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Phytochemicals and Therapeutic Potential of *Polyalthia bullata* King, *P. macropoda* King, and *P. longifolia* (Sonn.) Benth. & Hook.f. ex Thwaites (Annonaceae)

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ABSTRACT

Polyalthia is a genus of plants in the Annonaceae family with various bioactive compounds. This review summarizes the main constituents and pharmacological activity of three *Polyalthia* species, namely, *P. bullata*, *P. longifolia*, and *P. macropoda*. The literature on the phytochemistry and pharmacology of *Polyalthia* species was searched and reviewed utilizing databases such as PubMed, ScienceDirect, Scopus, and Google Scholar. The review revealed that *Polyalthia* species are rich sources of terpenes and alkaloids with various pharmacological activities. *P. longifolia* showed the most diverse and potent activities, followed by *P. bullata* and *P. macropoda*. The compounds isolated from *Polyalthia* species exhibited different modes of action, such as inhibiting enzymes, signaling pathways, cell proliferation, and oxidative stress. Therefore, *Polyalthia* species have great potential as natural sources of bioactive compounds for the treatment and prevention of various diseases. Further research is needed to elucidate the safety, efficacy, and optimal dosage of *Polyalthia* extracts and compounds, as well as to explore their synergistic effects and possible applications in modern medicine.

Keywords: *Polyalthia* spp., Annonaceae, Phytochemicals, Pharmacological activity, Bioactive compounds

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INTRODUCTION

Polyalthia Blume is a genus in the Annonaceae family with roughly 127 species in the world [1]. Species of this genus are mostly located in Asia, from the southern parts of Sri Lanka and India to the northern parts of Australia and Melanesia. *P. bullata* King is generally described by polymorphism in wing coloration and male genital structures. *Polyalthia* sp. is primarily found in tropical regions and has significant morphological diversity, and is commonly distributed in Myanmar, the Malay Peninsula, and Borneo [2]. *P. longifolia*, commonly known as the False Ashoka or Indian Mast Tree, is a prominent evergreen tree admired for its ornamental value and utility in traditional medicine. Native to the Indian subcontinent, it is widely cultivated in tropical and subtropical regions for its striking appearance and various uses [3]. On the other hand, *P. macropoda* is a species of evergreen tree found in tropical regions, particularly in Southeast Asia. This species is notable for its botanical features, potential medicinal and ecological significance [4].

Research studies on the extract of *Polyalthia* have shown hundreds of bioactive compounds, such as terpenes and alkaloids, including cytoprotective ability, such as anticancer [5-7], antitumor [8-10], antiinflammatory [11-13], antiplasmodial [14-16], antiviral [17, 18], antifungal [19], and antibacterial [20-22]. *P. longifolia* is often known as Ashoka in India because of its shape as a stupa. It is often planted as a landscaping tree in Taiwan to decrease excessive noise [23]. *P. longifolia* is an evergreen tree with green leaves that can grow to over 12 m tall [24]. A significant constituent of *P. longifolia* is shown to have antibacterial [25-28], anticancer [29], antitumor [29-31], and antidiabetic properties [32]. *P. bullata* is utilized as an herbal aphrodisiac by local citizens, particularly in Indonesia, Thailand, and Malaysia. The leaf, flower, and roots of the *P. bullata* plant have important roles in the treatment of diabetes, general tonic, skin disorders, and hypertension [33, 34]. *P. macropoda*, commonly known as *P. macropada* syn. *Monoon borneensis* is found in Southeast Asia, including Singapore, Indonesia, and Malaysia [35, 36]. Present phytoconstituent studies on *Polyalthia* species revealed that alkaloids and clerodane diterpenoids are the most abundant compounds in three species. The information on the medicinal uses, chemical constituents, and pharmacological activity of *P. bullata*, *P. longifolia*, and *P. macropoda* is still limited. Therefore, the objectives of this review are to document the medicinal uses, phytochemical constituents, and pharmacological activities of *P. bullata*, *P. macropoda*, and *P. longifolia* and to explore their therapeutic properties and potential health benefits, as well as to identify areas for further research and development in their medicinal and pharmaceutical applications.

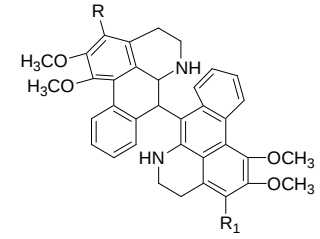
MATERIALS AND METHODS

P. bullata is a medicinal plant belonging to the Annonaceae family and the *Polyalthia* genus. It is traditionally used as a tonic for women and as an aphrodisiac for men [37]. It is used to treat

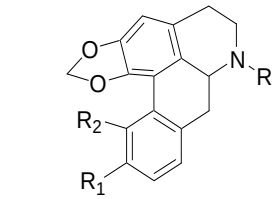
problems of the skin and sexual needs and is a general tonic for men. The root is boiled and then eaten. Leaves, flowers, and roots of *P. bullata* are used to treat diabetes and high blood pressure. *P. bullata* extract improves the function of the liver and resolves severe liver disorders. *P. longifolia* is used to treat helminthiasis, constipation, the digestive system, hypertension, diabetes, fever, and skin diseases [38]. *P. macropoda* is a versatile medicinal plant with a wide range of applications in traditional and modern medicine, like rheumatic fever, gastrointestinal ulcers, and leishmanicidal activity against *Leishmania donovani* [39].

Phytochemical Constituents

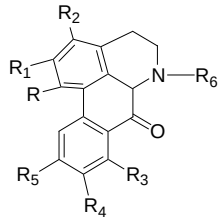
The bioactive compounds such as diterpenes, flavonoids, and alkaloids present in *P. macropoda*, *P. longifolia*, and *P. bullata* are shown in Table 1 and Fig. 1. *P. longifolia* is a rich source of mucilage, diterpenoids, tannins, and alkaloids [40, 41].



