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A Review of Ethnomedicine, Phytochemistry, and Pharmacological Studies on Yellow Roots (*Arcangelisia flava* (L.) Merr.)

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Yellow Root (*Arcangelisia flava* (L.) Merr.), a member of the Menispermaceae family, is a plant used in traditional Asian medicine, particularly in Indonesia, Malaysia, and the Philippines. This article attempts to summarise, based on scientific literature, the extensive ethnopharmacology, phytochemistry, and toxicology of this plant. Some bioactive of this plant may have multi-dimensional health benefits and provide a new foundation for future research on the mechanism and the creation of more effective medicinal agents and healthy products. Recent research has shown that this plant possesses a wide range of pharmacological properties, including aphrodisiac, anti-microbial, anti-depressant, anti-diarrhea, anti-helminthic, anti-inflammatory, anti-cancer, anti-malaria, antioxidant, atherosclerosis, jaundice, anti-diabetes, hyperlipidemia, and cardioprotective. No clinical trials have been conducted, which is a limitation of this review. Consequently, the effect of yellow roots on humans remains unknown; therefore, further research is required to explore the advanced clinical therapeutic applications and develop valuable products for this plant's commercial market of bioactive candidates for designing appropriate pharmaceuticals and complementary and effective medicines.

Keywords: Ethnomedicine; Ethnopharmacology; yellow root; *Arcangelisia flava*

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Arcangelisia flava (L.) Merr. is a plant from the Menispermaceae family and is widespread throughout Southeast Asia, from China to New Guinea. It is an endemic plant from Borneo with a unique bright yellow wood color [1]. Some local name in Indonesia are ki koneng (West Java), reuy ki koneng (Sunda); oyod sirawanan, sirawan kunyit (Java); wuh bulan (Ambon); kayo kuning (Palembang); oyod koneng (Madura); and mololeya gumini (Halmahera Utara) [2-3]. The traditional therapeutic use of this plant is to treat fever, diarrhea, hepatitis, worm infections, gastrointestinal disease, and thrush [4-5]. Dayak ot Danum tribe in the Kalimantan, precisely Tumbang Payang, uses the roots and stems of this plant to treat jaundice/hepatitis and liver disorders [6]. This plant contains several secondary metabolites such as saponins and tannins [7], and the leaf extract contains alkaloids, flavonoids, and terpenoids. The roots also contain glycosides and alkaloids, particularly isoquinoline groups such as berberine, jatrorizin, and palmatine [8], and some minor alkaloids include columbamine, dehydrokoridalmin, homoaromolin, and talifendin [7]. Global information on Yellow Root phytochemistry and their pharmacology effect might significantly contribute to developing new lead compounds and scaffolds. This is relevant to the future prediction of natural products, where it has the potential for pharmaceutical research and development of effective and new drugs to treat human diseases, specifically critical diseases.

Yellow Root's traditional medical applications and pharmacological effects must be adequately documented. Therefore, this article aims to provide a comprehensive summary of the published studies of ethnomedicine, pharmacology, and phytochemistry on yellow roots. The current review used scientific journals, *in-vitro*, *in-vivo*, and *in-silico* data to demonstrate their traditional applications.

METHOD

This review focuses on the practical use of the yellow root plant and several studies carried out *in-vitro* and *in-vivo*. Several global electronic databases are searched with no date limit using Google Scholar, Science Direct, and PubMed. The keywords used are "*Arcangelisia flava*", "Yellow Root", and "*Arcangelisia flava* uses".

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RESULTS AND DISCUSSION

1. Botanical Characterization and Distribution

Arcangelisia flava (L.) Merr is a type of plant that grows at altitudes between 100 and 800 m above sea level or at the forest's periphery. Along the ground or the stem of a plant, it is a liana and an ascending plant. Recently, this plant was collected from Central Kalimantan. Most of the leaves (Fig. IA & B) are alternate, thick, ovate-pointed, elips, and some resemble a heart; they are palmately 5-veined at the base, and they are green when juvenile and dark green when mature. The flowers shown by Lim et al., 2018 are unisexual, located in leaf axils, petalless, yellowish-white, and bud-bearing. Galingging et al, 2021 showed that this plant fruit is yellow with a club-shaped stalk endocarp that is woody, slightly laterally, transversely subovoid, slimy, and has a feeble, bitter odor and flavor. Their endosperm, cotyledons, and seed are broadly ellipsoidal. The bark shows rough and dark brown, while the interior is brilliant yellow and a thick taproot with dark-brown roots (Fig. I C & D). The word "yellow" refers to the color of the wood and the yellow colour that comes out of the trunk when cut. Berberine is a golden-yellow alkaloid found in the roots and stems of the plant [6].

2. Traditional Uses and Ethnopharmacology

The Philippines, Maluku, and Irian communities commonly use Yellow Root stems for the natural dye [9]. This plant has long been used as a traditional medicine for jaundice, diarrhea, fever, malaria, etc in Indonesia (Central Kalimantan, Southeast Sulawesi, Ambon, Central Java, East Java, and West Sumatra), Malaysia, and the Philippines (**Tabel 1**).

Figure 1. *Arcangelisia flava* leaves (A & B), stem (C & D), and root (E).

Table 1. Traditional uses of Yellow Root (*Arcangelisia flava* (L.) Merr).

