group and control group respectively	[55]
Radio-sensitization	Pallasone A	145 patients with nasopharygeal carcinoma	ER of trial and control group were 1.17 and 1.07 respectively in primary focus, and it was 1.20 and 1.05 respectively in metastatic focus.	[56]
Radio-sensitization	Pallasone A	New Zealand rabbits	The 1 and 2 h T/M ratios and RIs decreased gradually when the radiation dose reached 12 or 18 Gy in the treatment groups, whereas these values increased continuously in the control group.	[57]
Radio-sensitization	Pallasone A	C6 rat and glioma cells	The downregulation of HIF-1 is the main mechanism underlying this radiosensitizing effect	[58]
Radio-sensitization	Pallasone A	Cells MDA-MB231and BALB/c nude mice	^{18}F-FLT microPET/CT can evaluate the radiosensitization effect of IR on breast cancer in nude mice	[59]
Radio-sensitization	Pallasone A	Cells MDA-MB231	The Warburg effect of MDA-MB231 cells was inhibited by down-regulating the expression of HKII gene	[60]
Boost immunity	Pallasone A	Mice	Promoting the phagocytosis of the mouse liver reticuloendothelial system	[61]
Boost immunity	Pallasone A	Mice	Enhancing the immune function of normal mouse cells, and can regulate humoral immunity	[62]
Anti-oxidantion	Malinzi oil	DPPH, FeSO4	When the Malinzi oil concentration was 14 mg/mL, he DPPH free radical scavenging activity is 71.42 %. When the concentration of Malinzi oil was 168 mg/mL, which was 0.4207 mmol/L FeSO4 equivalent.	[63]
Anti-fertility	Malinzi alcoholic infusion	Mice	The seed coat has anti-fertility and anti-germinal effects, but the seed kernel had no effect.	[64]
Glucolipid metabolism	Vitisin B	Cells 3T3-L1	Reducing the expression levels of PPARγ, C/EBPα, and aP2 proteins	[65]
Glucolipid metabolism	Oligostilbenes from Malinzi	HFD/STZ-induced diabetic mice and 3T3-L1 cells	Regulating the expression of C/EBPβ and PPARγ	[66]
Glucolipid metabolism	Oligostilbenes from Malinzi	Cells C2C12	Inhibit lipogenesis and promote lipolysis via the PKA/HSL pathway during adipogenic transdifferentiation of C2C12 cells	[67]

bioavailability to 133.9 % [31].

1.3.3. Chemical constituents

To date, 31 compounds have been isolated and identified from Malinzi. These chemical constituents are divided into four groups based on their structures: flavonoids (1–6), quinones (7-11), oligostilbenes (12–20), and others (20–31). Its main active components are flavonoids and benzoquinones. These compounds were derived from 5 different extraction solvents. Among them, 4 were extracted from NaOH aqueous solution, 4 from 85 % ethanol, 5 from Ethyl acetate, 5 from 95 % ethanol, 7 from petroleum ether, and 6 from the ether (Tables 2 and 3 and Figs. 2 and 3).

1.3.3.1. Flavonoids. Malinzi contains a lot of flavonoids. In recent years, researchers have carried out many isolation and analysis studies and obtained a variety of flavonoids with novel structures.

(−)-catechin (2) isolated by Wei Hou from the crude extract of Malinzi 95 % ethanol and extracted with petroleum ether [33]. Huanhuan et al. separated the seed coat extracted by ethyl acetate, *n*-butanol, and water, and the ethyl acetate fraction was eluted with a silica gel column. The eluted fractions were finally separated by high-speed countercurrent chromatography (HSCCC) to get Catechin (1), ProcyanidinB1 (3), procyanidin B3 (4), and procyanidin B7 (5) [32]; further separation obtained prodel-phinidin B3 (6) [34].

