

Mining Bioactive Compounds against Drug-Resistant Microorganisms from Ethnomedicine: Examples of 32 Ethnic Medicines in Yunnan

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ABSTRACT

In the next 25 years, more than 39 million deaths worldwide could be attributed to bacterial resistance to antibiotics. Urgent action is needed to discover new antibacterial compounds. Traditional medicines worldwide have been used in traditional folk remedies for various ailments, such as stomachache and scalds, which are often associated with infections. However, the underlying mechanisms of action for their antimicrobial compounds remain largely unexplored. This review highlights 32 medicines in combating drug resistant microorganisms. It explores correlations between traditional uses and antibacterial activities, identifies bioactive constituents effective against drug resistant pathogens, and aims to inform the discovery of novel antimicrobial agents. In total, these plants yield 62 compounds active against Methicillin-Resistant *Staphylococcus aureus* (MRSA), Vancomycin-Resistant Enterococcus (VRE), and *Candida albicans*, with minimum inhibitory concentration ranging from 0.12 to 8 µg/mL. By disrupting bacterial membranes, these compounds reduce the likelihood of resistance emergence. Twelve of these compounds demonstrate synergistic effects with antibiotics, highlighting their potential as adjuvants. This review consolidates current findings and proposes strategic priorities for the future antimicrobial therapeutics.

Keywords: Drug-resistant pathogens, Ethnic medicines, Plant-derived natural products, Anti-resistant pathogen compounds, Inhibitory mechanisms, Synergy.

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INTRODUCTION

The overuse of antibiotics has led to the irreversible emergence of Multidrug-Resistant Organisms (MDROs), including so-called “superbugs” (Honigsbaum, 2018) and “super fungi” (Pappas *et al.*, 2018). In 2019, bacterial infections-both MDROs and antibiotic-sensitive-became the second leading cause of mortality worldwide after ischemic heart disease, accounting for approximately 7.7 million deaths directly attributed to bacterial pathogens (Wang, Z.-J. *et al.*, 2024a). Among them, Methicillin-Resistant *Staphylococcus aureus* (MRSA) alone was responsible for over 100,000 deaths (Collaborators, 2023). That same year, Antimicrobial Resistance (AMR) contributed to an estimated 4.95 million deaths globally (Tang *et al.*, 2024; Vos *et al.*, 2020), with projections indicating that this figure could rise to 10 million annually by 2050 (Wang, Z.-J. *et al.*, 2024; Wang, Z.-J. *et al.*, 2024a; Wei *et al.*, 2024). Epidemiological studies show that MRSA and Vancomycin-Resistant *Enterococcus* (VRE) are the most prevalent pathogens causing hospital-acquired infections (Shi, N. *et al.*, 2024). In recognition of the growing threat to public health, the United States Centers for Disease Control and Prevention (CDC) classified both MRSA and VRE as “serious threats” in its 2019 Antibiotic Resistance Threats Report. With the emergence of COVID-19 as a global pandemic, co-infections became increasingly common: over half of critically ill patients were found to harbor concurrent bacterial or fungal infections, and more than 30% of COVID-19 patients developed secondary bacterial infections (Caiazzo *et al.*, 2022). Alarmingly, MDROs were detected in up to 80% of these co-infections (Kreitmann *et al.*, 2023). In the post-pandemic era, the acceleration of bacterial resistance driven by COVID-19 has elevated long-standing concerns into an urgent global crisis (Hsu, 2020). As a result, the development of novel therapeutic agents targeting MDROs has become imperative.

Over the past two decades, only five novel classes of antibacterial agents with distinct chemical structures-cyclic lipopeptides, oxazolidinones, teixobactins, pleuromutilins, and diarylquinolines-have been approved for clinical use (Cook and Wright, 2022). However, clinical strains resistant to these drugs have already emerged. Developing a new antibiotic typically requires over a decade, while bacterial resistance can develop within just 1-2 years, raising the alarming prospect of a future with no effective antibiotics for humans (Macesic *et al.*, 2025). Bacterial resistance is a survival strategy driven by microbial adaptation to antibiotics (Wang, Z. *et al.*, 2018). The issue of antibiotic resistance reflects shifts in ecologic niche overlap and competitive dynamics within microbial communities, involving trade-offs in resistance costs and the persistence of resistant pathogens (Silva *et al.*, 2016). While resistance has coexisted with antibiotics of microbial origin (Porras *et al.*, 2021), Natural Products (NPs) may offer advantages in overcoming resistance due to their unique structures (Porras *et al.*, 2021), mechanisms of

action (Kumar and Engle, 2023), and targets (Porras *et al.*, 2021; Woo *et al.*, 2023), which differ from conventional antibiotics (Wang *et al.*, 2019).

In response to the urgent global demand for novel antimicrobial agents, mining antimicrobial bioactive compounds from traditional medicinal plants is an effective method. Our previous research found that itchy-sore ulceration (Wang *et al.*, 2020), stomachache (Wang *et al.*, 2023), upper respiratory tract infection (Wang *et al.*, 2021a), vomiting (Wang *et al.*, 2021b), diarrhea (Zhu *et al.*, 2021), strains (Ma *et al.*, 2022), beriberi (Xu *et al.*, 2022), shigellosis (Wang, Z.J. *et al.*, 2024b), scald (Zeng *et al.*, 2022), dyspepsia (Tang *et al.*, 2024), conjunctivitis (Luo *et al.*, 2023), gastralgia (Wen-Biao *et al.*, 2024), pharyngitis (Chen *et al.*, 2024), gonorrhea (Wen-Biao, 2024), pertussis (Liu *et al.*, 2024), common cold (Shen *et al.*, 2024), phthisis (Luo *et al.*, 2024), scabies and tinea (Luo-EE *et al.*, 2024), chronic tracheitis (Shi *et al.*, 2024), skin infections (Shi, Y.-Z. *et al.*, 2024), and tetanus (Zhou *et al.*, 2024) of botanical drugs contain compounds with anti-MDROs activity. These findings encouraged us to revisit key traditional pharmacopoeias, including the *Dictionary of Chinese Ethnic Medicine, Essentials of Chinese Ethnic Medicine, and ZhongGuo MinZu YaoZhi Yao*, to further explore the ethnomedical basis of these treatments.

Literature Search Strategy

A comprehensive literature search was conducted using multiple databases, including SciFinder, Google Scholar (<https://sci.673.org/index.html>), Scopus (Elsevier), Medline, Web of Science, X-MOL (www.x-mol.com), PubMed, and the China National Knowledge Infrastructure. The search targeted publications related to the Latin names of the 32 selected plant species, as well as their reported antimicrobial properties, inhibitory concentrations, activities against MDROs. In addition, local records, monographs, and non-English-language journals were reviewed to supplement the database search (up to March 2025).

Plant Characteristics

Geographic Distribution

The symptoms corresponding to these traditional uses are summarized in Table 1. Based on this ethnobotanical survey, we investigated the traditional applications of ethnic medicinal plants and their associated antibacterial bioactive compounds. We found that the folk usage of 32 ethnic medicinal plants implies the presence of compounds with activity against MDROs. This review systematically examines the antibacterial chemical constituents, synergistic interactions, mechanisms of action, and pharmacological properties of 32 representative medicinal plant species from Yunnan Province and their derived NPs, covering research published between 2000 and 2025.

32 plant names, including *Morus alba*, *Scoparia dulcis*, and *Cannabis sativa* are listed in Table 1. These NPs active against

Table 1: The palynomorphs of 32 medicinal resource plants in Yunnan.

Name	Producing area	Growth environment	Altitude	Phytomorph	Medicinal parts
<i>Morus alba</i> L.	Temperate regions of Asia (China, Afghanistan, etc.)	Warm and humid forests, shady slopes, valleys.	100-1,200 m	Shrubs or trees, with leaf and stem thickness of 1-2 mm, fleshy and hairy buds, and leaves measuring 2 – 13 (–20) × 1.5-9 (–14) cm, Hairless, elliptical, peduncle spiny rootlike	Root bark
<i>Scoparia dulcis</i> L.	South, North America, temperate regions of Asia	Enjoying moisture, on barren lands, slopes, and roadsides	20-450 m	One year or perennial grass leaves elliptical, blunt or conical, dull, flowers white or blue, four petals, seeds prismatic.	Root, stem
<i>Cannabis saliva</i> L.	China, five Central Asian countries, Pakistan	Warm and humid, sunny valleys, fields	100-2,900 m	Herbaceous, hollow stem, angular, covered with short hairs, opposite leaves, needle-shaped triangular, toothed margin, inflorescence loosely conical	Roots, stems, and leaves
<i>Euphorbia hirta</i> L.	Mexico, Brazil, introduced to China	Common weeds on roadsides, fields, and yards	900-2,100 m	Herbs, round and jointed stem, slightly hairy, ovate leaves, serrated, short peduncle	Stem, leaf
<i>Flemingia prostrata</i> Roxb. Junior ex Roxb	Tropical and temperate Asia	Open fields, grasslands	50-300 m	Semi shrub, with finger-shaped leaves, 3 leaves, linear-lanceolate bracts, purple corolla	Root
<i>Lithocarpus polystachyus</i> Rehder	Tropical Asia	Mixed coniferous and broad-leaved forests, low mountains, rainforests, sandstones	60-2,100 m	5-20 m tall tree, with gray short hairs on the small branches, elongated leaves, leathery leaves, separate male and female inflorescences, spike-shaped, and fragrant	Roots, leaves, and fruits
<i>Setaria viridis</i> (L.) P. Beauv.	South America, Asia, Europe	Forest, wilderness	10-4,000 m	Annual herb, with needle-shaped leaves, smooth, and fine hairs on the edges, and a conical inflorescence	Whole plant
<i>Chaenomeles speciosa</i> Sweet	Temperate Asia (China)	Radiant slopes, forest edges, and roadsides	500-1,000 m	Deciduous shrub, thorny, branches brownish black, leaves ovate, edges with short serrations, petals red	Fruit
<i>Zanthoxylum khasianum</i> Hook. F	Yunnan, myanmar, India, Nepal	Sparse forests or shrubs	1,500-2,500 m	Shrubs or small trees, small branches gray, thorny, compound leaves 5-13, alternate, margin with fine teeth, umbels, flowers with 4 petals	Fruit, leaves
<i>Acorus tatarinowii</i> Schott	Asia temperate and tropical	Waterside, swamps, wetlands, or floating islands in lakes	20-2,600 m	Perennial herb, with yellow-brown rhizomes, branching, succulent roots, sword-shaped linear leaves, and triangular inflorescence stalks	Root, stem
<i>Caryopteris trichosphaera</i> W.W. Sm.	Yunnan, Tibet	hillside shrubs, arid grasslands in river valleys	2,700-3,300 m	shrubs with dense white hairs and glandular spots on their branches, wide ovate leaves, and inflorescence with a nearly head-like inflorescence	flowers, leaves