Region/Country	Empirical Use
Central Kalimantan	The Dayak people used decoction for stomach pain, jaundice, and eye pain medicine [9], to cure malaria, diarrhea, and fever.
Southeast Sulawesi	The decoction is used to treat abdominal pain [4], maintain health (tonic), fever (antimalarial), internal pain (jaundice), treat eye pain (juice), and urinary tract infections. Usually, it is used as an herbal mixture.
Southeast Asia	It is used as internal medicine, especially for thrush and internal heat. This decoction with betel leaves and oranges for jaundice
Ambon	Ambonese people use wood scraps for smallpox medicine in plaster form [9].
Central Java and East Java	Branches of this plant mixed with other family plants and traded in the world of medicine under the name "wood sprue" [10].
Malaysia	The aqueous decoction is used to cure jaundice, intestinal worms, and digestive disorders, while the wood is made as smoked cigars for respiratory tract (nose) and mouth disorders [10].
Philippines	The decoction from the roots and stems is used as a fever reducer, tonic, stomach pain, expectorant, and launch menstruation but is abortive depending on the amount of decoction. It is also used as external medicine to rinse wounds, itching, and other skin diseases [10].
West Sumatra	The native Palupuh ingested Yellow Root extract to cure gastrointestinal illness gradually within two months. It is also beneficial for malignancies of bumps on his body and disappears after three months [7].

3. Phytochemistry of Yellow Roots

A total of thirty-three phytochemistry have been found on Yellow Root and their structures were shown in Figure 2, such as 6-hydroxyarcangelisin **(1)**, 6-hydroxyfibraurin **(2)**, 8-hydroxy-berberine **(3)**, 20-hydroxyecdysone **(4)**, berberine **(5)**, berberubine **(6)**, columbamine **(7)**, dehydrocorydalmine **(8)**, dihydro-berberine **(9)**, fibleucin **(10)**, fibraurin **(11)**, homoaro-moline **(12)**, jatrorrhizine **(13)**, limacine **(14)**, pachy-basin **(15)**, palmatine **(16)**, palmatrubine **(17)**, p-nonyl-phenol **(18)**, pseudocolumbamine **(19)**, pycnarrhine **(20)**, stigmastan 3-5-diene **(21)**, stigmastan-5-en-3-ol **(22)**, thalifendine **(23)**, tinophyllol **(24)**, pseudo-jatorrhizine **(25)**, palmatine 7-n-oxide **(26)**, ergost-5-en-3-ol **(27)**, berberine 7-n-oxide **(28)**, 6-hydro-xyfibleucin **(29)**, 2-dehydroaxyarcangelisinol **(30)**, 2a,3a-epoxy-2,3-dihydropenianthic acid methyl ester **(31)**, 2a,3a-epoxy-2,3,7,8a-tetrahydropenianthic acid methyl ester **(32)**, and 2β, 3α-dihydroxy-2,3,7,8α-tetrahydropenianthic acid-2,17-lactone **(33)** [1, 15, 17, 20, 21, 22, 24].

Our previous research analyzed the compounds contained in the 70% ethanol extract of *Arcangelisia flava* (L.) Merr using liquid chromatography-mass spectrometry (LC-MS/MS), and found compounds such as fibleucin, jatrorrhizine, berberine, palmatine, pycnarrhine, isopycnarrhine, sinapic acid, pallidinine, 3-hydroxy-3',4',5'-trimethoxyflavone, demethylene-berberine, stepharanine, docosanoic acid, and fissisaine [16]. The most common bioactive compound is berberine (5) which is used as an anti-bacterial by inhibition of protein and cell wall synthesis bacteria [17], an anti-inflammatory by inhibition of iNOS [18], an anti-malaria [19], an anti-cancer against MCF-7 (breast adenocarcinoma), and inhibit EGFR-2 (HER2-Positive) breast cancer line [11].

The potential anti-bacterial activity of 6-hydro-xyarcangelisin **(1)**, 6-hydroxyfibraurin **(2)**, 8-hydroxy-berberine **(3),** homoaromoline **(12)**, tinophyllol **(24)**, 6-hydroxyfibleucin **(29)**, and 2-dehydroaxyarcangelisinol **(30)** showed their activities through various pathways including inhibition protein synthesis bacteria (PDB ID: 4WYC) using molecular docking approach [17]. Other phytochemicals have been predicted to inhibit *bacterial metabolites* and the synthesis of proteins in bacteria such as pachybasin **(15)** [12, 13], columbamine **(7)**, fibraurin **(11)**, jatrorrhizine **(13)**, and palmatine **(16)** [17]. As well as *in-silico* research showed that the photochemistry compounds of 20-hydroxyecdysone **(4)**, dehydrocorydalmine **(8)**, dihydroberberine **(9)**, limacine **(14)**, pycnarrhine **(20)**, and thalifendine **(23)** have decrease inflammatory as iNOS inhibitors (PDB ID: 3E7G) [14, 18].