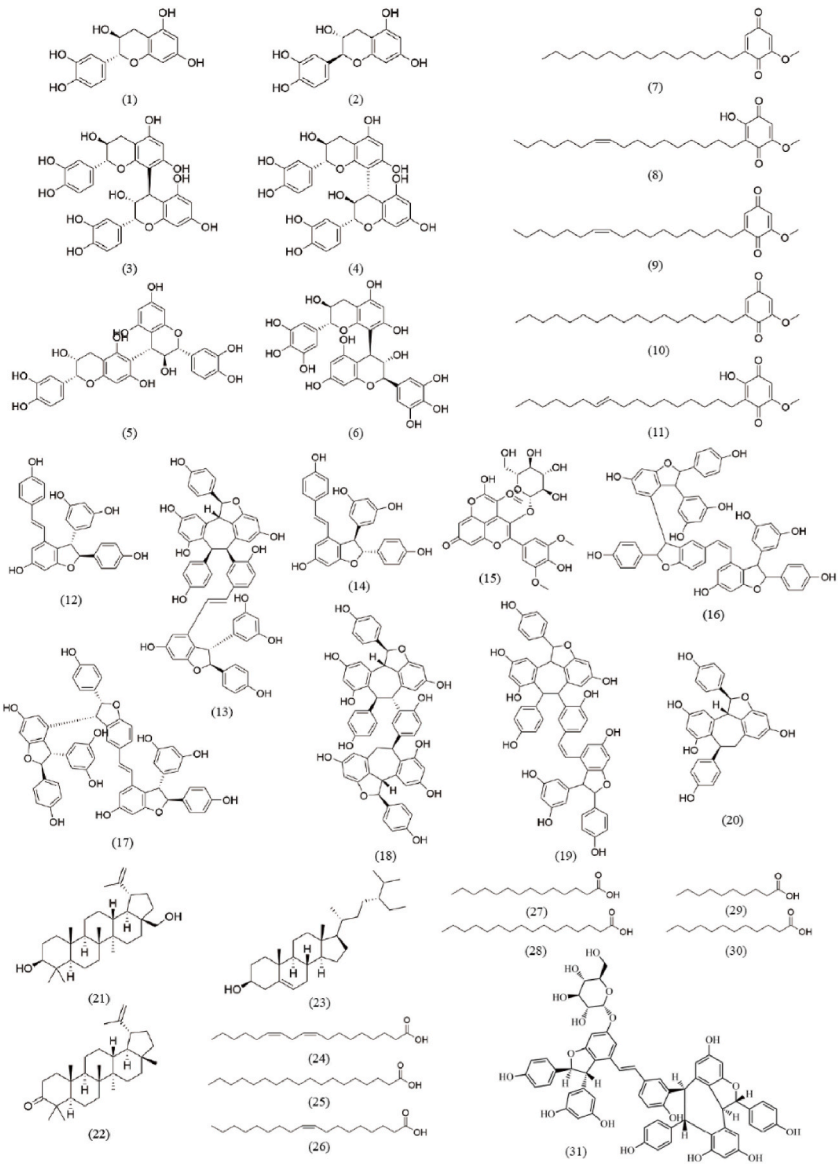

Fig. 2. Chemical structures of 31 compounds isolated from Malinzi (1-31).