Name	Producing area	Growth environment	Altitude	Phytomorph	Medicinal parts
<i>Lysimachia tengyuehensis</i> Hand-Mazz.	Southwest Yunnan region	stream, fields	1,200-2,400 m	Perennial herb, stem reticular, yellow with long soft hairs, leaves opposite, ovate, flower head clustered, corolla yellow.	whole plant
<i>Sarcococca hookeriana</i> var. <i>digyna</i> Franch.	Southern China, Bhutan, Nepal	under the shade of the forest	300-3,500 m	branches with opposite leaves at the top, elliptical lanceolate leaves	stem
<i>Carex baccans</i> Nees	Southern China, Southeast Asia	by the forest, river, and village	200-2,700 m	perennial herb with dense clusters of stems, basal leaves, and inverted spherical fruit sacs	whole plant
<i>Sigesbeckia orientalis</i> L.	Southern China, Europe, Russia	mountains, wastelands, shrubs, and undergrowth	110-2,700 m	annual herbaceous plant, with stems branching into a complex bipartite shape, leaves triangular and oval, and a head-shaped inflorescence	whole plant
<i>Rohdea aurantiaca</i> (Baker) N. Tanaka	Southwest China	forests, ravines, and mountain slopes	1,800-2,900 m	shrubs, rhizomes cylindrical, leaves basal, lanceolate, lanceolate	whole plant
<i>Gomphrena globosa</i> L.	North America Mexico, South America Brazil, introduced to Asia	dry, its areas for cultivation as ornamental plants	1,200 m	annual herbaceous plant, with upright stems and multiple branches, single leaves opposite each other, long elliptical, inflorescence sessile, spherical, red	flower
<i>Salvia przewalskii</i> Maxim.	Western China	by the stream, at the edge of the forest, in the bushes	2,100-4,500 m	Perennial herb, stem base partially branched, densely covered with short hairs, leaves triangular sharp-toothed to oblong-lanceolate, terminal inflorescence in racemes.	whole plant
<i>Anemone rivularis</i> Buch-Ham. Ex DC	China	mountains, grassy slopes, streams	850-4,900 m	perennial herb, branched stem, branched leaf stem	whole plant
<i>Garcinia hanburyi</i> Hook.f.	Yunnan and South-East Asia	hills, slopes, mixed forests	100-1,600 m	Evergreen tree, about 15-18 m, square small branches, opposite single leaves, leathery	resin
<i>Caesalpinia sappan</i> L.	Yunnan and South-East Asia	valleys, jungles, or cultivation areas	200-1,050 m	small tree with branches covered, 7-13 pairs of leaves, opposite growth	tree core
<i>Ocimum gratissimum</i> Forssk.	Asia, Europe, Africa	valleys, forests, grasslands	500-2,200 m	perennial herb with upright stems, multiple branches, white powder on the surface	whole plant
<i>Eucalyptus globulus</i> Labill.	Australia introduced to Southwestern and Southeastern China	cultivated fields	0-2,000 m	large tree with gray, flaky bark, slightly angular tender branches, opposite young leaves, ovate, blue-green, covered in white powder	leaves, fruits, and essential oils
<i>Euphorbia royleana</i> Boiss.	Yunnan, South Asia, South-East Asia	mountains, hills, forests, grasses	50-1,500 m	shrubs, upright stems and leaves with thorns, waxy leaves on the surface	stem, leaves
<i>Glechoma longituba</i> (Nakai) Kuprian	southern and eastern of China	forests, grasslands, and riverbanks	50-2,500 m	perennial herb, stem quadrilateral, red, leaves herbaceous, heart-shaped, umbel inflorescence	aboveground

Name	Producing area	Growth environment	Altitude	Phytomorph	Medicinal parts
<i>Liriope spicata</i> Lour.	Southern China and South-East Asia	hillsides, valleys, roadsides, and wetlands	50-1,400 m	perennial herb with rhizomes, creeping stems, basal leaves, gramineous leaves, and small flowers, clustered in the axils of bracts	root tuber
<i>Schisandra chinensis</i> (Turcz.) Baill.	Southwest and central China	mountain slopes, wilderness, and shrubs	250-1,600 m	parasitic on plants such as <i>Rhus chinensis</i> and <i>Populus euphratica</i>	gall
<i>Tripterygium hypoglaucum</i> (H.Lév.) Hutch	Yunnan, South-East Asia	hillsides, forest edges, and shrubs	1,500-3,000 m	deciduous shrub, reddish brown, angular, leaves ovate, inflorescence terminal	whole plant
<i>Rhododendron spinuliferum</i> Franch.	Southwest China and South Asia	mixed forests, valleys, and shrublands	1,900-2,500 m	Shrubs, old branches brownish red, young branches gray, leaves papery, inverted.	roots, leaves, and flowers
<i>Pachysandra axillaris</i> Franch.	Southwest China	shrubs, mountains, forest edges, and understory	600-2,500 m	Evergreen subshrubs, with hard papery leaves, axillary inflorescences, yellow or red fruits when ripe, spherical	whole plant
<i>Alpinia japonica</i> (Thunb.) Miq.	Southern China, Japan	under the forest, by the stream, in rock crevices	100-1,500 m	perennial herb with rhizomes and branches, lanceolate leaves, terminal inflorescence with dense hairs on the inflorescence axis, spherical fruit, polygonal seeds, and a camphor smell	whole plant
<i>Vincetoxicum forrestii</i> (Schltr.) C.Y. Wu and D.Z.Li	Yunnan, South-East Asia	forest edges, grasslands, roadsides, and shrubs	1,000-3,500 m	perennial erect herb, single stem, covered with single row soft hairs, leaves opposite, thinly papery, broadly ovate	root

(The data were sourced from Flora of China and the Web site www.theplantlist.org and <https://wfoplantlist.org/>, the plant names were checked with <http://www.world-floraonline.org> and <http://mpns.kew.org>), March 12, 2025.

MDROs mainly comprise over 160 bioactive compounds, including oxylipins, alkaloids, resorcinol terpenoids, triterpenoid saponins, cannabinoids, and isopentenyl flavonoids.

Correlation Analysis Between Traditional Use and Anti-MDROs Activity

The traditional uses of the selected medicinal plants were categorized into various traditional application domains. There are, hypertension, diabetes mellitus, itchy-sore ulceration, cephalalgia, nephritis, sore throat, scabies, shigellosis, eczema, beriberi, scald, tonsillitis, ascites, gastralgia, influenza, conjunctivitis, menorrhagia, dyspepsia, hepatitis, bronchitis, tussis, diarrhea, skin pruritus, head trauma, pyrexia, toxic heat, deficiency heat, rubeola, pertussis, varicella, hematuria, gastric and oral ulcers, rheumatic arthralgia, weakness, soreness of the waist and knees, heating-clearing and toxicity-removing, diuretic, persistent headache, ocular pain, carbuncle, cystitis, malaria, upper respiratory tract infection, pneumonia, urticaria, herpes zoster, joint stiffness, foot edema, vomiting, infection, gonorrhoea, swelling-reducing, detoxification, antibacterial effect, enteritis, injuries, dysentery, pulmonary tuberculosis, tetanus, insecticidal

antipruritic, rheumatoid arthritis, traumatic injuries, fracture, anti-inflammatory, and gynecologic diseases. A correlation analysis was then performed between their traditional uses and anti-MDROs activity. Frequency data for each application category and corresponding antimicrobial activity were analyzed using origin software, and the results were visualized in a correlation diagram (Figure 1).

Characteristics of 32 Ethnic Medicinal Medicines

Yunnan Province, recognized as China's most botanically diverse region, is widely known as the "Kingdom of Plants" (Zhao Mingxu *et al.*, 2024), the "Kingdom of Animals" (Yi, 2014), and the "Kingdom of Wild Fungi" (Committee, 2016). These reputations are attributed to its unique geographic and climatic diversity, as well as its rich traditions in ethnic medicine. However, the region also faces several challenges, including low rates of technological transformation, tensions between resource conservation and exploitation, and a lack of standardization in medicinal plant practices (Zhang Xuejia *et al.*, 2023). This review compiles detailed botanical profiles of 32 ethnic medicinal plant species, which can be categorized into herbaceous plants, shrubs,

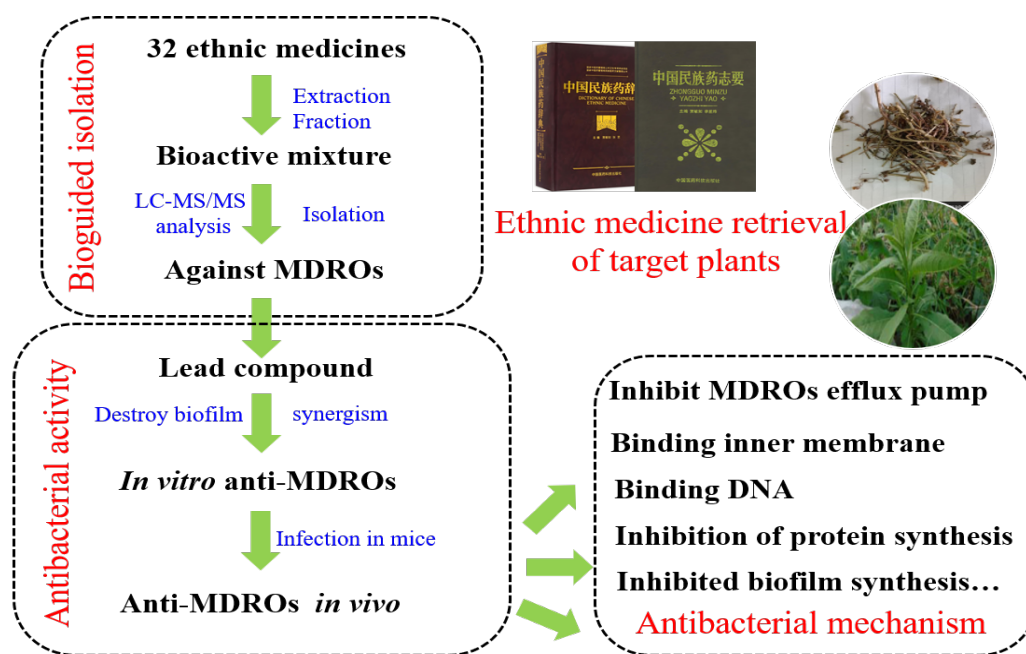


Figure 1: Flowchart of the process for mining bioactive compounds.

and trees based on their traditional uses, bioactive constituents, and demonstrated antimicrobial activity. For each species, information is provided on their origins and distribution in China, ecological growth conditions, altitude ranges, and key morphological features of stems, leaves, flowers, and fruits. A summary of these characteristics is presented in Tables 1 and 2.

Correlation Between Ethnomedicinal Practices and Antibacterial Properties

As one of the most bio-diverse and ethnoculturally rich regions in China, Yunnan is home to extensive traditional medicinal practices deeply rooted in its ethnic minority communities (LI Yao *et al.*, 2020). The indigenous knowledge embedded in these ethnic medicines reflects unique ethnopharmacological traditions and has increasingly attracted scientific interest for their antibacterial potential (Wang *et al.*, 2021a; Wang *et al.*, 2020). For example, the De'ang people use *C. sativa* to treat toothaches, with cannabinoids identified as its active antimicrobial constituents (Yadav *et al.*, 2023). The Dai people use *M. alba* (Sangbaipi) to manage itchy sores and ulcerations (Jia Min-Ru and Yi, 2010), where the active compound morusin has been shown to exhibit activity against MDROs by disrupting bacterial cell membranes (Yadav *et al.*, 2023). Both the Yi and Bai ethnic people apply *P. polyphylla* (Dianchonglou) to clear heat and toxins (Jia Min-Ru and Yi, 2010; Min-Ru, 2005), with its steroidal saponins demonstrating antibacterial effects via inhibition of key bacterial enzymes (Tagousop *et al.*, 2018). In the Yi community, *L. pterodonta* (Choulingdan), a traditional anti-inflammatory herb, is used




to treat respiratory infections and has been found to contain sesquiterpene lactones with pathogen-suppressing properties (Liu *et al.*, 2007). Moreover, 95% ethanol extracts from widely used ethnomedicinal plants-such as *H. cordata* (Yuxingcao), *M. haplocalyx* (Bohecao), and *P. vulgaris* (Xiakucao)-have shown inhibitory effects against MRSA (Karthikeyan *et al.*, 2020).

These examples highlight the value of integrating ethnomedicinal knowledge with modern biotechnological approaches to accelerate the discovery of plant-based anti-infective agents (Wang *et al.*, 2021a). However, diseases related to the digestive, respiratory, endocrine, nervous, and musculoskeletal systems, as well as conditions affecting the skin and facial regions, have often been overlooked in the past studies, primarily because they were not directly associated with MDROs infections. Although infectious diseases are most commonly associated with MDROs infections, our analysis suggests that a wider spectrum of disease categories also deserves attention. Numerous plant-derived compounds have been applied in treating ailments beyond classical infectious diseases. As shown in Figure 2A, antibacterial relevance was observed across various systems, including the digestive, respiratory, urinary, immune, cardiovascular, endocrine and metabolic, neurological, musculoskeletal, dermatologic, sensory organs, trauma-related, gynecologic, and diseases categorized under Traditional Chinese Medicine (TCM). The correlation between the traditional ethnomedicinal uses of these plants and their antibacterial properties is illustrated in Figure 2B and detailed in Table 2. Specifically, Table 2 summarizes the ethnomedicinal applications of 32 plant species reviewed here.