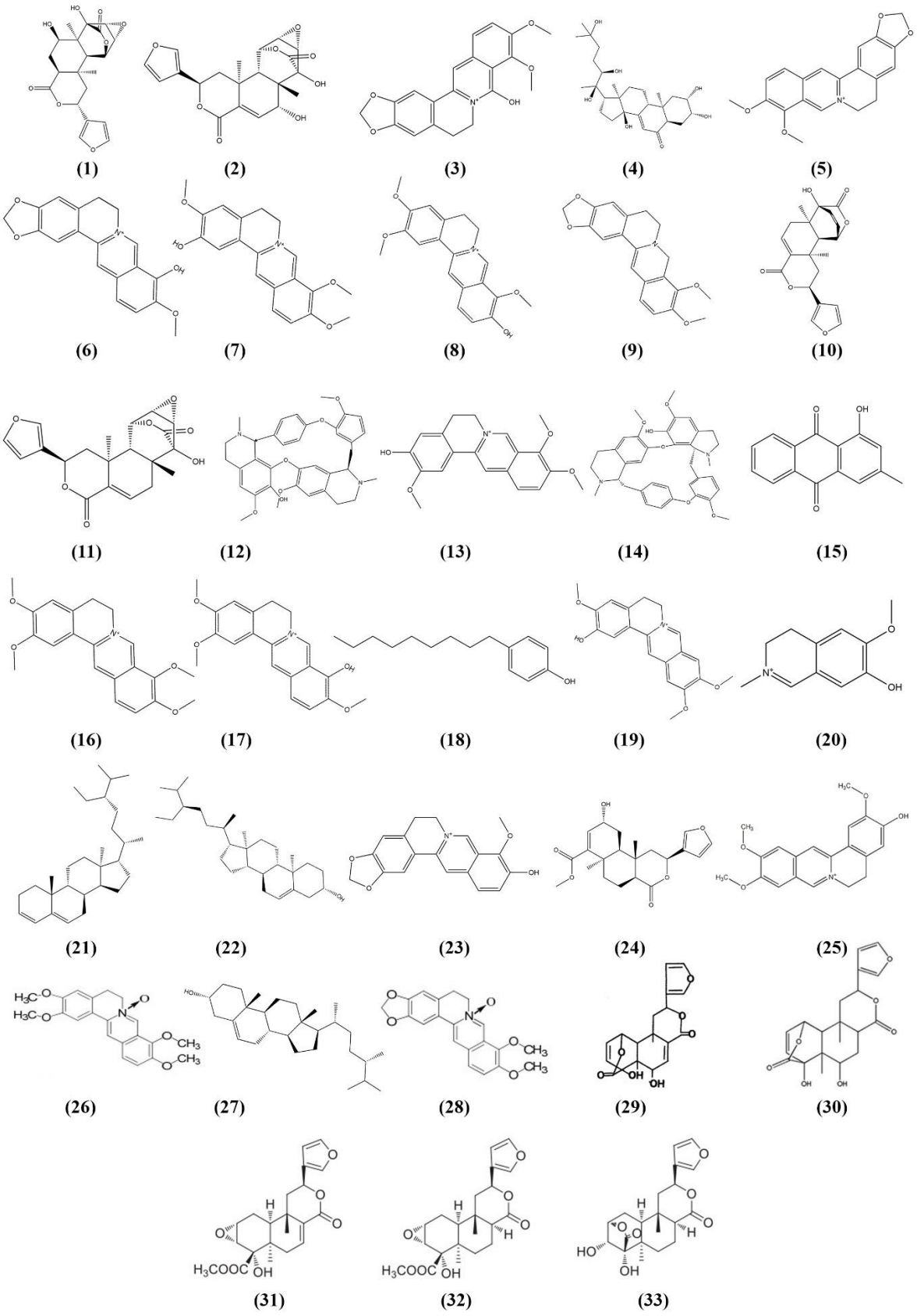

Figure 2. Phytochemistry of *Arcangelisia flava* (L.) Merr.

Table 2. Bioactivity of *Arcangelisia flava* (L.) Merr.

Activity	Extract	Mechanism	Reference
Aphrodisiac	The stem ethanol extract	Increase introduction and locomotor activity	[20]
Anti-microbial	The stem ethanol extract	Inhibit against *Streptococcus mutans*, *Porphyromonas gingivalis*, and *Enterococcus faecalis*	[21]
		Inhibit against *Staphylococcus aureus* and *Escherichia coli*	[22]
	The leaf methanol extract	Inhibit against *Pseudomonas fluorescens*	[23]
	The chloroform extract	Inhibit against *Aeromonas hydrophila*	[24]
	Pachybasin	Inhibit against *E. coli*, *B. subtilis*, *M. luteus*, *S. cerevisiae*, *C. albicans*, *A. niger*, *A. flavus*, *S. aureus* and *F. oxysporum*	[13]
	The water extract	Inhibit against *Salmonella typhii*, *Staphylococcus aureus*, and *Trichophyton rubrum*	[25]
		Inhibit against *Candida albicans* and *Trichophyton mentagrophytes*	[26]
	Diterpene furan	Inhibit against *Trametes versicolor* and *Fomitopsis palustris*	[27]
Anti-depressants	The water extract	Immobility time	[28]
Anti-diarrhea	The aqueous decoction	Minimum Inhibitory Concentration (MIC) and Minimum Kill Concentration (MCC) of *Shigella flexneri*	[4]
Anti-helminthic	The stem ethanol extract	Decrease in the number of larvae-3 *Ascaridia galli*	[29]
Anti-inflammatory	The water extract	Decrease COX-2 expression	[30]
Anti-cancer	The ethanol extract	IC_{50} against HepG2 cells	[31]
		IC_{50} value HeLa human cervical carcinoma cells	[32]
		Nilai IC_{50} value WiDr human cervical carcinoma cells	[33]
Anti-malaria	The water extract	Growth of *Plasmodium falciparum* strain 3D7 dan IC_{50} extract	[34]
		Heme polymerization inhibition (IC_{50}) of *Plasmodium falciparum*	[35]
Antioxidant	The methanol extract		
		Percent value of DPPH, superoxide, and hydroxyl radicals inhibition	[36]
Atherosclerosis	The leaf methanol extract	Decreased cell number and atherogenic index	[24]
Jaundice	The sap extract	a non-significant decrease in total bilirubin levels in hyperbilirubinemia (jaundice) rats	[37]
Nephrotoxic	The water decoction and brackish water	Kidney damage and harmfulness significantly increase blood urea nitrogen (BUN) levels.	[38]
Anti-diabetes Mellitus	The stems and roots ethanol and aqueous extract	IC_{50} inhibitory value	[39]
	The ethyl acetate extract	Percent values of α-amylase and α-glucosidase Inhibition	[36]
Hyperlipidemia	The methanol extract	Total cholesterol reduction of various extract doses	[40]
Cardioprotective	The leaf chloroform extract	Decreased cardiotoxicity	[41, 98]