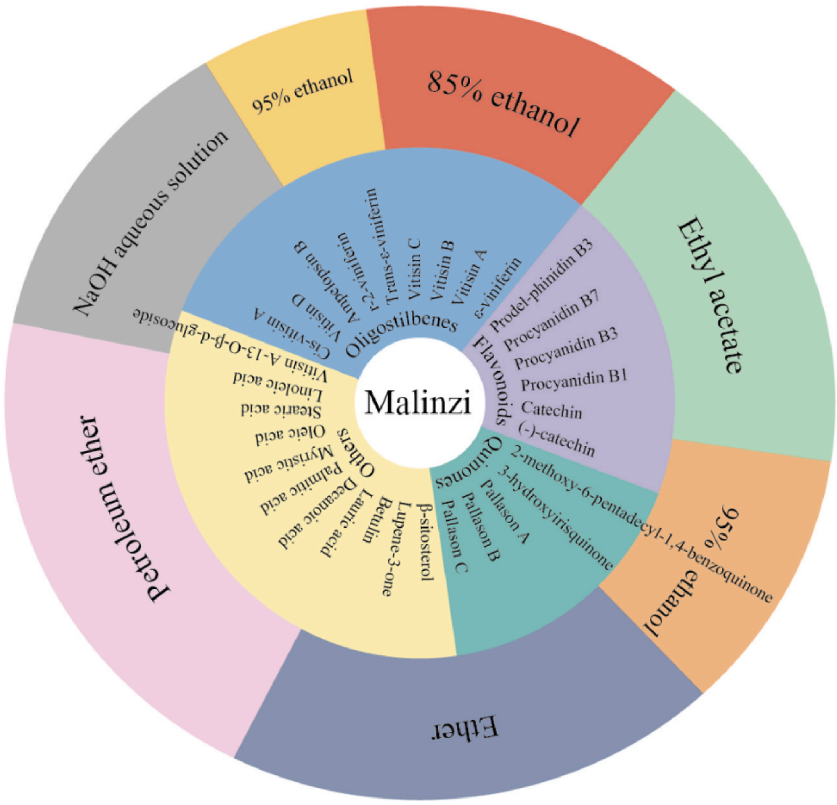

Fig. 3. The 31 compounds isolated and identified in Malinzi were arranged in a circle. The inner circle shows the chemical structure classification, and the outer circle shows the extraction solution category.

1.3.3.2. Quinones. Quinones are another major active component in Malinzi. The compounds have various pharmacological activities, such as anti-tumor, anti-radiation, and cell proliferation. Wei Hou [33] obtained 2-methoxy-6-pentadactyl-1,4-benzoquinone (7) and 3-hydroxyirisquinone (8) from 95 % ethanol extract of the crude extract of Malinzi. Wu et al. [35] isolated pallason A (9) from the ether extract of the seed coat of Malinzi, the same substance as irisquinone reported in the paper. Pallason B (10) and Pallason C(11) are two other new quinones that Wu identified subsequently from ether extracts [36].

1.3.3.3. Oligostilbenes. Oligostilbenes have anti-oxidation functions, anti-tumor, liver protection, and nerve protection [50,68–70]. The oligostilbenes are receiving much attention as potential therapeutic agents for several pathological diseases [71]. Wei Hou [37] immersed the Malinzi powder in 95 % ethanol, refluxed for 12 h to obtain *trans*-ε-viniferin (12) and r-2-viniferin (13). Huanhuan Lv et al. [38] separated and purified four oligostilbenes by HSCCC with two sets of the two-phase solvent system. The first separation mainly isolates vitisin A (15), ε-viniferin (14)I, then the second separation separated vitisin B (16) and vitisin C (17) from peak II in 2014. After that, Huanhuan et al. [39] adopted the alkaline extraction–acid precipitation method for extraction of oligostilbenes from the seed kernel of Malinzi, and vitisin D (18), *cis*-vitisin HSCCC fractionated a (19), and ampelopsin B (20) with a two-phase solvent system.

1.3.3.4. Volatile components. Li et al. [72] used the GC-MS to separate the ethyl ether extraction from the coat of Malinzi and confirmed the presence of 26 peaks using a NIST workstation and reference materials. Pallason A, (E) irisquinone isomer, and pallason B all had high concentrations. Saturated fatty acid ester, unsaturated fatty acid ester, fragrance ester, organic acid, and alkaloid were the main components. Luan et al. [73] extracted the Malinzi oil under optimal extraction conditions; the chemical components of Malinzi oil were identified by GC–MS. The primary fatty acids found in Malinzi oil were oleic acid (34.74 %), linoleic acid (41.31 %), and docosahexaenoic acid (3.18 %).

1.3.3.5. Others. In addition to the compounds mentioned above, Malinzi contains many fatty acids and trace elements. Wu [40] extracted the coarse powder of Malinzi by ether refluxing, then separated and identified to obtain betulin (21), lupene-3-one (22), and β-sitosterol (23). Zang et al. Petroleum ether was used to extract the Malinzi seed kernels, and the solvent was then drained away to produce Malinzi oil [41]. By separation and identification, linoleic acid (24), stearic acid (25), oleic acid (26), myristic acid (27), palmitic acid (28), decanoic acid (29), and lauric acid (30) were obtained. Liping et al. [74] found Cr, Zn, Cu, Tl, Sb, and Cd in Malinzi by inductively coupled plasma-optical emission spectrometry (ICP-OES) with microwave digestion. Malinzi macerated with 5.0 %

NaOH aqueous solution using the alkaline-acid method, and vitisin A-13-*O*-β-*d*-glucoside (31) was separated by the semi-preparative HPLC [42].