Table 2: Correlations between the folk medicinal and antibacterial properties of the 32 plants.

Plant pictures ^a	DCEM ^b name	Scientific name	Ethnicity used ^c	Applied category ^d	Plant pictures ^e	DCEM ^b name	Scientific name	Ethnicity used ^c	Applied category ^d
	SangBaiPi, NangRiJiao, HuaiLangTao, BaiManShua	<i>M. alba</i>	Achang, Blang, Bouyei, Dai, Hani	hypertension, diabetes mellitus, itchy sore ulceration		Chinese magnolia vine	<i>Saccharomonospora viridis</i>	Miao, Yao	stomachache, urticaria, herpes zoster
	BieBuLie, MuFanLong	<i>S. dulcis</i>	Achang, Dai, De'ang, Jinuo, Jingpo, Li, Wa	cephalalgia, nephritis, sore throat, odontalgia		flowering quince, Tiejiao Li	<i>C. speciosa</i>	Dai, dong, Gelao, Lisu, Naxi, Yi, Zhuang	abdominal pain, gastric ulcer, beriberi, joint stiffness, foot edema
	AngGeiDang, HuoMa, hemp seed	<i>C. saliva</i>	De'ang, Hani, Kazakh, Jingpo, meng	scabies, shigellosis, eczema, beriberi, scald		Shan Jiao, Japanese pepper	<i>Z. khasianum</i>	Yi, Hani, Dai, Bai, Naxi	relieve itching and eliminate foul odor, relieve pain, detoxify
	KaoShaZhi, BeiNiu, YaXiYi, MaDuYe	<i>E. hirta</i>	Achang, Dai, Hani, De'ang, Li, dong, She, WA, Miao, Yi, Zhuang	tonsillitis, ascites, eczema, gastralgia, influenza, conjunctivitis		ChangBieLao, GeMiQin, ChangPulLeng, XiGuShan, LuMaGuJi, JiabaoYe	<i>tatarinowii</i>	buyei, Dai, dong, Li, Gelao, Hani, Yi, Miao, She, WA, Yao	dyspepsia, diarrhea, vomiting, common cold, nephritis
	YeBaiDian, LaoShuWei, YaFengBi, TouDiLong	<i>F. prostrata</i>	Bai, dong, Li, Yao, Maonan, Yi, Zhuang	menorrhagia, dyspepsia, tonsillitis, hepatitis, bronchitis		PuErCha, PuNa	<i>trichosphaera</i>	Tibetan	infectious disease, fever, pharyngitis, leprosy, jaundice
	DuoKeSui	<i>L. polystachyus</i>	Yao	tussis, diarrhea, shigellosis, skin pruritus		LuBianHuang	<i>L. tengyuehensis</i>	Han, dong	digestive diseases, urological diseases, burn, detoxifying, infection
	SuErGong, SuoGongBa	<i>S. hookeriana</i>	Zang	head trauma, sore throat, pyrexia, toxic heat, deficiency heat		KuaGongCai, KuangGaoCai, MinJin, LaLai, Ma WuLin, RiXiFan	<i>A. rivularis</i>	Bai, Dai, De'ang, dong, Yi, Hani, Wa, Jingpo, Lisu, Lahu	traumatic injury, malaria, gonorrhoea, toothache, sinusitis, rhinitis

	ZheJianQing, GanKa, BiaoBoRen, SanJiaoCao	<i>C. baccans</i>	Achang, Bai, Dai, De'ang, dong, Hani, nu, Wa, Yi	rubeola, pertussis, varicella, hematuria, gastric and oral ulcer		YuHuang, YueHuang	<i>G. hanburyi</i>	Uyghur, Yao, Dai, Zhuang	reduce swelling, detoxify, antibacterial and anti-inflammatory
	ShengCao, HuangHuaZai, XijiMi	<i>S. orientalis</i>	Dai, Miao, Shui, she, dong, Tujia, Yao, Zhuang	rheumatic arthralgia, weakness, and soreness of the waist and knees		PaiRanJiMu XiKe	<i>O. gratissimum</i>	Uyghur	nasal congestion and common cold, cough, phlegm
	Kaikoujian	<i>R. aurantiaca</i>	Han	clear heat and remove toxicity, diuretic		GeFang, JunMo, MaiFang, ZeiGuoWo, ZuoMoXing	<i>sappan</i>	Achang, Dai, dong, De'ang, Yi, Hani, Jino, Yao, Lisu, Yao, Jingpo	enteritis, injuries, dysentery, pulmonary tuberculosis, tetanus
	RiRiHong, NuoHanBeng, <i>globe amaranth</i>	<i>G. globosa</i>	Bai, Dai, dong, Yao, Maonan, Tujia	persistent headache, ocular pain, shigellosis, pertussis, carbuncle		ZhiBaZi	<i>E. globulus</i>	Achang, Lisu, Naxi, Miao	common cold, fever, enteritis, headache, skin ulcer, upper respiratory tract
	red sage root, LuPo	<i>S. przewalskii</i>	Naxi, Zang, Yi	cough, hepatitis, phthisis, oral ulcer, dentalgia		BaWangBian	<i>E. royleana</i>	Dai	dispel wind and detoxify, insecticidal antipruritic, scabies, and tines
	NaTaiLian, JiaoSanXing, RuGuShao, TouGuXiao	<i>G. longituba</i>	Bai, buyei, Jinuo, Dai, dong, she, Miao, Yao, Mongolian, Tujia, Yi	tracheitis, cystitis, malaria, upper respiratory tract infection, pneumonia		torch flower, HeJianHuang, JiMenLaDuo, CheYouGen	<i>T. hypoglaucaum</i>	Achang, Dai, Hani, De'ang, Lisu, Miao, Yao, Yi	rheumatoid arthritis, traumatic injuries, fracture
	Tumendong, Tumaidong	<i>L. spicata</i>	De'ang, dong, Yi, Maonan, Qiang, Shui, Tujia	relieve cough, throat obstruction, and sore throat		PaoZhangHua	<i>R. spinuliferum</i>	Yi	anti-inflammatory, gynecologic diseases

	Hanbeizi, Baichongcang, Mufuzi	<i>S. chinensis</i>	Mongolian, Uyghur, Dai	astringe the intestines and stop diarrhea, dry dampness and promote wound healing		JiRuHen ChaBaGa, JiRuHen ChaBaGa, JiRuHen ChaBaGa	<i>P. axillaris</i>	Hani, Mongol, Tujia, Yao, Wa, Zang, Zhuang	treat burns and scalds, dyspepsia, indigestion
	wild ginger, Ganao dou	<i>Amycolatopsis japonica</i>	Miao, Zhuang, Dai	vomiting and diarrhea, traumatic injury, detoxification		kaPuDeLuo	<i>C. forrestii</i>	Tibetan	treat common cold, pneumonic fever

* Picture sourced from the Flora of China and Web site: <https://www.iplant.cn/>, March 12, 2025.^{b,c,d} Date from Dictionary of Chinese Ethnic Medicine, essentials of Chinese ethnic medicine, and Zhong Guo MinZu YaoZhi Yao.

Traditional uses for conditions such as itchy sores and ulcerations, stomachaches, upper respiratory tract infections, vomiting, diarrhea, sprains, strains, beriberi, shigellosis, heat-clearing and detoxification, scalds, dyspepsia, conjunctivitis, gastralgia, pharyngitis, gonorrhoea, pertussis, common colds, phthisis, scabies, tinea, chronic tracheitis, and tetanus are likely associated with microbial infections. These patterns provide meaningful directions for future research into the antibacterial mechanisms and bioactive compounds targeting MDROs.

Antimicrobial Compounds

Overview

In this review, 32 plant species were identified as exhibiting antibacterial activity, with 30 demonstrating efficacy against MRSA, VRE, and *Candida albicans*. Over the past three decades, the development of new antibiotics-particularly those targeting Gram-negative bacteria-has been severely limited. Today, we may find that existing treatments are increasingly inadequate in addressing emerging resistance mechanisms, and antimicrobial resistance, especially multidrug resistance, has escalated into a major challenge for clinical therapy (Wang, Z.-J. *et al.*, 2024a). Given that resistance among Gram-negative bacteria has become a global public health crisis (Apostol and Collaborators, 2024; Macesic *et al.*, 2025), compounds with Minimum Inhibitory Concentration (MIC) values $\leq 64 \mu\text{g/mL}$ against Gram-negative strains were also catalogued. These included 87 phenolics and their derivatives, 48 terpenoids and derivatives, 8 alkaloids and derivatives, 6 oxylipins, and 11 other types of metabolites. In total, over 160 compounds with activity against MRSA, VRE, *C. albicans*, and Gram-negative bacteria were isolated from approximately 32 ethnomedicinal plant species. Phenolics and their derivatives, terpenoids and derivatives, alkaloids and derivatives, oxylipins, and other metabolites accounted for 54.4% (87), 30% (48), 5% (8), 3.8% (6), and 6.8% (11) of the total compounds, respectively. The botanical origins, chemical structures, antimicrobial activities against MDROs, and structure-activity relationships of these plant-derived NPs are discussed in detail below. A summary of the antimicrobial bioactivities of these NPs against MDROs and Gram-negative bacteria is provided in Table 3.

Phenolics and Their Derivatives

Phenolic secondary metabolites are key functional bioactive compounds produced by plants during their growth and development (Kumrungeet *et al.*, 2023). In this review, NPs with antibacterial activity include simple phenols, phenylpropanoids, xanthones, flavanones, resorcinols, quinonoids, isoflavones, lignans, chalcones, tannins, flavanonols, flavan-3-ols, among others. The basic structural classes of phenolics are illustrated in Figure S1.

Chlorogenic acid (3), isolated from *C. speciosa* and *O. gratissimum*, has been reported to exhibit antibacterial activity against

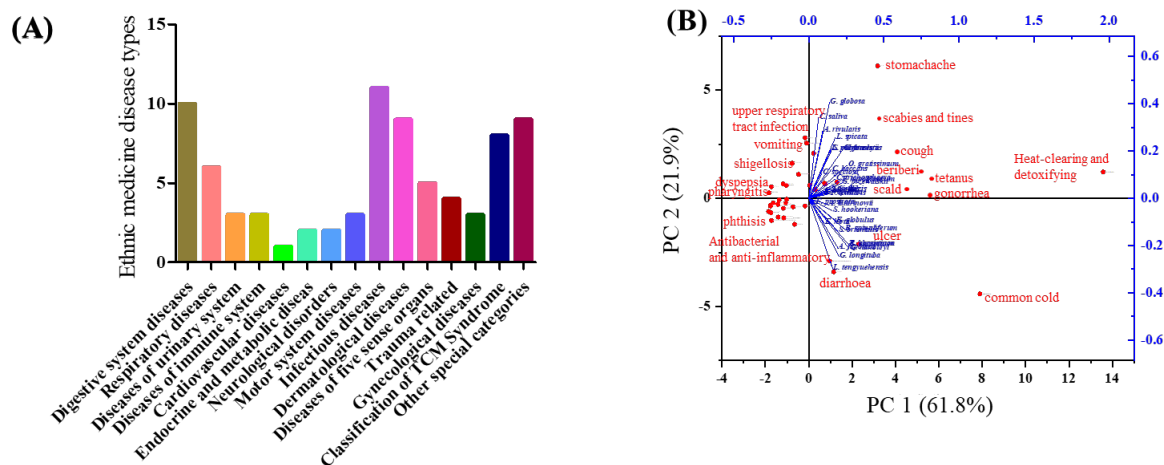


Figure 2: (A) Types of diseases treated with ethnic medicinal plants. (B) Correlations between folk ethnobotanical medicinal and antibacterial properties.