4. Pharmacological Activities

According to the findings of the article-based research, the Yellow Root engages in sixteen different activities. This type of research was conducted *in-vitro* and *in-vivo* (**Table 2**).

The most pharmacological activity of *Arcangelisia flava* (L.) Merr is inhibition on the cellular pathway or protein target. It can be determined by *in-silico* compound activity profiling. A schematic illustration of their possible mechanism action on important diseases is shown in **Figure** . Significant progress in this field was owed to the use of computational approaches and essential tools that were able to provide valuable information on the structural characterization of protein targets and the compounds necessary for favorable interaction and desired inhibitory activity.

The molecular activity of several phyto-chemicals in *Arcangelisia flava* (L.) Merr as a drug candidate is shown in **Table 3**. A few *in-silico* research on this plant may be starting points for developing novel bioactive drug pharmacological activities.

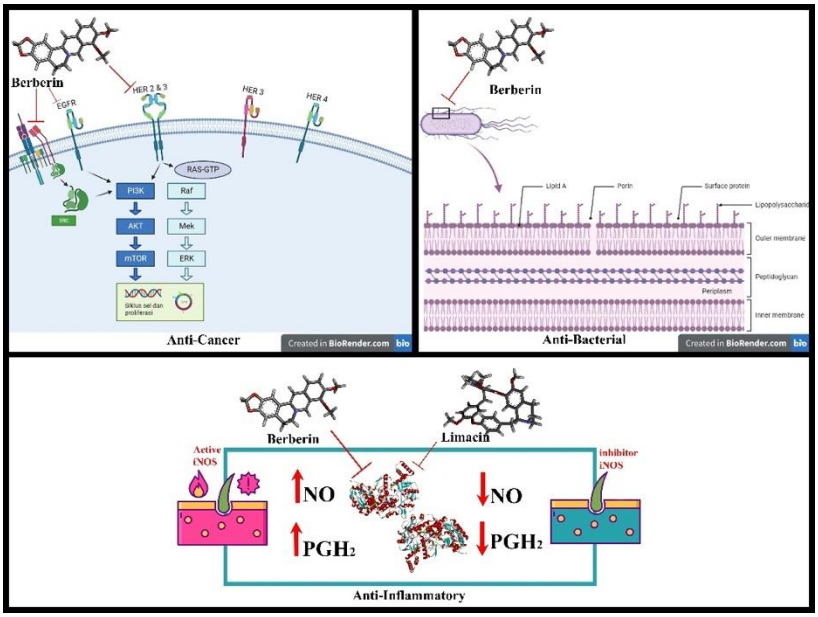

Figure 3. The potency of *Arcangelisia flava* (L.) Merr polyphenols in a cellular pathway inhibition.

Table 3. Bioactivity of *Arcangelisia flava* (L.) Merr using an *in-silico* study.

Activity	Receptor	Result	Reference
Anti-bacterial	Antimetabolites and inhibition of cell wall synthesis, protein synthesis, and nucleic acid synthesis	Berberine showed affinity as a protein and cell wall synthesis inhibitor	[17]
Anti-inflammatory	Inhibitor nitric oxide synthase (iNOS) PDB: 4NOS	Limacine showed affinity as an iNOS inhibitor	[18]
	Inhibitor nitric oxide synthase (iNOS) PDB: 3E7G	Berberine showed affinity as an iNOS inhibitor	[18]
Anti-cancer	HER2 inhibitor TAK-285 PDB ID: 3PP0	Berberine-6 (deleting N-8) showed affinity as an HER-2 inhibitor	[1]
	EGFR-1, EGFR-2, EGFR-3 and EGFR-4 Inhibitor	Berberine had the highest negative free energy and lowest inhibition constant for all EGFRs	[11]
	Proto-oncogene tyrosine-protein kinase Src inhibitor PDB ID: 2HCK	Berberine showed the lowest free energy of binding as an SRC inhibitor	[42]

Structure-activity relationships of proto-berberines showed Protoberberines with different types of positions of the O-alkyl substituents on rings A, C, and D had their effects against Gram-positive, Gram-negative, and fungal microorganisms. Berberine and columnbin are alkaloids that can interfere with peptidoglycan cross-bridges that hold together the bacterial cell wall so that the *interference will* cause the cell wall layer to not be *formed* intact and cause cell death [43].