1.3.4. Pharmacological activities

Modern pharmacological studies have revealed that Malinzi has several pharmacological properties, including anti-tumor, radio-sensitization, boost immunity, anti-oxidantion, anti-fertility, and glucolipid metabolism, which may explain why Malinzi is used as a folk remedy for a variety of diseases (Fig. 4). Malinzi's radio-sensitization pharmacological activity has received the most attention, and pallasone A is its most potent ingredient. The pharmacological actions of constituents or extracts from Malinzi were displayed in Table 3. According to the theory of traditional Chinese medicine, Malinzi have antispasmodic and analgesic effects, which can relieve pain, spasm and other symptoms caused by inflammation or cancer, and help control the development of cancer and inflammation. In modern research, some compounds in Malinzi have been confirmed to influence anti-cancer and boost immunity. More and more researchers are using modern scientific methods to explain the principles and mechanisms of traditional uses.

1.3.5. Anti-tumor

Pallasones are benzoquinone compounds extracted from Malinzi. As a natural anti-tumor drug, it has the advantages of high efficiency and low toxicity [75,76]. It has a good curative effect on the lung, head, neck, nasopharyngeal, esophageal, liver, ovarian, etc. [77,78]. Pallasone A is the main chemical component that exerts the effect of Malinzi. Pallasone A can inhibit lung metastasis in tumor-bearing animals. The mechanism enhances cellular immunity and reduces tumor vascular endothelial growth factor and micro-vessel density [43]. Pallasone A combined with chemotherapeutic drugs can influence cell cycle regulation and the induction of apoptosis, significantly inhibiting tumor cell proliferation [44]. Li et al. has confirmed that pallasone A extracted from Malinzi can reverse the drug resistance of ovarian cancer cisplatin-resistant cell line COC1/DDP, increase the content of intracellular cisplatin and significantly reduce IC50. The mechanism may interfere with the intracellular GSH/GST detoxification system [45]. Cai et al. found that pallasone A has cytotoxic effects on various nasopharyngeal cancer cell lines and can induce the apoptosis of CNE2, SUNE1, and Fadu [46]. Pallasone A broadly has anticancer activity *in vitro* and can induce apoptosis of leukemic cell K562. Pallasone A influenced the cell cycle of K562, and the proportion of cells with pallasone A in the G0/G1 phase was more than that of control cells but less in the S phase significantly [47]. Pallasone A can inhibit the proliferation and induce apoptosis of NCI–H1975 cells. Its inhibition of human non-small cell lung adenocarcinoma NCI–H1975 cells' proliferation and apoptosis could be connected to suppressing IAPs family proteins [48]. It also work by blocking the Rho signalling pathway-mediated epithelial mesenchymal transition process, which in turn prevents PANC-1 cells from proliferating, invading, and migrating [49].

In addition to pallasones, several other substances in Malinzi play an anti-cancer effect. Viniferin are important chemical component in Malinzi, a potent antioxidant, anti-tumor, and free radical scavenger. Hou Wei isolated two compounds, *trans*-ε-viniferin, and r-2-viniferin, from the Malinzi for the first time. The MTT assay found that the *trans*-ε-viniferin had an anti-proliferation effect on HepG2 cells of liver cancer [37]. He also found that 2-*r*-viniferin can increase the reactive oxygen species (ROS) level in HepG2 cells and reduce the mitochondrial membrane potential. Therefore, it is speculated that the mechanism of 2-*r*-viniferin promoting apoptosis may be achieved by blocking the G2/M phase and increasing intracellular reactive oxygen species [33]. Colin et al. found that viniferin and its polymers have antiproliferative effects on hepatic HepG2 cells [50].

The occurrence and development of tumors are closely related to reducing human immune monitoring ability, especially removing cellular immune function [79]. Therefore, immunotherapy to mobilize the body's anti-cancer defense ability has become one of the