Streptococcus pneumoniae, *S. aureus*, *Bacillus subtilis*, *Shigella dysenteriae*, and *Salmonella typhimurium*, with MICs ranging from 20 to 40 $\mu\text{g}/\text{mL}$ (Ugbogu *et al.*, 2021). Chlorogenic acid (3) displays broad-spectrum activity against both Gram-positive and Gram-negative bacteria. Several phenylpropanoids isolated from *M. alba*, including moracin C (6), mulberrofuran B (7), albafrican A (8), moracin G (9), mulberrofuran G (12), mulberrofuran K (13), albanol B (14), and mulberrofuran Q (15), exhibit anti-MRSA activity with MICs ranging from 2 to 16 $\mu\text{g}/\text{mL}$ (Zhu *et al.*, 2021; Zhu *et al.*, 2024). Additionally, flavonoid compounds such as 18-21, 25-26, and 41-43, also from *M. alba*, demonstrate potent activity against MDROs, with MICs in the same range (Zhu *et al.*, 2021; Zhu *et al.*, 2024). Moreover, kuwanon O (43) has been shown to inhibit the MRSA efflux pump (Zhu *et al.*, 2021), while morusin (20) targets bacterial inner membrane phospholipids, disrupts membrane integrity, and induces the generation of Reactive Oxygen Species (ROS) (Zhu *et al.*, 2024). These mechanisms differ from those of conventional antibiotics and suggest a lower likelihood of inducing resistance development.

Flavonoid derivatives have a wide range of antibacterial and antioxidant activities. Daphnin (16) is isolated from *S. viridis* (Cottiglieri *et al.*, 2001; Gong Jiang *et al.*, 2010), while xanthotoxin (17), obtained from *Z. khasianum*, shows antibacterial activity against *S. aureus* and *Methylococcus luteus* with MIC 30 $\mu\text{g}/\text{mL}$ (Walasek *et al.*, 2015; Wang *et al.*, 2021b). Based on structural analyses of compounds such as α -, β -, and γ -mangostin, cratoxylone, gambogenic acid, neo-morellic acid (22), gambogic acid (23), neogambogic acid (24), and related derivatives, Tang *et al.*, (2024) identified hydroxyl groups, isopentenyl substituents, and carboxyl groups at the C-5 position as key contributors to antibacterial activity against VRE. Further mechanistic studies demonstrated that morellic acid (22) binds to phosphatidylglycerol in the bacterial inner membrane, disrupting the proton motive force

and membrane rigidity. This disruption causes oxidative stress via the accumulation of ROS, ultimately resulting in bacterial cell death (Tang *et al.*, 2024). Transcriptomic analyses further linked these effects to perturbations in glycerophospholipid metabolism and fatty acid biosynthesis pathways. Notably, morellic acid exhibits dose-dependent eradication of up to 80% of mature VRE biofilms, with efficacy comparable to that of ampicillin, used as a positive control. These findings highlight the promise of structural optimization in enhancing antimicrobial agents against resistant pathogens (Tang *et al.*, 2024).

Additional flavonoid derivatives-including linarin (27), cirsimarin (28), luteolin (31), sappanone B (37), (8,3'-diprenyl-5,7,4'-trihydroxyflavanone (40), phloretin (44), aromadendrin (45), genistin (46), 4-hydroxyboesenbergin B (49), and galangin (50)-are isolated from *S. dulcis*, *C. trichosphaera*, *C. sappan*, *F. prostrata*, *L. polystachyus*, *S. viridis*, and *A. japonica*, respectively. Among these, linarin (27) exhibits particularly potent activity against *S. aureus*, with a MIC as low as 0.38 $\mu\text{g}/\text{mL}$ (Davoodi *et al.*, 2022). Although luteolin (31) exhibits an MIC of 32 $\mu\text{g}/\text{mL}$ against MRSA, it showed synergistic effects when combined with gentamicin (Qiu *et al.*, 2011). Kaempferol derivatives (32-35) have demonstrated activity against *P. aeruginosa* and are found to disrupt the bacterial surface structure (Ugbogu *et al.*, 2021; Xu *et al.*, 2022). Phloretin (44), isolated from *L. polystachyus*, has been reported to possess broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria, with MIC values ranging from 32.4 to 100 $\mu\text{g}/\text{mL}$ (Park *et al.*, 2012; Shang *et al.*, 2022; Wang, G. *et al.*, 2018). It targets *E. coli* biofilms and inhibits the expression of the virulence factor sortase B (SrtB). Galangin (50) has been shown to suppress bacterial toxin production (Lee *et al.*, 2008; Ma *et al.*, 2017).

Cannabinoids (51, 52) have demonstrated potent antibacterial activity against MDROs, particularly MRSA and VRE, with

MIC values ranging from 1 to 8 $\mu\text{g}/\text{mL}$ (Appendino *et al.*, 2008; Schofs *et al.*, 2021). Alpininone (57) exhibits activity against VRE with an MIC of 32 $\mu\text{g}/\text{mL}$ (Giang and Son, 2007). Resorcylic acid derivatives (58-61), isolated from the *L. genus*, show strong antibacterial effects against MRSA and VRE (MICs = 2-8 $\mu\text{g}/\text{mL}$) (Shi, N. *et al.*, 2024). Mechanistic studies reveal that these compounds disrupt biofilm formation and damage the bacterial membrane by inducing metabolic imbalance. SAR analyses indicate that the presence of lipophilic long carbon chains at C-5/C-6 and hydrophilic hydroxyl/carboxyl groups are essential for anti-MRSA and anti-VRE activity.

The compound 1,7-bis-(4'-hydroxy-3'-methoxyphenyl)-5(R)-methoxyheptan-3-one (62) exhibit antibacterial activity against various Gram-negative bacteria, with an MIC of 71.2 $\mu\text{g}/\text{mL}$ (Liang Hui *et al.*, 2022). Grevillol derivatives (63-66), also derived from *Lysimachia*, display MIC values of 4-8 $\mu\text{g}/\text{mL}$ against both VRE and MRSA (Chen Li Li *et al.*, 2024; Shi, N. *et al.*, 2024). Curcusinol (67), isolated from *C. baccans*, exhibit similar activity against MRSA with MICs of 4-8 $\mu\text{g}/\text{mL}$ (Liu *et al.*, 2024). Brazilin (68) and brazilein (69), isolated from *C. sappan*, exhibit synergistic effects with aminoglycoside antibiotics-brazilein with hygromycin B-against MDROs (Lee *et al.*, 2014; Nirmal and Panichayupakaranant, 2014; Xu and Lee, 2004). Brazilin

(68) is also found to inhibit bacterial protein synthesis (Zuo *et al.*, 2014). Protosappanin A (70) and protosappanin B (71) show synergistic effects with gentamicin and amikacin against MRSA (Zuo *et al.*, 2015). Phloroglucinol trimers (74-77), isolated from *R. tomentosa*, demonstrate potent anti-MRSA activity with MICs ranging from 0.5 to 2 $\mu\text{g}/\text{mL}$ (Luo *et al.*, 2023).

Terpenoids and Derivatives

Terpenoids, a diverse group of NPs, are structurally defined by their isoprene unit framework, with Mevalonic Acid (MVA) serving as a central precursor in their biosynthetic pathways. Their classification hinges on the count of isoprene units, leading to subcategories such as monoterpenoids, sesquiterpenoids, diterpenoids, sesterterpenoids, and triterpenoids.

Sesquiterpenoids and monoterpenoids are major constituents of plant volatile oils and are important raw materials in the fragrance and pharmaceutical industries. Sesquiterpenoids consist of three isoprene units (15 carbon atoms) and are biogenetically derived from farnesyl pyrophosphate. The MICs of anti-MRSA activity of Δ^9 -tetrahydrocannabinol (79), cannabichromene (80), cannabidivarin (81), and other cannabinoids (82-85) are 1-8 $\mu\text{g}/\text{mL}$ (Appendino *et al.*, 2008; Berardo *et al.*, 2024; Russo *et al.*, 2021; Schofs *et al.*, 2021). They are isolated from *C. saliva*,

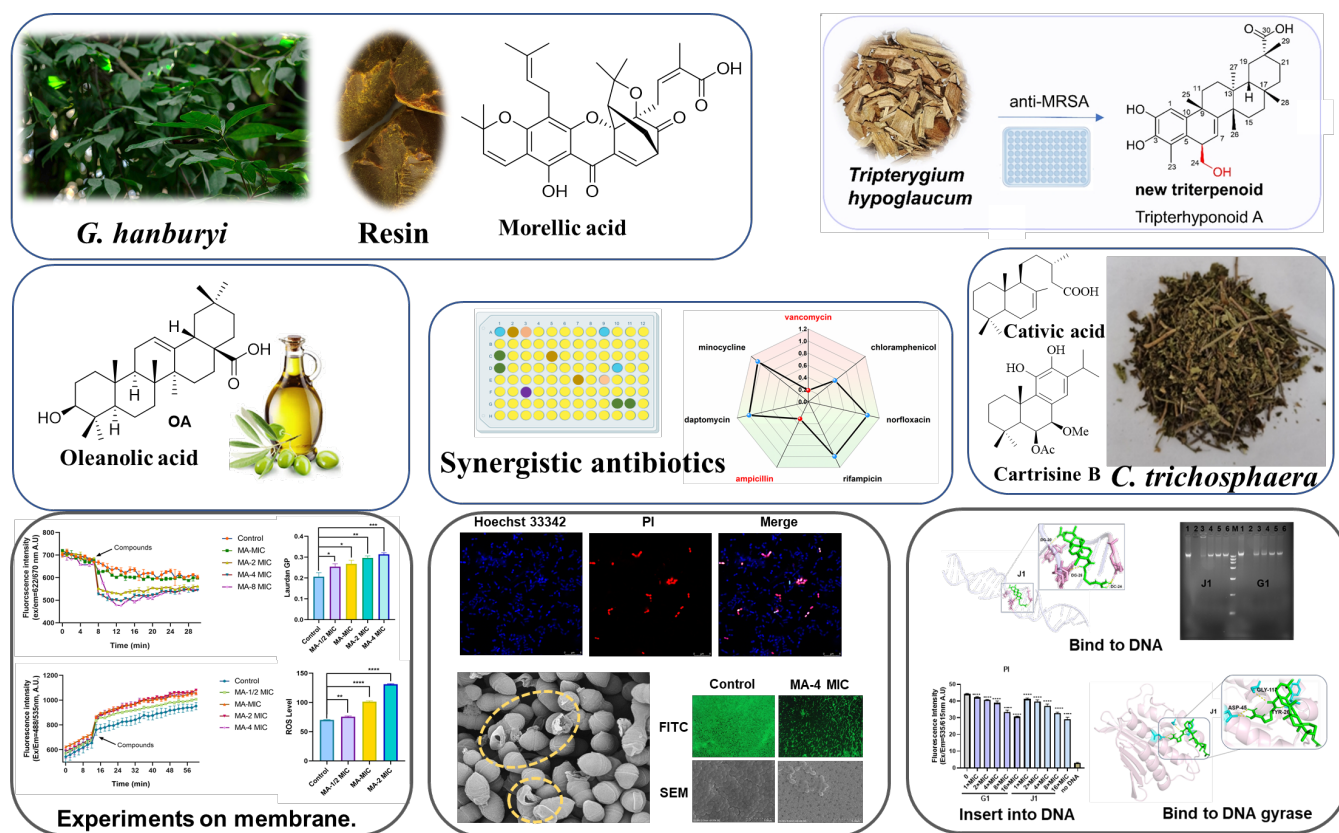
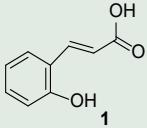
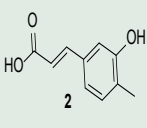
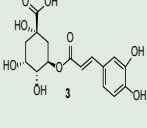
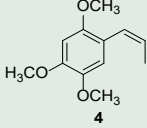
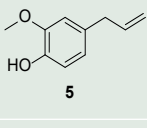
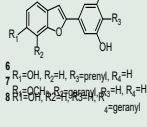
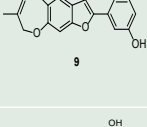
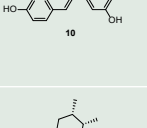
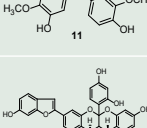
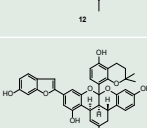
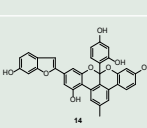