Yu H et al, 2019 showed molecular docking predicted that jatrorrhizine might inhibit bacterial drug efflux through the binding of NFX as anti-bacterial activity. A hydrophobic cleft, H-bonds, and electrostatic interactions between jatrorrhizine and amino acid residues were formed in the binding site, providing extra stability to the complex and contributing to a stable NorA-jatrorrhizine complex. This may be associated with inhibited bacterial drug efflux and synergistic activities against MRSA. Palmatine with *H. pylori* strains resistant showed that the substituent of secondary amine at the 9-position of Palmatine was the main factor for antibacterial potency. Palmatine had an ionizable nitrogen that was beneficial for the accumulation of small-molecule antibacterial in gram-negative bacteria [45]. Yellow Root contains furano-diterpene such as 6-hydro-xyarcangelisin, 2-dehydroarcangelisinol, tinophyllol, and 6-hydroxyfibleucin. In general, diterpenoids were have *p*-benzoquinone ring C may have a role in the antimycobacterial activities and the substituents at C-6 and C-7 in ring B could considerably influence the antitubercular activity [46].

4.1. Aphrodisiac

Yellow Root is included in the list of plant species used as aphrodisiac. This plant extract boosted the introduction activity, but as the dose of the extract increased, the activity dropped [47]. Locomotor activity increased at a dose of 250 mg/kg BW, but at doses of 150 and 200 mg/kg BW were decreased. Therefore, it can be inferred that a dose of 250 mg/kg BW of the extract increased locomotor activity, which was more than that of Neo Hormoviton capsules [48].

4.2. Anti-microbial

Yellow Roots stems ethanolic extract exhibited anti-microbial effects by looking at the diameter value of the inhibition zone of *Streptococcus mutans* of 8.39 mm, *Porphyromonas gingivalis* of 5.88 mm, and *Enterococcus faecalis* of 9.31 mm [21]. This extract also inhibited *Escherichia coli* and *Staphylococcus aureus* by 12.27 mm and 14.44 mm, respectively [27]. The methanol extract inhibited the growth of *Pseudomonas fluorescens* at 7.18 mm [23], while the chloroform extract inhibited the growth of *Aeromonas hydrophila* at 17.25 mm [49]. Another crude extract was also active against *Staphylococcus aureus* and *Bacillus cereus* (49). The water extract inhibited the growth of *Salmonella typhi* (19.35 mm), *Staphylococcus aureus* (16.98 mm), *Trichophyton rubrum* (19.78 mm) [25], *Candida albicans* (16.31 mm) and *Trichophyton mentagrophytes* (6.55 mm) [26]. Apart from the extract, pachybasin showed an anti-microbial activity by looking at the MIC value against *E. coli* (64.0 μg/mL), *B. subtilis* (64.0 μg/mL), *M. luteus* (64.0 μg/mL), *S. cerevisiae* (64.0 μg/mL), *C. albicans* (64.0 μg/mL), *A. niger* (64.0 μg/mL), *A. flavus* (64.0 μg/mL), *S. aureus* (32.0 μg/mL) and *F. oxysporum* (16.0 μg/mL) [13].

4.3. Anti-depressant

The anti-depressant impact of Yellow Root water extract (312 mg/kg BW) produced the best effect on the immobility time of male white Balb-c mice utilizing the forced swimming test [28]. It was also discovered that berberine inhibited monoamine oxidase inhibitor (MAO)-A. MAOs are enzymes that catalyze the oxidative deamination of amines, are dependent on FAD, and could remove the neuro-transmitters norepinephrine, serotonin, and dopamine from the brain [51]. Berberine modulates depressive symptoms by inducing antidepressant-like effects in rodents, as measured by the forced swim test and the tail suspension test. Their antidepressant effects were not comparable to those of the standard antidepressant desipramine at 20 mg/kg. This compound may exert an antidepressant-like effect by interacting with adrenoceptors, 5-HT, dopamine receptors, and monoamine oxidase, thereby increasing NA, 5-HT, and dopamine levels in rodents' brains [52]. Jatrorrhizine at 25 and 50 M strongly inhibited 5-HT and NE uptake in synaptosomes, indicating that it can disrupt 5-HT and NE reuptake routes in synapses [53].

4.4. Hepatoprotective

The stem methanol extract of Yellow Root at 250 mg/kg BW for 28 days did not elevate SGPT or SGOT levels in rats. This treatment range indicated a safe dose to protect hepar [54]. However, in this extract at 500 and 750 mg/kg BW, there was a significant increase in SGOT levels accompanied by histopathology demonstrating congestion of hepatic blood vessels and minor bleeding in the glomerulus and interstitial. Higher oral doses of 400 and 800 mg/kg BW substantially prevented the biochemical parameter changes (SGOT, SGPT, GGT) as well as elevated serum transaminases and transferases, a symptom of damaged liver cell membranes following acetaminophen administration [56]. Palmatine reduced hepatotoxicity by inhibition of oxidative stress and apoptosis, and TUNEL with a decrease in plasma AST, ALT, hepatic malondialdehyde, apoptosis, and an increase in hepatic glutathione [56].