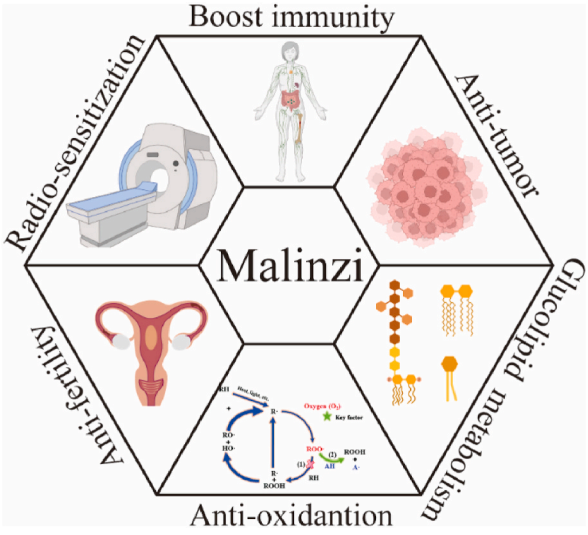

Fig. 4. Statistical chart of the pharmacological activities of Malinzi (Adapted from "Gut-Brain Axis Regulators", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates).

ways of modern cancer treatment [80]. Li Weimin [51] found that the oral or intraperitoneal injection of pallasone A emulsion or powder can increase the delayed hypersensitivity reaction of tumor-bearing mice and improve the body's cellular immunity at appropriate doses.

1.3.5.1. Radio-sensitization. Studies have confirmed that many hypoxic cells exist in solid tumors, while radiotherapy and chemotherapy are insensitive to hypoxic cells [81]. It affects the short-term efficacy of radiotherapy and chemotherapy, and the residual hypoxic cells can easily lead to tumor recurrence [82]. Pallasone A is an active substance found in Malinzi, and studies have shown that it is a bioreductive tumor radiosensitizer [83]. Experiments have demonstrated that pallasone A can be metabolized and activated by reductase *in vivo*, increasing hypoxic cells' sensitivity to radiation and killing hypoxic cells [84]. Therefore, it will significantly improve the effect of radiotherapy, reduce the recurrence rate of the tumor, and improve the cure rate of cancer [85]. In recent years, studies have found that the combination of pallasone A and radiotherapy significantly treats liver, lung, esophageal, nasopharyngeal, and cervical cancer, and has almost no toxic side effects [52–56,86,87]. Xu et al. observed the radiosensitive effect of pallasone A on rabbit VX2 lung transplant tumors using fluorine-18-deoxyglucose positron emission tomography/computed tomography [57]. Wang et al. indicated that pallasone A enhanced the radiosensitivity of C6 rat glioma cells *in vitro* and *in vivo*. The downregulation of HIF-1 is the primary mechanism underlying this radiosensitizing effect [58]. Irisquinone also has a radiosensitizing effect on breast cancer in nude mice, which was evaluated by ^{18}F-FLT micro PET/CT [59]. Irisquinone can increase the sensitivity of breast cancer MDA-MB231 cells to radiotherapy. The radiosensitization can inhibit the Warburg effect of breast cancer MDA-MB231 cells by down-regulating the expression of the HKII gene [60].

1.3.6. Boost immunity

According to *Chinese Tibetan Medicine* [61], the radioactive intensity of the liver of mice was much higher than that of the control group 3 min after administration of colloidal Au. This indicates that pallasone A significantly promotes the phagocytosis of the mouse liver reticuloendothelial system. Wang et al. found that the serum IL-2 of normal mice increased with the administration dose, while the effect on the level of sIL-2R decreased with the increase. This result indicates that pallasone A can enhance normal mouse cells' immune function and regulate humoral immunity [62].

1.3.6.1. Anti-oxidantion. Modern pharmacological studies have shown that the accumulation of free radicals produced by the body's metabolism causes various diseases. This study's Malinzi oil obtained through subcritical fluid extraction technology has a high total polyphenols content and potent antioxidant activity. When the Malinzi oil concentration was 14 mg/mL, the DPPH free radical scavenging activity reached the maximum value of 71.42 %. The total antioxidant activity reached its most potent when the concentration of Malinzi oil was 168 mg/mL, which was 0.4207 mmol/L $FeSO_4$ equivalent [63].

1.3.7. Anti-fertility

The oral administration of Malinzi alcoholic infusion to mice showed anti-fertility and anti-germinal effects. The study found that the anti-fertility and anti-implantation effects of normal mice were caused by taking the alcohol extract of Malinzi. It was also found that taking the alcohol extract of the seed coat had the effects of anti-fertility and anti-implantation. Still, the seed kernel had no impact [64].