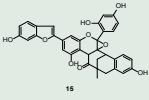
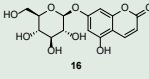
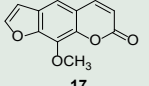
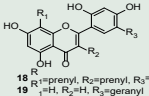
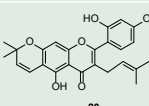
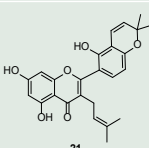
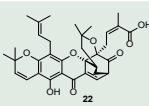
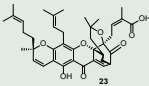
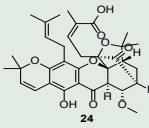
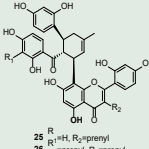
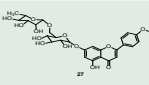
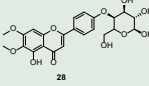
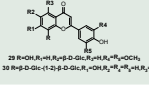
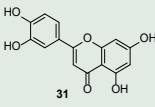
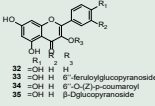
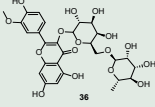


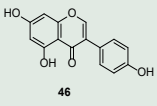
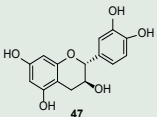
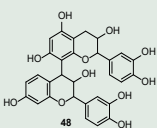
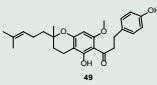
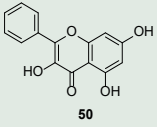
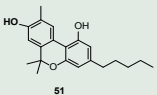
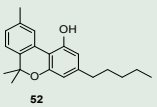
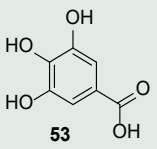
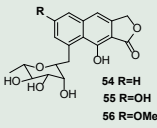
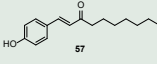
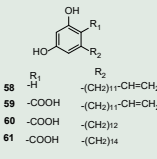
Figure 3: Chemical structures of morellic acid, tripterhyponoid A, oleanolic acid, and cativic acid. Synergistic antibiotics and their antibacterial mechanism. Reprinted with permission from Yunnan University, from (Construction and activity screening for the multicomponent library of medicine plant resources, and study on anti-VRE activity of Morellic acid) and (Structural optimization and against drug-resistant bacteria of natural flavonoids, triterpenes, and phloroglucinols).

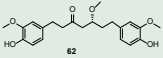
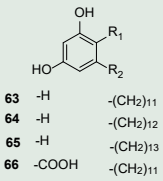
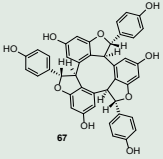
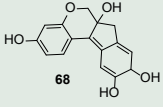
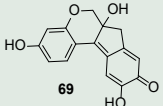
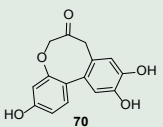
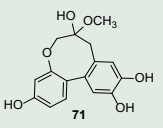
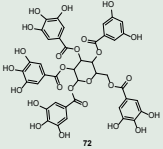
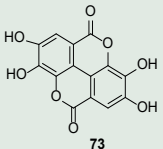
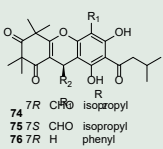
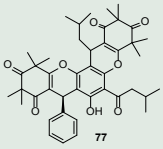
Table 3: Plant natural products (NPs) and antibiotics synergize against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), *C. albicans*, and Gram-negative bacteria.

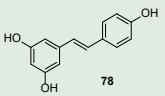
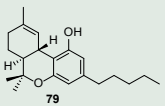
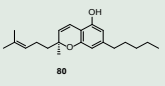
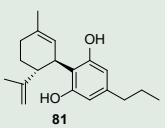
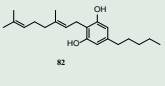
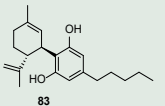
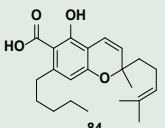
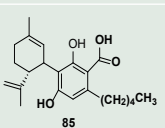
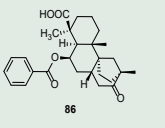
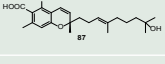
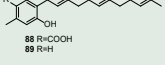
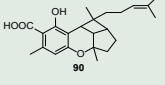
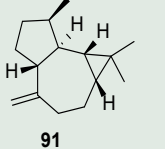
Sl. No.	Compounds	Chemical structure	Plants	Strains	MIC ($\mu\text{g}/\text{mL}$)	Mechanism and highlights	References
Phenylpropanoids							
1	o-coumaric acid (1)		<i>E. hirta</i>	MRSA	15.2 mm	inhibition of T3SS gene expression in MRSA	Abdelkhalek <i>et al.</i> (2018) and Erdogan Eliuz <i>et al.</i> (2022)
2	caffeic acid (2)		<i>E. hirta</i>	MRSA	500	-	Yuxia (2017)
3	chlorogenic acid (3)		<i>C. speciosa</i> , <i>O. gratissimum</i>	<i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> , <i>Shigella dysenteriae</i> , <i>S. Typhimurium</i>	20-40	increase membrane permeability, leakage of intracellular solutes	Lou <i>et al.</i> (2011) and Ugboqu <i>et al.</i> (2021)
4	β -asarone (4)		<i>A. tatarinowii</i>	<i>C. albicans</i> (08030401)	100	destruction of biofilm, inhibition of biosynthesis of cell wall	Wang <i>et al.</i> (2020) and Zhao <i>et al.</i> (2023)
5	eugenol (5)		<i>O. gratissimum</i>	MRSA	102.4	basil essential oil containing eugenol for resistance to MDROs	Ugboqu <i>et al.</i> (2021)
6	moracin C (6), mulberrofuran B (7), albufuran A (8)		<i>M. alba</i>	MRSA (031, 011, 003), <i>Staphylococcus aureus</i> (ATCC4330)	2-8	-	Zhu <i>et al.</i> (2021)
7	moracin G (9)		<i>M. alba</i>	MRSA (031, 011, 003), <i>Staphylococcus aureus</i> (ATCC4330)	8-16	-	Zhu <i>et al.</i> (2021)
8	3, 5 ft, 2, 4-tetrahydroxy-4 (3-methyl-1-butenyl) stilbene (10)		<i>M. alba</i>	MRSA (031, 011, 003), <i>Staphylococcus aureus</i> (ATCC4330)	4-8	-	Zhu <i>et al.</i> (2021)
9	4,4'-([2R,3S]-2,3-dimethylbutane-1,4-diyl)-bis-(2-methoxyphenol) (11)		<i>E. hirta</i>	MRSA, <i>Mycobacterium tuberculosis</i>	50	anti- <i>Mycobacterium tuberculosis</i> (H37Rv, G122, G133)	Reyes-Melo <i>et al.</i> (2017)
10	mulberrofuran G (12)		<i>M. alba</i>	MRSA (031, 011, 003), <i>Staphylococcus aureus</i> (ATCC4330)	8	-	Zhu <i>et al.</i> (2021)
11	mulberrofuran K (13)		<i>M. alba</i>	MRSA (031, 011, 003), <i>Staphylococcus aureus</i> (ATCC4330)	4-8	-	Zhu <i>et al.</i> (2021)
12	albanol B (14)		<i>M. alba</i>	MRSA (031, 011, 003), <i>Staphylococcus aureus</i> (ATCC4330)	8	-	Zhu <i>et al.</i> (2021)

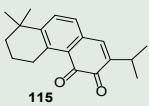
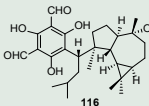
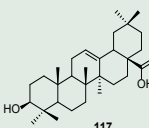
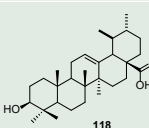
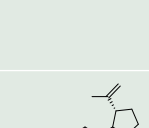
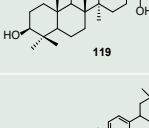
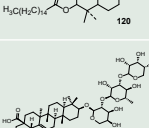
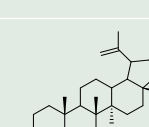
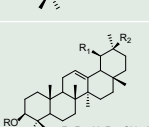
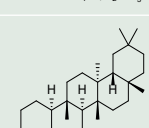
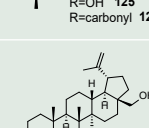
Sl. No.	Compounds	Chemical structure	Plants	Strains	MIC ($\mu\text{g}/\text{mL}$)	Mechanism and highlights	References
13	mulberrofuran Q (15)		<i>M. alba</i>	MRSA (031, 011, 003), <i>Staphylococcus aureus</i> (ATCC4330)	8-16	-	Zhu et al. (2021)
14	Daphnin (16)		<i>Saccharomonospora viridis</i>	<i>Staphylococcus aureus</i>	100	-	Cottiglia et al. (2001) and Jiang et al. (2010)
15	xanthotoxin (17)		<i>Z. khasianum</i>	<i>Staphylococcus aureus</i> (ATCC 43300), <i>Methylococcus luteus</i> (ATCC 10240)	30	destroy cell membrane	Walasek et al. (2015) and Wang et al. (2021)
Flavonoids							
16	kuwanon C (18), 5'-geranyl-5, 7, 2',4'-tetrahydroxyflavone (19)		<i>M. alba</i>	MRSA (031, 011, 003), <i>Staphylococcus aureus</i> (ATCC4330)	2-4	-	Zhu et al. (2021)
17	morusin (20)		<i>M. alba</i>	MRSA (031, 011, 003), <i>Staphylococcus aureus</i> (ATCC4330)	2-8	combining membrane PE/PG/CL, disrupting membrane function	Zhu et al. (2021) and Zhu et al. (2024)
18	kuwanon B (21)		<i>M. alba</i>	MRSA (031, 011, 003), <i>Staphylococcus aureus</i> (ATCC4330)	4	-	Zhu et al. (2021)
19	Morellic acid (22)		<i>G. hanburyi</i>	MRSA, VRE (ATCC51299)	1, 4	affects fatty acid biosynthesis and glycerophospholipid metabolism	Tang et al. (2024)
20	gambogic acid (23)		<i>G. hanburyi</i>	MRSA, VRE (ATCC51299)	2.5	destruction of biofilm	Pang et al. (2024) and Tang et al. (2024)
21	neo-gambogic acid (24)		<i>G. hanburyi</i>	MRSA	25	destruction of biofilm	Jia et al. (2015) and Tang et al. (2024)
22	kuwanon G (25), kuwanon H (26)		<i>M. alba</i>	MRSA (031, 011, 003), <i>Staphylococcus aureus</i> (ATCC4330)	2-4	-	Zhu et al. (2021)
23	linarin (27)		<i>S. dulcis</i>	<i>Staphylococcus aureus</i>	0.38	-	Davoodi et al. (2022)
24	cirsimaritin (28)		<i>S. dulcis</i>	<i>Staphylococcus aureus</i> (ATCC25923)	125	-	Vukovic et al. (2011)
25	tricin-7-O- β -D-glucoside (29), vitexin-2''-O- β -D-glucoside (30)		<i>Saccharomonospora viridis</i>	<i>Escherichia coli</i> (ATCC 25922)	100.6, 32.4	-	Fan et al. (2014)

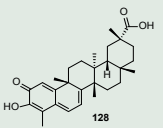
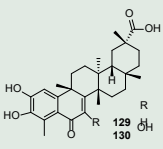
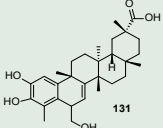
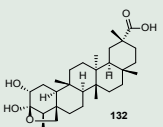
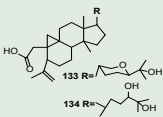
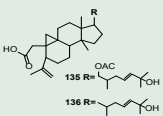
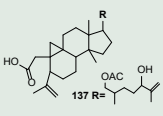
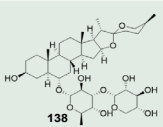
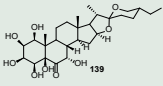
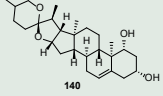
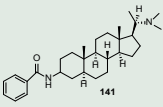
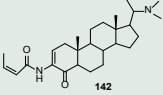
Sl. No.	Compounds	Chemical structure	Plants	Strains	MIC ($\mu\text{g}/\text{mL}$)	Mechanism and highlights	References
26	luteolin (31)		<i>C. trichosphaera</i>	MRSA (ATCC 29213)	32	inhibition of bacterial alpha toxin production	Qiu et al. (2011)
27	kaempferol derivatives (32, 33, 34, 35)		<i>G. globosa</i> , <i>O. gratissimum</i>	<i>P. aeruginosa</i> .	8-128	destruction of bacterial surface structure	Ugbogu et al. (2021) and Xu et al. (2022)
28	isorhamnetin 3-O- β -rbinobioside (36)		<i>G. globosa</i>	<i>Mycobacterium phlei</i>	50	-	Pomilio et al. (1992) and Xu et al. (2022)
29	sappanone B (37)						