4.5. Jaundice

In local traditional medicine, the decoction of the bark of Yellow Root was believed to cure jaundice [10]. Berberine is responsible for its bilirubin-lowering ability to prevent jaundice. Recent studies have determined that this sap extract statistically did not cause a significant decrease in the total bilirubin levels of the phenylhydrazine-induced male *Rattus norvegicus* (40). The post-treatment bilirubin levels of phenobarbital (0.13 ± 0.06) were lower than this extract (0.16 ± 0.05) [37]. So, Yellow root sap extract did not prevent jaundice potential by possessing bilirubin-lowering levels. Several new research thought that berberine had many mechanisms to induce hyperbilirubinemia, including an increase in the free bilirubin concentration by displacing bilirubin from serum-binding proteins and causing jaundice, interfering with bilirubin metabolism in infants [57], increasing liver enzymes and bilirubin, and inducing liver and kidney enlargement [58].

4.6. Antidiarrhea

In testing the antidiarrheal activity *in-vitro*, the decoction Yellow Root extract had the Minimum Inhibitory Concentration and Minimum Kill Concentration against the bacterium *Shigella flexneri* ATCC 12022 of 1.2% and 2.4%, respectively. The decoction of their stem bark was not toxic *in-vivo* with an LD_{50} > 31.5 g/kg BW. This decoction at 48 mg/kg BW was given twice a day reducing bacteria to 100% on the fifth day [4]. Berberine shortened the duration of diarrhea. Moreover, it inhibited ion transport (blocked basolateral K^+ channel) chloride ion-producing colonic epithelia in humans unable to secrete into the intestinal cavity and to lead antidiarrheal. It also prevented mucosal adenylate cyclase and intestinal ion secretion [59]. The effect of gut microbiota dysbiosis by berberine repaired the enteric nervous system's structural and functional integrity. It may be associated with preventing the gut from dysmotility, increasing long GI transit time, and reshaping gut microbial structure [60].

4.7. Anthelmintic

The 70% ethanol extract of Yellow Root stem had an effect as an anthelmintic against 1000 infectious larva-3 *Ascaridia galli* in broilers aged two weeks. At 104 mg/400g BW of extract had strong anthelmintic power by giving a higher number of dead larvae [29]. Isoquinoline alkaloids (berberine and palmatine) suppressed GI nematode infections at 8 g/kg by exhibiting inhibitory capabilities against worm movement [61]. Alkaloids act on the nervous system of helminths and cause paralysis. These paralyzed helminths in the digestive tract are inadequate to remain adhered to the intestinal wall of the host and are removed through peristalsis [70-71]. *Strongyloides venezuelensis* third-stage larvae (L3) were also tested for berberine's efficacy as a treatment for helminthic illnesses transmitted through the soil [64].

4.8. Anti-Inflammatory

The Yellow Root aqueous extract had an anti-inflammatory on the cyclooxygenase-2 enzyme expression in Wistar rats stimulated with Complete Freunds Adjuvant (CFA) at 450 mg/kg BW [30]. The *in-silico* research strategy used inducible Nitric Oxide Synthase (iNOS) as a receptor and Nitric Oxide (NO) as a regulator of inflammation promotion. Inflammation will induce NOS and COX-2, which will cause increased levels of NO and PGE2 [65]. The human iNOS crystal structure used is complex with AT2 and had the PDB ID 3E7G [66] and 4NOS (SEITU). Phytochemical constituents in Yellow Root had potential anti-inflammatory effects with a specific mechanism by inhibiting iNOS using a molecular docking approach [18]. Berberine suppresses NF-B signaling via a signaling pathway that is dependent on sirtuin-1 and is associated with inflammation [75]; [76], also inhibits T helper cell (Th)1/Th7 differentiation, IFN-γ, IL-17, IL-6, IL-1β and TNF-α [69]. Additionally, berberine inhibited the binding of AP-1 that mediated levels of prostaglandin E2 and COX-2 expression. So berberine had a high potential to play a role in anti-inflammatory activity. Then, palmatin also had an anti-inflammatory effect via increasing prostaglandin E2 (PGE2) levels and decreasing platelet-activating factors in gastric tissue [70].

4.9. Immunomodulatory

Yellow Root extract at 0.7 gr was used as an immunostimulant. The activated mitogenic induces cell mitosis and stimulates the development of cellular defense (leukocytes) and prevents phagocytizing pathogens. Steroids, flavonoids, phenol, and tannin [49] have immunity functions as mitogens that might be able to activate cellular defense [71].

4.10. Nephrotoxicity

Pramono *et al.* [118] analyzed the blood biochemical and histological profiles of renal and uterine in Wistar female rats by giving Yellow Root decoctions of salty water and water. All decoctions (1.25, 2.5, and 5 g/kg BW) caused kidney damage significantly affecting blood urea nitrogen (BUN) levels. The kidney histopathological at 5 g/kg BW of water decoction showed blood capillary destruction, damage to the epithelium, necrosis of cells, degenerative uterine damage, and inflammatory infiltration. This activity was caused by berberine absorption which harmful to renal function and the uterus [85-86].

4.11. Anti-cancer

Yellow root ethanolic extracts could act as an anti-cancer on HepG2 cancer cells [31] and WiDr

colorectal cancer cells [33]. The cell proliferation decreased significantly within 48 and 72 hours after treatment with IC_{50} of 77.5% and 64.3%, respectively. Then its activity on colorectal WiDr cancer cells was tested using an MTT assay by comparing different areas, namely Samarinda, Banjarmasin, East Barito, Malinau, and Balikpapan. The lowest IC_{50} value was from the Malinau district with a value of 114.119 µg/mL.