1.3.8. Glucolipid metabolism

The study found that the proanthocyanidins isolated from the seed coat of Malinzi and the oligomeric stilbene compounds isolated from the seed kernel can reduce lipids. Vitisin B can reduce the expression levels of PPARγ, C/EBPα, and aP2 proteins in 3T3-L1 cells, thereby reducing the aggregation and accumulation of lipid droplets in adipocytes. In addition, vitisin B can activate AMPK to enhance the expression level of GLUT4 protein. It indicated that vitisinB could promote glucose uptake in 3T3-L1 adipocytes without increasing the accumulation of lipids in the cells [65]. Some oligostilbenes from Malinzi inhibit adipogenesis and adipocyte differentiation and improve lipid metabolism. Vitisin A, vitisin B, *cis*-vitisin A strongly influence the expression of PPARγ, leading to subsequent downregulation of PPARγ mediated adipocyte-specific genes during adipogenesis [88]. Tie's study indicates a lipid-lowering effect of oligostilbenes from Malinzi in HFD/STZ-induced diabetic mice and adipogenesis/lipogenesis suppressing effect in 3T3-L1 cells via regulating the expression of C/EBPβ and PPARγ [66]. Aditionally, the five oligostilbenes from Malinzi were tested for their regulatory effects on adipogenic transdifferentiation of C2C12 myoblast cells. To be more precise, VitAOG, VitA, and Hop prevent C2C12 myoblasts from becoming adipogenic by downregulating PPARγ, FABP4, and C/EBPβ, whereas VitD and Isohop promote this process by upregulating PPARγ and FAS [67].

2. Discussions and conclusions

As a traditional Chinese herbal medicine, Malinzi has been used as ethnic medicinal plants to treat various diseases and extensive clinical application value for thousands of years, the use area is mainly concentrated in East Asia. In recent years, Malinzi has gradually gained attention in modern times especially its traditional use. To better understand the chemical composition and pharmacological activity of Malinzi, this paper reviews the research progress of botany, medical application, chemical constituents and pharmacological activities of Malinzi.

Based on the research literature of Malinzi, we found it has many pharmacological effects, including anti-tumor, radio-

sensitization, boost immunity, anti-oxidantion, anti-fertility, and glucolipid metabolism. It contains various chemical components, such as flavonoids, quinones, oligostilbenes, and other constituents, which are closely related. Nevrtheless, the chemical conponents of Malinzi remain under-researched, with only 31 components having been definitively identified and isolated. As a traditional Chinese medicinal plant, it is expected that there are numerous metabolites beyond these few components. The systematic isolation and identification of these components has become a research focus in recent years. However, due to the complexity and diversity of traditional Chinese medicine components, this task is labor-intensive and challenging. On the other hand, the research on the chemical constituents and pharmacological effects of Malinzi is mainly limited to pallasone A, while the research on other components and their efficacy has not been in-depth. In traditional applications, Malinzi has been used to treat various conditions, yet its pharmacologically active ingredients remain elusive. Therefore, the analysis of different effects of its components holds great potential for further development and exploration. Additionally, the majority of the identified compounds were not verified *in vivo* despite undergoing a number of *in vitro* activity assessment assays to show that they have pharmacological action. The in *vivo* pharmacodynamic evaluation and molecular biological mechanism studies are essential for the promotion of traditional and modern drug development. Based on the above summary, the following research directions for Malinzi should be focused on three aspects. Firstly, a more systematic isolation and identification of its chemical components is necessary to better analyze their pharmacodynamic properties. Secondly, in addition to the follow-up studies on pallasone A, more attention should be paid to the pharmacodynamic studies of other components. Finally, the pharmacological experiments of Malinzi and its components should be deepened, which the mechanisms should be explained scientifically through multi-omics approaches and bioavailability should be tested.

In summary, Malinzi, as a folk medicine in China, has been widely used and distributed in China and other Asian countries. Its traditional uses, phytochemical information, and pharmacological studies should be comprehensively understood for clinical use. Therefore, it is of great significance to conduct in-depth research on other chemical constituents and pharmacological activities of Malinzi on the existing basis to comprehensively explore the medicinal value of Malinzi and expand its clinical application more rationally and effectively.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

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CRediT authorship contribution statement

Run-Xiang Zhai: Writing – original draft. **Xian-Jun Fu:** Writing – review & editing, Funding acquisition. **Xia Ren:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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