Sl. No.	Compounds	Chemical structure	Plants	Strains	MIC ($\mu\text{g}/\text{mL}$)	Mechanism and highlights	References
37	genistin (46)	 46	<i>F. prostrata</i>	MRSA (562), <i>Staphylococcus aureus</i> (ATCC 25923), <i>Staphylococcus epidermidis</i> (ATCC 12228), <i>Pseudomonas aeruginosa</i> (ATCC 7853), <i>Escherichia coli</i> (ATCC 25922)	34	-	Madan et al. (2008)
38	(+)-catechin (47)	 47	<i>Z. khasianum</i> , <i>O. gratissimum</i>	MRSA, <i>Pseudomonas aeruginosa</i> , and <i>Escherichia coli</i>	161-512	synergistic anti MRSA with norfloxacin and gentamicin	Gomes et al. (2018), Ugbogu et al. (2021) and Wang et al. (2021)
39	Epifisetinidol-(4 β ,8)-epicatechin (48)	 48	<i>F. prostrata</i>	MRSA	64	synergistic effects with penicillin, ampicillin, imipenem, and amikacin	Ze-Ping (2022)
40	4-hydroxyboesenbergin B (49)	 49	<i>Amycolatopsis japonica</i>	VRE	16	inhibition of biofilm formation gene AtlA, SgrA, GelE, and Ace	Giang and Son (2007) and Ma et al. (2017)
41	galangin (50)	 50	<i>Amycolatopsis japonica</i>	MRSA	15.6	synergistic with gentamicin	Lee et al. (2008) and Ma et al. (2017)
Other phenols							
42	8-hydroxycannabinol (51)	 51	<i>C. saliva</i>	<i>Candida albicans</i>	128	destruction of biofilm	Schofs, Sparo, and Sánchez Bruni (2021)
43	cannabinol (52)	 52	<i>C. saliva</i>	<i>Staphylococcus aureus</i> (1199B, ATCC25923), MRSA (RN-4220, XU212), EMRSA (15, 16)	1, 1, 1, 1, 1	destruction of biofilm	Appendino et al. (2008)
44	gallic acid (53)	 53	<i>E. hirta</i>	MRSA	500-1,000	-	Yuxia (2017)
45	naphthol rhamnosides (54-56)	 54 R=H 55 R=OH 56 R=OMe	<i>Saccharomonospora viridis</i>	<i>Staphylococcus aureus</i> (ATCC 29213)	3.2-23.3	-	Fan et al. (2014)
46	Alpininone (57)	 57	<i>Amycolatopsis japonica</i>	VRE	32	-	Giang and Son (2007)
47	5-(12-tridecene-1-yl)-1,3-benzenediol (58), 6-(12-tridecene-1-yl)-2,4-Dihydroxy benzoic acid (59), 2,4-dihydroxy-6-dodecyl benzoic acid (60), 2,4-dihydroxy-6-tetradecyl benzoic acid (61)	 58 R ₁ R ₂ 59 R ₁ R ₂ 60 R ₁ R ₂ 61 R ₁ R ₂	<i>L. tengyuehensis</i>	VRE (<i>Enterococcus faecalis</i> ATCC 51299), MRSA	4-8	bacterial metabolic imbalance	Shi et al. (2024a)

Sl. No.	Compounds	Chemical structure	Plants	Strains	MIC ($\mu\text{g}/\text{mL}$)	Mechanism and highlights	References
48	1,7-bis-(4'-hydroxyl-3'-methoxyphenyl)-5(R)-methoxyheptan-3-one (62)		<i>Salvia cavaleriei</i>	<i>Pseudomonas fluorescens</i> , <i>Solanacearum</i> , <i>Clostridium perfringens</i>	71.2	-	Hui et al. (2022)
49	5-dodecyl-1,3-benzenediol (63), grevillol (64), 2,4-dihydroxy-6-undecyl benzoic acid (65), 2,4-dihydroxy-6-tridecyl benzoic acid (66)		<i>L. tengyuehensi</i>	VRE (<i>Enterococcus faecalis</i> ATCC 51299), MRSA	4-8	destruction of biofilm	Li et al. (2024) and Shi et al. (2024a)
50	Curcusinol (67)		<i>C. baccans</i>	MRSA (170402019), MRSA (170107359), MRSA (170208345)	8-16	inhibition of arginine biosynthesis	Liu et al. (2024)
51	brazilin (68)		<i>C. sappan</i>	MRSA, VRE (#228), <i>Burkholderia cepacia</i> (91.452), <i>Propionibacterium acnes</i>	32, 16, 32, 15.6	inhibition of DNA and protein synthesis, synergistic with aminoglycoside antibiotics	Nirmal and Panichayupakaranant (2014), Xu and Lee (2004) and Zuo et al. (2014)
52	brazilein (69)		<i>C. sappan</i>	MRSA	12.8	synergistic anti-MRSA activity with brazilein and hygromycin B	Lee et al. (2014)
53	protosappanin A (70)		<i>C. sappan</i>	MRSA	64	used in combination with amikacin or gentamicin	Zuo et al. (2015)
54	protosappanin B (71)		<i>C. sappan</i>	MRSA	128	used in combination with amikacin or gentamicin	Zuo et al. (2015)
55	pentagalloylglucose (72)		<i>S. chinensis</i>	<i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> , <i>Shigella</i> , <i>Salmonella</i> , MRSA	250	interference with cell wall synthesis and damage to cell membrane	Tian et al. (2009)
56	ellagic acid (73)		<i>S. chinensis</i>	<i>Streptococcus mutans</i> (ATCC 25175), <i>Lactobacillus acidophilus</i> (ATCC 4356)	125	anti-biofilm activity	Chittrarasu, Ahamed, and Ravi (2021)
57	phloroglucinol dimers (74, 75, 76)		<i>R. tomentosa</i>	MRSA	0.5-1	-	Luo et al. (2023)
58	phloroglucinol trimers (77)		<i>R. tomentosa</i>	MRSA	1-2	-	Luo et al. (2023)

Sl. No.	Compounds	Chemical structure	Plants	Strains	MIC ($\mu\text{g}/\text{mL}$)	Mechanism and highlights	References
59	trans-resveratrol (78)		<i>C. baccans</i>	MRSA	500	50 $\mu\text{g}/\text{mL}$ inhibits the synthesis of virulence factors in MDROs	Alqahtani <i>et al.</i> (2024) and Dávid, Hohmann, and Vasas (2021)
Terpenoids							
60	Δ^9 -tetrahydrocannabinol (79)		<i>C. saliva</i>	<i>Staphylococcus aureus</i> (1199B, ATCC25923), MRSA (RN-4220, XU212), EMRSA (15, 16)	2, 1, 1, 1, 2, 0.5	destroy cell membrane	Appendino <i>et al.</i> (2008) and Vozza Berardo <i>et al.</i> (2024)
61	cannabichromene (80)		<i>C. saliva</i>	<i>Staphylococcus aureus</i> (1199B, ATCC25923), MRSA (RN-4220, XU212), EMRSA (15, 16)	2, 2, 1, 2, 2, 2	destroy cell membrane	Schofs, Sparo, and Sánchez Bruni (2021)
62	cannabidivarin (81)		<i>C. saliva</i>	<i>Neisseria gonorrhoeae</i> (573 clinical)	2-8	destruction of the inner membrane	Russo <i>et al.</i> (2021) and Yang <i>et al.</i> (2022)
63	cannabigerol (82)		<i>C. saliva</i>	MRSA	0.5-2	disrupting the plasma membrane and increasing membrane permeability	Schofs, Sparo, and Sánchez Bruni (2021)
64	cannabidiol (83)		<i>C. saliva</i>	MRSA, <i>Listeria monocytogenes</i> , MRSE, <i>Enterococcus faecalis</i> .	4, 4, 4, 8	inducing diaphragm formation and reducing ezcA gene	Schofs, Sparo, and Sánchez Bruni (2021)
65	Cannabichromenic acid (84)		<i>C. saliva</i>	MRSA, MSSA	3.9, 7.8 μm	changing membranes and nucleoids to inhibit bacterial division	Schofs, Sparo, and Sánchez Bruni (2021)
66	cannabidiolic acid (85)		<i>C. saliva</i>	MRSA (United States 300), <i>Staphylococcus epidermidis</i> (CA71)	1, 2	change membrane potential	Schofs, Sparo, and Sánchez Bruni (2021)
67	4-epi-scopadulcic acid B (86)		<i>S. dulcis</i>	MRSA (B26), MRSA (K1)	125	-	Phan <i>et al.</i> (2006)
68	Capitachromenic acid E (87)		<i>R. rubiginosum</i>	MRSA, VRE	9.56, 9.56	destruction of biofilm	Luo (2024)
69	Grifolic acid (88), Grifolic (89)		<i>R. rubiginosum</i>	MRSA, VRE	8.33-24.4	destruction of biofilm	Luo (2024)
70	Rhododaurichromanic acid A (90)		<i>R. spinuliferum</i>	MRSA, VRE	5.37	destruction of biofilm	Luo <i>et al.</i> (2024)
71	aromadendrene (91)		<i>E. globulus</i>	MRSA, VRE	120, 250	synergistic anti-MRSA activity with 1,8-cineole	Mulyaningsih <i>et al.</i> (2010)

Sl. No.	Compounds	Chemical structure	Plants	Strains	MIC ($\mu\text{g}/\text{mL}$)	Mechanism and highlights	References
83	miltirone (115)		<i>S. przewalskii</i>	MRSA and MSSA	4-8	interfering with bacterial energy metabolism, inhibiting the synthesis of bacterial cell	Huang-Huan (2024)
84	macrocarpal B (116)		<i>E. globulus</i>	MRSA	2	destruction of cell membrane and inhibition of biofilm formation	Jiang et al. (2025)
85	oleanolic acid (117)		<i>L. polystachyus</i> and <i>C. speciosa</i>	MRSA, VRE, and <i>Staphylococcus aureus</i>	32, 8.4, 200	combining NDM-1, H1a proteins, and β -lactase	Ming et al. (2017), Shenghua et al. (2010) and Yong-Lin (2021)
86	ursolic acid (118)		<i>C. speciosa</i>	<i>Streptococcus mutans</i> , <i>Streptococcus sobrinus</i> , <i>Mycobacterium tuberculosis</i> , <i>S. pneumonia</i> , MRSA, <i>Bacillus subtilis</i> , <i>Bacillus cereus</i>	2, 2, 100, 16, 64, 8, 6.25	destruction of cell membrane and inhibition of biofilm formation	Jesus et al. (2015) and Wang et al. (2021)
87	betulinic acid (119)		<i>C. speciosa</i>	MRSA	16-64	synergistic effect with ciprofloxacin on efflux pump	Chung, Gan, and Chin (2022), Pereira da Silva et al. (2025) and Zhang et al. (2014a)
88	Olean-9(11),12-dien-3-O-palmitate (120)		<i>A. rivularis</i>	<i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i>	50-75	-	Zhao, Shao, and Fan (2012)
89	prosapogenin CP4 (121)		<i>A. rivularis</i>	<i>C. albicans</i> (ATCC 14053)	16	synergistic inhibition of fungal cell wall formation with vancomycin and oleanolic acid	Wen-Biao (2024)
90	lupeol (122)		<i>E. royleana</i>	<i>S. schenckii</i> , <i>Microsporium canis</i> , <i>Aspergillus fumigatus</i>	12-93.5	-	Kgosiemang et al. (2025)
91	α -amyrin (123), and β -amyrin (124)		<i>E. royleana</i>	<i>Candida krusei</i> , <i>C. albicans</i>	30-125	widely resistant to animal and plant pathogenic fungi	Johann et al. (2007) and Kgosiemang et al. (2025)
92	3 β -Friedelinol (125), friedelin (126)		<i>E. royleana</i>	MRSA	7.5-10	acting on the cell membrane to cause K ⁺ leakage	Inoue et al. (2004), Kgosiemang et al. (2025) and Ogunnusi, Oso, and Dosumu (2010)
93	betulin (127)		<i>G. longituba</i>	MRSA	400	destruction of biofilm	Zhou et al. (2021)