Their anti-cancer activity on hepatocellular carcinoma HepG2 cell lines showed a high cytotoxic effect at 109.14 µg/Mr. It significantly decreased intact cells, increased early apoptosis cells of HepG2, and inhibited cancer cell proliferation selectivity. Berberine induces tumor cell apoptosis by activating TP53 (wild-type tumor protein p53) and controlling Apaf-1 regulation. Palmatine was proven selectively to inhibit breast cancer cell proliferation [31].

Yellow Root leaves chloroform extract at 180 µg/ml caused WiDr cells to go into apoptosis against almost all colorectal cancer cells and induced apoptosis cells at 82.153% and cells undergo necrosis up to 11.802% [74]. The stem methylene chloride extract exhibited higher efficacy against cancer cells than cyclohexane, methylene chloride, crude extract, and methanol extracts. Human cervix cancer cells (HeLa) and normal human diploid embryonic lung cells (MRC5) of methylene chloride extract exhibited high selectivity index (SI) values of 25.0 and 161.4, respectively. Those who displayed excellent selectivity ought to be able to provide safer treatment. This selectivity index (SI) is inversely proportional to the IC_{50} value of their toxicity against cancer HeLa and MRC5 cell lines (8.8 and 56.5 µg/ml) [32].

The IC_{50} values for the ethanolic extract on the HeLa, MCF-7, and WiDr cancer cell lines were 467±70; 136±17; and 213±79 µg/ml, respectively. On the other hand, a higher IC_{50} value caused necrosis and cancer to grow malignantly, giving rise to a worse prognosis [75]. Palmatine potentially as a metastatic prostate cancer treatment [90], decreases the small intestine and colon tissue in colorectal cancer and dysplastic [67]. The extracts were used as empirical tumor therapy, as shown by the informants' experience in research [7]. The Yellow Root had a gastrointestinal condition that gradually improved and was deemed cured after two months. The tumor on his body had vanished after three months.

4.12. Anti Malaria

The Yellow Root aqueous extract inhibition *P. falciparum* strain 3D7 growth was described by the IC_{50} value of 1.811 mg/ml [34]. Berberine had antimalarial activity by inhibiting *Plasmodial* with an IC_{50} value of 0.96 µg/ml [19] and dose-dependently decreased telomerase activity throughout a range of 30-300 µM. New *in-silico* research using homology modeling and docking studies showed berberine specifically could inhibit DNA synthesis and telomerase reverse transcriptase (TERT) sequence from *Plasmodium falciparum (*PfTERT) [77]. Columbamine, jatrorrhizine, and thalifendine had antiplasmodial with IC_{50} values between 1 and 10 µM. Stigmastan-5-en-3-ol had been isolated from an aqueous extract of this bark and suppressed heme polymerization as potent antimalarial effects (IC_{50} = 601 ppm) at 2 mg/ml with 76.22% (16). The solid antiplasmodial activity from methylene chloride extract of this stem showed the highest inhibition than other plants with IC_{50} of 0.4 µg/ml against *Plasmodium falciparum* [32]. The community in Kalimantan stem and drank this yellow root to cure jaundice and avoid mosquito bites. It is also used in traditional Vietnamese medicine to treat illnesses. The growth of the chloroquine-resistant *P. falciparum* strain FCR-3 was found to be inhibited by twenty-four extracts from this plant, with an EC_{50} value of less than ten g/mL [78].

4.13. Antioxidant

The methanol extract of Yellow Root had an EC_{50} value of 25 µg/ml (18), a % inhibition value of 79.68%, and a hydroxyl radical inhibition was 90.51% against DPPH (*1,1-diphenyl-2-picrylhydrazyl*). While the inhibition of superoxide radicals in the ethyl acetate extract was a value of 22.16% [36]. Berberine showed intense antioxidant activity by inhibiting reactive oxygen species in both broncho-epithelial cells (16HBE) and macrophages, which helps to explain a variety of biological actions (RAW264.7), decreased the total ROS production and reactive oxygen/nitrogen species, increased associated genes (Gpx2, Nqo1) [80], and significantly increased CSE expression of antioxidant genes as a cytoprotective response [81]. It also worked through the Pl3K/Akt/ Bcl-2 and Nrf2/HO-1 pathways to reduce oxidative stress. The P13K/AKT/Bcl-2 pathways play a crucial part in the antioxidant action. Through the activation of Nrf2, Berberine also raises HO-1 mRNA, which regulates the expression of numerous antioxidant enzymes, including LPO, NO, GSH, and SOD (96). It can negatively affect NADPH oxidase by activating AMPK [83].

4.14. Atherosclerosis

Atherosclerosis is caused by several kinds of conditions such as heart attacks and strokes by inflammation and hyperlipidemia through oxidative stress. Yellow Root extract was found to lower the atherogenic index and the number of foam cells. Berberine in this plant reduced lipid synthesis in the body and had a protective effect on atherosclerosis by lowering cholesterol. It significantly increased hepatic low-density lipoprotein (LDLR) receptor expression, decreased LDL levels and total cholesterol, and reduced aortic lesions [84]. In another study, the methanol extract from leaves lowered the atherogenic index and the number of foam cells using rats fed a high-fat and fructose diet for 45 days. According to the number of foam cells, the

extract at 250 and 500 mg/kg BW showed a decrease of 20.86 and 14% [24].