Sl. No.	Compounds	Chemical structure	Plants	Strains	MIC ($\mu\text{g}/\text{mL}$)	Mechanism and highlights	References
94	celastrol (128)		<i>T. hypoglaucum</i>	MRSA (United States 300)	4	inhibition of 1-pyrroline-5-carboxylate dehydrogenase (P5CDH), interference bacterial metabolism	Wei et al. (2022) and Yuan et al. (2023)
95	Wilforol A (129), regeol C (130)		<i>T. hypoglaucum</i>	MRSA, VRE	2, 4-32	anti-biofilm activity	Jin-Qiong (2024)
96	6-ethanoltriptohypol C (131)		<i>T. hypoglaucum</i>	MRSA, VRE	2, 8	destruction of biofilm	Jin-Qiong (2024)
97	Orthosphenic acid (132)		<i>T. hypoglaucum</i>	MRSA	8	-	Jin-Qiong (2024)
Steroid compounds							
98	3,4-seco-cycloartane derivatives 1 (133), lithocarpic acid D (134)		<i>L. polystachyus</i>	<i>S. aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Methylococcus luteus</i> , <i>Bacillus subtilis</i> .	3.1-50	-	Fan, Gao, and Yue (2016), Ming et al. (2017) and Tian-Tian (2020)
99	Lithocarpic acid F(135), coccinetane B (136)		<i>L. polystachyus</i>	<i>S. aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Methylococcus luteus</i> , <i>Bacillus subtilis</i> .	3.1-6.3	-	Fan, Gao, and Yue (2016) and Wang et al. (2014)
100	Lithocarpic acids I (137)		<i>L. polystachyus</i>	<i>S. aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Methylococcus luteus</i> , <i>Bacillus subtilis</i> .	12.5	-	Fan, Gao, and Yue (2016), Wang et al. (2014) and Zhang, Wang, and Zhao (2023)
101	6 α -O-[\beta-D-xylopyranosyl-(1 \rightarrow 3)-\beta-D-quinovopyranosyl]-(25S)-5 α -spirostan-3 β -ol (138)		<i>R. aurantiaca</i>	MRSA (003)	4	destruction of cell membrane and cell wall	Shi et al. (2024b)
102	Wattigenin C (139)		<i>R. aurantiaca</i>	<i>R. stolonifera</i>	inhibition rate 90%	-	Yao et al. (2022)
103	(25RS)-ruscogenin (140)		<i>L. spicata</i>	VRE (ATCC 51299)	10	destruction of bacterial inner membrane	Zhang et al. (2014b)
Alkaloids							
104	epipachysamine D (141)		<i>P. axillaris</i>	<i>C. albicans</i> (ATCC 14053)	4	destroy cell membrane	Duan et al. (2025)
105	pachysamine M (142)		<i>P. axillaris</i>	<i>C. albicans</i> (ATCC 14053)	4	inhibition of ergosterol biosynthesis	Duan et al. (2025)

Sl. No.	Compounds	Chemical structure	Plants	Strains	MIC ($\mu\text{g}/\text{mL}$)	Mechanism and highlights	References
106	6-acetyl-dihydroneid-ine (143), 6-acetyl-dihydrofagaridine (144), 6-acetyl-dihydrochelerythrine (145)		<i>Z. nitidum</i>	<i>Staphylococcus aureus</i> (ATCC 25923) and MRSA	8-16, 32	applied to efflux pump	Ombito (2021), Wang et al. (2021) and Zeng et al. (2022)
107	dihydrochelerythrine (146)		<i>Z. rhetsa</i>	MRSA (SK1) and <i>Escherichia coli</i>	8, 16	-	Ombito (2021) and Tantapakul et al. (2012)
108	γ -sanshoöl (147)		<i>Z. bungeanum</i>	<i>C. albicans</i>	32	destruction of biofilm	Ma et al. (2022) and Wang et al. (2021)
109	sarcovagine D (148)		<i>S. hookeriana</i>	<i>C. albicans</i> (08030401)	16	disrupting membrane potential, generating ROS	Shen et al. (2024)
110	hookerianamides O (149)		<i>S. hookeriana</i>	<i>Streptococcus minor</i>	16	-	Devkota et al. (2010)
111	Antofine (150)		<i>C. forrestii</i>	<i>Penicillium</i> , <i>Escherichia coli</i> , and MRSA	3-10	-	Qu et al. (2013)
112	schinifoline (151)		<i>Z. motuoense</i>	MRSA (011)	20	destruction of biofilm	Wang et al. (2024b) and Wang et al. (2021)
113	γ -fagarine (152)		<i>Z. motuoense</i>	MRSA (011)	128	destruction of biofilm	Wang et al. (2024b)
114	neochinulin A (153)		<i>Z. motuoense</i>	MRSA (003)	128	-	Wang et al. (2024b) and Wang et al. (2023)
Other compounds							
115	Heptacosan-1-ol (154)		<i>E. royleana</i>	<i>C. albicans</i>	15	-	Salehi et al. (2019)
116	phvto-oxvlipins siegeooxvlipin A (155), phvto-oxvlipins siegeooxvlipin B (156)		<i>S. orientalis</i>	MRSA, VRE	4-8	bacterial membrane damage	Zhou et al. (2025)
117	siegesoxylipin D (157), siegesoxylipin E (158)		<i>S. orientalis</i>	MRSA, VRE	8	characteristics of anionic surfactants	Kim et al. (2012) and Zhou et al. (2025)
118	Siegesoxylipin F (159), siegesoxylipin G (160)		<i>S. orientalis</i>	MRSA, VRE	8	characteristics of anionic surfactants	Wu et al. (2020) and Zhou et al. (2025)

with potent activity against MRSA and Methicillin-Susceptible *Staphylococcus aureus* (MSSA) (Yang *et al.*, 2022). The MIC of anti-MRSA of 4-epi-scopadulcic acid B (86) is 125 µg/mL (Phan *et al.*, 2006). Capitachromenic acid E (87) and grifolic derivatives (88, 89), isolated from *R. rubiginosum*, display activity against MRSA and VRE with MICs ranging from 8.33 to 24.4 µg/mL (Luo-EE, 2024). Rhododaurichroman acid A (90), derived from *R. spinuliferum*, exhibits broader antibacterial activity with an MIC of 5.37 µg/mL (Luo *et al.*, 2024).

Aromadendrene (91) demonstrates anti-MRSA activity when combined with 1,8-cineole (Mulyaningsih *et al.*, 2010). The anti-MRSA and VRE activities of (+)-15, 16-epoxy-8(17), 13(16), 14-labdatriene (93) are 32 µg/mL (Ma *et al.*, 2017). Spinulinoid A-C (94-96), also isolated from *R. spinuliferum*, demonstrate antibacterial activity against VRE and MRSA with an MIC ranging from 2.7 to 5.37 µg/mL (Luo *et al.*, 2024). *E*-confluentin (97), *Z*-confluentin (98), and anthopogochromene C (99), isolated from *R. rubiginosum*, demonstrate anti-MRSA and anti-VRE activities with MICs between 3.07-18.4 µg/mL (Luo-EE, 2024). Ferruginol (100), 19-hydroxyferruginol (101), sugiol (102), and 6 α -hydroxydemethylcryptojaponol (103), isolated from *C. trichosphaera*, exhibit antimicrobial activity against MRSA and VRE, with MICs ranging from 4 to 32 µg/mL (Lu *et al.*, 2025). Ferruginol (100) has been shown to modulate membrane permeability and fluidity in MRSA, leading to membrane depolarization and subsequent structural disruption (Lu *et al.*, 2025). 14-deoxycoleon U (104), cativic acid (105), and cartrisine B (106), isolated from *C. trichosphaera*, show anti-MRSA activities with MIC 16-32 µg/mL (Lu *et al.*, 2024; Lu *et al.*, 2025). Research has found that cartrisine B (106) shows synergistic effects with tetracycline against MDROs (Joshi *et al.*, 2021). A series of 16 β -hydro-ent-kauran-17,19-dioic acid derivatives (107-110) demonstrate potent anti-MRSA activity, with MICs ranging from 0.12 to 0.5 µg/mL (Yang *et al.*, 2016). Sigesbeckin A (111) and 18-hydroxy-kauran-16-ent-19-oic acid (112), isolated from *S. orientalis*, show synergistic effects with vancomycin and doxorubicin, respectively (Zhou *et al.*, 2024). Their mechanism involves disruption of bacterial membrane integrity, contributing to their activity against MDROs. Cryptotanshinone (113), przewaquinone (114), and miltirone (115), isolated from *Salvia miltiorrhiza* and *S. przewalskii*, exhibit broad-spectrum activity against MRSA, MSSA, and VRE, with MICs ranging from 0.9 to 8 µg/mL (Huang-Huan, 2024; Zhong *et al.*, 2021). In addition to antibacterial activity, compounds such as spinulinoids A-C (94-96), confluentins (97-99), 14-deoxycoleon U (104), and miltirone (115) are reported to inhibit the biosynthesis of key biofilm components by down-regulating biofilm-associated genes. Furthermore, cryptotanshinone (113) and przewaquinone (114) inhibit bacterial pyruvate kinase, interfering with energy metabolism in MRSA and MSSA (Zhong *et al.*, 2021). Macrocarpal B (116), isolated from *Eucalyptus* spp., exhibit anti-MRSA activity with an MIC of 2 µg/mL (Jiang *et al.*, 2025).

Additionally, oleanolic acid (117), ursolic acid (118), and betulinic acid (119), obtained from *L. polystachyum* and *C. speciosa*, exhibit antimicrobial activity against MRSA, with MICs ranging from 2 to 64 µg/mL (Lei Ming *et al.*, 2017; Wang *et al.*, 2021a). Olean-9(11),12-dien-3-O-palmitate (120) inhibit the growth of *Bacillus subtilis* and *S. aureus* with effective concentrations of 50-75 µg/mL (Zhao *et al.*, 2012). The MIC of anti-*C. albicans* of prosapogenin CP4 (121), epipachysamine D (141), pachysamine M (142), sarcovagine D (148), and hookerianamides O (149) is 16-30 µg/mL (Duan *et al.*, 2025; Shen *et al.*, 2024; Wen-Biao, 2024). Lupeol (122) inhibits *Sporothrix schenckii*, *Microsporium canis*, and *Aspergillus fumigatus* with MICs 12-93.5 µg/mL (Kgosiemang *et al.*, 2025). Additionally, α -amyryn (123) and β -amyryn (124) inhibit *Candida krusei* and *C. albicans* with MIC 30-125 µg/mL. These compounds show great capacity to resist pathogenic fungi of both animal and plant origin (Johann *et al.*, 2007; Kgosiemang *et al.*, 2025). The MIC of anti-MRSA or VRE of 3 β -friedelinol (125), friedelin (126), celastrol (128), wilforol A (129), regeol C (130), 6-ethanoltriptohypol C (131), orthosphenic acid (132) ranges from 2 to 32 µg/mL (Ogunnusi *et al.*, 2010). Betulin (127) can clear MRSA biofilms with less likely to cause drug-resistance in bacterial (Zhou *et al.*, 2021).

The MIC of 3, 4-seco-cycloartane derivatives I (133), lithocarpic acid D (134), lithocarpic acid F (135), coccinetane B (136), lithocarpic acids I (137), against various bacteria (*S. aureus*, *S. epidermidis*, *M. luteus*, *B. subtilis*) ranges from 3.1 to 32 µg/mL (Fan *et al.*, 2016; Tian-Tian, 2020). The MIC of anti-MRSA of 6 α -O-[β -D-xylopyranosyl-(1 \rightarrow 3)- β -D-quinovopyranosyl]-(25S)-5 α -spirostan-3 β -ol (138) is 4 µg/mL (Shi, Y.-Z. *et al.*, 2024). Wattigenin C (139) inhibits *Rhizopus stolonifera* with the rate of 90%. Additionally, (25R, S)-ruscogenin (140) shows anti-VRE activity with an MIC of 10 µg/mL.

Alkaloids

Alkaloids represent one of the most important elements in plant secondary metabolites, with many alkaloids showing excellent antibacterial activity. A series of alkaloids, such as the 6-acetyl-dihydronitidine (143), 6-acetyl-dihydrofagaridine (144), 6-acetyl-dihydrochelerythrine (145), dihydrochelerythrine (146), schinifoline (151), γ -fagarine (152), and neoechinulin A (153) have been isolated from the *Zanthoxylum* genus, exhibiting anti-MRSA activity with MICs ranging from 8 to 128 µg/mL (Ombito, 2021; Wang *et al.*, 2021b). Among them, compound (143-145) exhibits antibacterial activity against *S. aureus* with MIC 8-16 µg/mL and were found to inhibit efflux pumps of MRSA (Zeng *et al.*, 2022). The compound *y-sanshoöl* (147) also shows antibacterial activity against *C. albicans* with an MIC of 32 µg/mL; it can destroy the biofilm of fungi (Ma *et al.*, 2022). Antofine (150), isolated from *C. forrestii*, shows antibacterial activity against *Penicillium*, *E. coli* and MRSA, with MIC ranging from 3 to 10 µg/mL (Qu *et al.*, 2013).

Other Metabolites

In addition to the plant NPs discussed above, notable antibacterial and antifungal activities against MDROs and *C. albicans* have also been identified in several other compound classes, including fatty acids, phenylpropanoids, phyto-oxylipins, and miscellaneous metabolites (see Table 3 for details). Phenylpropanoid, isolated from *A. tatarinowii* and *O. gratissimum*, shows anti-MRSA and *C. albicans* activities with an MIC of 100 µg/mL. Heptacosan-1-ol (154), isolated from *E. royleana*, shows anti-fungal activity against *C. albicans* with MIC 15 µg/mL (Salehi *et al.*, 2019). Siegeoovlipin A-G (155-160), a compound of oxylipins isolated from *S. orientalis*, shows anti-MRSA activities, with an MIC ranging from 4-8 µg/mL (Zhou *et al.*, 2025). These compounds functions as anionic surfactant, contributing to bacterial membrane disruption.

Mechanisms of plant-derived NPs against MRSA, VRE, and *C. albicans*

O-Coumaric acid (1) inhibits the expression of the T3SS gene in MRSA, thereby suppressing the biofilm synthesis pathway (Abdelkhalek *et al.*, 2018). The antibacterial mechanism of antibiotics is to inhibit cell wall and protein synthesis, interfere with nucleic acid metabolism, and damage the outer membrane of gram-negative bacteria (Eliuz *et al.*, 2022). These antibacterial mechanisms can easily lead to bacterial resistance. In this article, β-asarone (4), morusin (20), gambogic acid (23), neogambogic acid (24), kuwanon O (43), 4-hydroxyboesenbergin B (49), 8-hydroxycannabinol (51), cannabinol (52), 5-Dodecyl-1,3-benzenediol (63), ellagic acid (73), capitachromenic acid E (87), rhododaurichromanic acid A (90), (+)-15,16-Epoxy-8(17),13(16),14-labdatriene (93), spinulinoid A-B (94, 95), E-confluentin (97), Z-confluentin (98), anthopogochromene C (99), macrocarpal B (116), ursolic acid (118), betulin (127), wilforol A (129), regeol C (130), grifolic (145), γ-sanshoöl (147), schinifoline (151), and γ-fagarine (152) are included. They demonstrate the ability to inhibit the biofilm formation and disrupt formed biofilms of MDROs, particularly MRSA, VRE, and *C. albicans* (shown in Figure 3) (Tang *et al.*, 2024; Wang *et al.*, 2020; Wei *et al.*, 2024; Zhou *et al.*, 2024; Zhu *et al.*, 2021; Zhu *et al.*, 2024).

4-Hydroxyboesenbergin B (49) inhibits the expression of AtIA, SgrA, GelE, and Ace-key genes involved in biofilm formation in VRE and exhibits anti-VRE activity without promoting drug resistance (Ma *et al.*, 2017). Several plant-derived compounds, including xanthotoxin (17), morusin (20), morellic acid (22), pentagalloylglucose (72), cannabidivarin (81), cannabigerol (82), cannabichromenic acid (84), cannabidiolic acid (85), ferruginol (100), 19-hydroxyferruginol (101), sugiol (102), 14-deoxycoleon U (104), cativic acid (105), macrocarpal B (116), ursolic acid (118), 1,8-cineole (123), 3β-friedelinol (125), (25R, S)-ruscogenin (140), and siegeoovlipin A-G (155-160) act primarily on bacterial

membranes, including the inner membrane, outer membrane, and plasma membrane. And they alter membrane permeability, damage membrane structure, inhibit membrane function, and disrupt bacterial appearance, thereby exerting activity against MDROs (Tang *et al.*, 2024; Zhou *et al.*, 2025; Zhu *et al.*, 2024).

Phloretin (44) targets and inhibits the pathogenic factor SrtB, thereby preventing the formation in Gram-negative bacterial (Shang *et al.*, 2022; Wang, G. *et al.*, 2018). Cannabidiol (83) interferes with bacterial cell division by stimulating diaphragm formation and suppressing the expression of the essential division gene *ezrA*, showing MIC values of 4-8 µg/mL against MRSE, *Listeria monocytogenes*, and *Enterococcus faecalis* (Schofs *et al.*, 2021). Oleanolic acid (117) inhibits the expression of bacterial resistance proteins, including NDM-1, H1a, and β-lactamases, and exhibits broad-spectrum antibacterial activity (Yong-Lin, 2021). Celastrol (128) suppresses deoxyribonucleic acid synthesis by binding to P5CDH in MRSA (Yuan *et al.*, 2023).

Oleanolic acid (117) and prosapogenin CP4 (121) exhibit synergistic antifungal activity against fungi by inhibiting the fungal cell wall synthesis pathway (Wen-Biao, 2024). These two compounds, along with sarcovagine D (148), demonstrate potent activity against *C. albicans* and are less likely to cause drug resistance (Shen *et al.*, 2024). Sarcovagine D (148) disrupts mitochondrial membrane potential and induces ROS generation, ultimately promoting the death of *C. albicans* (Shen *et al.*, 2024).

CONCLUSION

This paper reviews the botanical characteristics, phytochemistry, ethnobotanical applications, and antimicrobial activities of 32 ethnic medicinal plants from Yunnan. Current research primarily centers on the pharmacological activities of crude extracts or fractions. While known bioactive constituents include terpenoids, flavonoids, alkaloids, and polyphenols, the discovery of novel active compounds remains limited and requires further investigation. It is also evident that there is a lack of research methodologies integrating traditional usage, standard practices of bioactive ingredients isolation, and evaluation against MDROs. The mechanisms underlying their antimicrobial actions have not been fully elucidated. Although some studies have examined the mechanisms of action of plant-derived NPs against MRSA, VRE, and *C. albicans*, such investigations remain relatively superficial. Fewer than 10% of the previous studies have proposed potential molecular targets or pathways, as revealed by metabolomic, transcriptomic, and network pharmacology analysis. Comprehensive methodological frameworks to explore the mechanisms of plant NPs against MRSA, VRE, and *C. albicans* are still wanted. These mechanisms need to be validated using molecular biology techniques such as Western blotting, gene knockout, and gene over-expression.

Moreover, the currently available murine models of MRSA, VRE, and *C. albicans* infections are limited, making it difficult

to fully simulate such clinical infections. This hampers research into the distribution and efficacy of bioactive compounds within infected tissues. There is also a need to improve administrative routes and develop targeted drug delivery strategies. To date, few studies have reported the *in vivo* pharmacological effects and tissue distribution of these active compounds. Additionally, many plant NPs effective against MRSA, VRE, and *C. albicans* exhibit poor solubility, permeability, and selectivity. Optimizing and synthesizing new derivatives with enhanced antibacterial efficacy and low toxicity against MDROs is likely to be a key direction for future research.

Currently, the clinical management of MDRO infections often involves combination therapies. Numerous plant-derived NPs have demonstrated strong synergistic effects when paired with existing antibiotics. This strategy of “drug repurposing” not only reduces the risk and cost associated with new drug development but also provides a practical solution to address the escalating issue of MDROs infections, which represents a major breakthrough in overcoming challenges of current antimicrobial drug development. Soon, combinations of plant-derived NPs and antibiotics hold significant potential for clinical translation and market application.

In the future, interdisciplinary collaboration among phytochemists, synthetic chemists, pharmacologists, and artificial intelligence researchers will be essential for the efficient screening, discovery, and development of the next generation of anti-MDRO therapeutics.

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ABBREVIATIONS

CL: Cardiolipin; **DOX:** Doxorubicin; **MDROs:** Multidrug-Resistant Organisms; **MIC:** Minimum Inhibitory Concentrations; **MRSA:** Methicillin-Resistant *Staphylococcus aureus*; **NPs:** Plant-Derived Natural Products; **PE:** Phosphatidylethanolamine; **PG:** Phosphatidylglycerol; **PK:** Pyruvate Kinase; **ROS:** Reactive Oxygen Species; **VAN:** Vancomycin; **VRE:** Vancomycin-Resistant Enterococcus.

AUTHOR CONTRIBUTIONS

Li-Li Chen, Liu Min and Wu-Feng Yang provided the necessary plant resources and contributed to the drafting of the initial manuscript. Yun-Xiu Cheng searched for the folk use of plants.

Tian-Zhen Xie was responsible for the illustration of the compounds' structure. Xiao-Yuan Zhu revised the manuscript. Zhao-Jie Wang, Shuang-Long Yang, Wei-You Xie, and Ming Gong were involved in project design, manuscript revision, and funding. All authors reviewed and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that there no conflict of interest.

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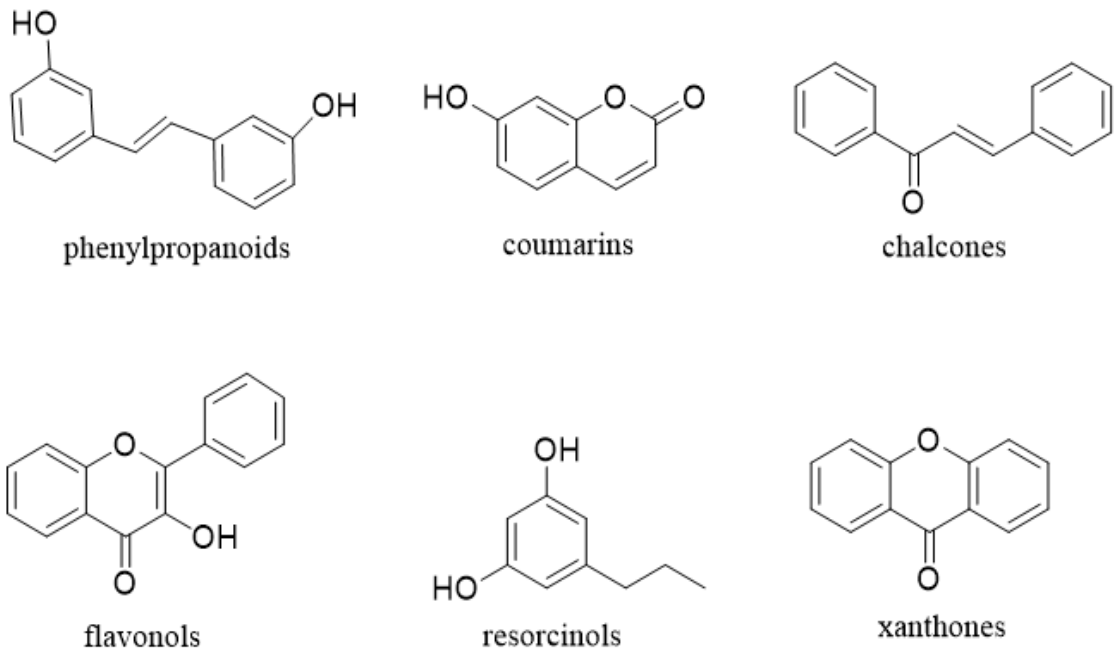


Figure S1: The basic skeleton of the major structural types of phenolics.