4.15. Anti-Diabetes Mellitus

Current studies have shown some mechanisms of the antihyperglycemic from Yellow Root ethanol and aqueous extracts of leaves, stems, and roots that observed their activity against inhibiting the α-glucosidase enzyme. This measurement was seen from the value of p-nitrophenol produced. The IC_{50} values for aqueous extracts from leaves stems, and roots were 195.161, 138.9881, and 48.68632 µg/mL, while the IC_{50} values of the ethanolic extract were 365.8793, 123.0814, and 66.9616 µg/mL, respectively. So the roots had better activity in inhibiting the α-enzyme than the leaves and stems and the aqueous extract had the best activity in blocking of the glucosidase enzyme [39]. Then, the ethyl acetate was found to inhibit α-amylase and α-glucosidase was 78.96%, which was higher than that of acarbose (54.85%) [36]. This extract contained most flavonoids with high dose oral administration (28 mg/kg of a fraction) on rats that had been conditioned as type 2 Diabetes Mellitus ATAU (that had been induced with type 2 Diabetes Mellitus). It reduced blood glucose levels to 165 mg/dL and increased peroxidase inhibition and catalase activation [85]. Isoquinoline alkaloid, palmatine, improved the comorbidity of diabetic neuropathic pain and depression with a decrease in the up-regulated expression of the P2X7 receptor and then release of TNF-α and IL-1β [86].

Although berberine possesses anti-inflammatory and antioxidant properties, it can treat diabetic neuropathy, diabetic nephropathy, and diabetic cardiomyopathy [87]. It has multiple mechanisms for antihyperglycemic activity, such as improving insulin resistance and recovering islet function, promoting insulin secretion and enhancing the activity of *β*-cells pancreas, inhibiting gluconeogenesis in the liver [90], increasing insulin sensitivity [91], inducing glycolysis in peripheral tissue cells [92], modulating gut microbiota to prevent the effect type 2 diabetes mellitus of changes in gut microbiota composition [93], suppressing intestinal absorption of glucose [94], regulating the glucolipid metabolism [95] and modulating lipids metabolic effects.

4.16. Hyperlipidemia

The methanol extract of Yellow Root as anti-hypercholesterolemia uses an animal model induced by cholesterol administration. This extract at 9.5, 19.0, and 38.0 mg/20 g BW lowered total cholesterol by 10, 13, and 17%, respectively. The 38.0 mg/20 gr BW dose caused the most significant reduction in total cholesterol [40]. Berberine has a beneficial effect on lowering LDL with a reduction rate of about 20 to 50 mg/dL and a reduction in TG of about 25 to 55 mg/dL [96]. The use of berberine taken together with simvastatin increased the expression of the LDLR gene significantly higher than that of berberine monotherapy. These results indicated that combination is more effective than monotherapy with simvastatin (28.3%) or berberine (26.8%) [97].

4.17. Cardioprotective

The long-term use of doxorubicin as cancer chemotherapy results in cardiotoxicity, it was the basis for this investigation. The parameters observed were vacuolization and necrosis. Doxorubicin cardiotoxicity was reduced at doses of 250 and 500 mg/kg BW by a chloroform extract of Yellow Root leaves [98]. Palmatine at 1, 5, and 10 µM for 16 hours reduced the high mobility group box 1 (HMGB1) release in LPS-stimulated RAW 264.7 cells [99]. So palmatine may benefit from preventing inflammatory damage to the myocardium after infarction. In animal models, palmatine successfully prevented myocardial injury by lowering inflammatory and oxidative damage by reperfusion [100].

4.18. Toxicity of *Arcangelisia flava* (L.) Merr

Toxicity research was conducted in the decoction of Yellow Root and was given orally to rats at 1.25, 2.5, and 5.0 g/kg BW. Measurement of hematological parameters, general blood biochemistry, histopathology, and closely related biochemistry of liver function were studied. The results indicated that the Yellow Root water decoction adversely affected liver function. After 28 days of therapy, female Wistar rats did not exhibit any harmful effects from this decoction. In subchronic toxicity, the extract at 250, 500, and 750 mg/kg BW resulted in hepatic vascular congestion but not necrosis. Histopathological observation of the kidney showed no inflammation but slight bleeding in the glomerulus and interstitial space [101].

CONCLUSION

Arcangelisia flava (L.) Merr is a plant traditionally used to treat jaundice/hepatitis, liver disorders, cancer, antimalaria, and diabetes. Some previous studies have shown that this plant and its compounds have the potential for human health, including as an aphrodisiac, antimicrobial, antidepressant, antidiarrhea, anti-helminthic, anti-inflammatory, anticancer, antimalarial, antioxidant, atherosclerosis, jaundice, antidiabetes Mellitus, hyperlipidemia, and cardioprotective. Pharmacological activity is associated with berberine. A limitation of this review is that no clinical trials have been conducted. Therefore, the effect of *Arcangelisia flava* (L.) Merr on humans remains unclear, so further research is needed to explore the effects on humans.

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DECLARATION OF COMPETING INTEREST

The authors declared that they have no conflicts of interest related to the publication of this study.

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