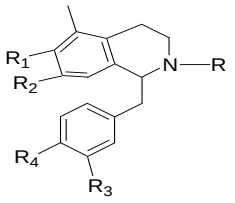
R=R1=OCH3
R=H; R1=OCH3
R=R1=H



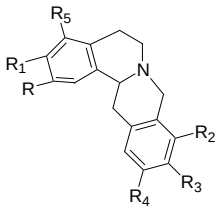
R1=OH; R2=H; R= OCH3
R1=H; R2= β-OH; R=CH3



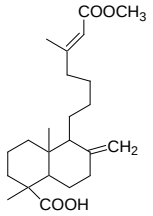
(6) R=R1=OCH2O; R2=R3=R4=R5=H



(7)
R=R3=H;R1=OCH3;R2=R4=OH



(8) R=R1=R2=OCH3; R3=R3=R5=OH;R4=H



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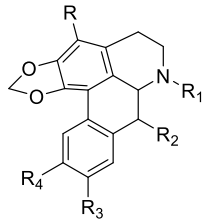
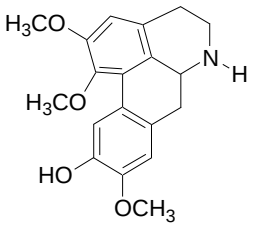


(10) R2=β-OH; R=R1=R3=R4=H



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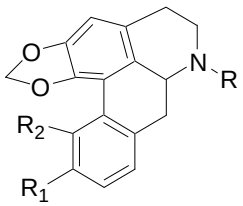
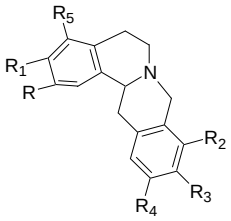
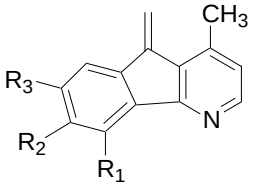


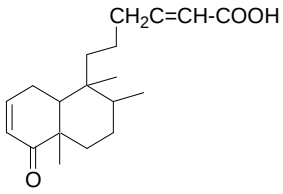
(12) R=CH3;R1=β-O; R2=α-CH3
(13) R=CH3;R1=α-O; R2= β-CH3
(14) R=H;R1=β-O; R2=α-CH3



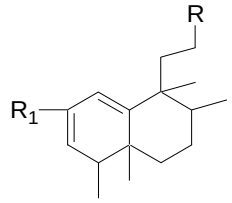
(15) R=R3=OH;R1=R2=OCH3;R4=R5=H



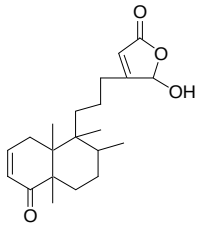
(16) R1=R2=OCH3;R3=OH
(17) R1=H;R2=R3=OCH3
(18) R1=H;R2=OCH3;R3=OH
(19) R1=R2=R3=H



(20)R1=H;R=OH
(21)R1=H;R=OCH3



(22) R=HOOC-CH=C-CHO;R1=H
(23) R=HOOC-CH=C-CH3;R1=H
(24) R=HOOC-CH=C-CHO;R1=H
(25) R=HOOC-CH=C-CH2OH;R2=H



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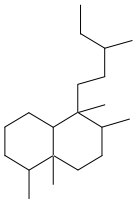

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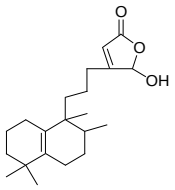

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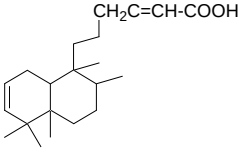

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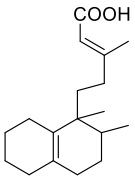

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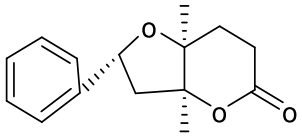

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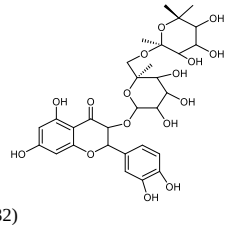

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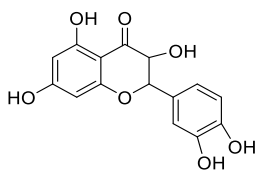

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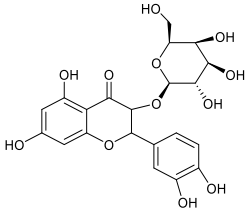

(34)

Fig. 1 Chemical structures of active compounds (1-34) of *P. bullata*, *P. macropoda* and *P. longfolia*.

Pharmacological Activity

Antileishmanial Activity

Leishmaniases are disorders that have a considerable probability of death and morbidity in the world, with 380 million people at risk and 70,000 deaths from the disease documented every year [42]. Leishmania parasites are responsible for a wide variety of diseases, including tegumentary leishmaniasis, *L. infantum*, and visceral leishmaniasis (VL), which is caused by the *Leishmania donovani* [39, 43]. Antileishmanial activity compounds such as (4S, 9R, 10R) methyl 18-carboxy-labda-8,13(E)-dien-15-oate (9), amphotericin B, and clioquinol were found in many herbs in nature [44].

The *P. macropoda* contains compounds with antiprotozoal activity in its stem bark, such as labdane diterpene compound, (4S, 9R, 10R) methyl 18-carboxy-labda-8,13(E)-dien-15-oate (9) [39] at a concentration of 1.5 mg/mL. They can inhibit the parasite's cells by approximately 100% [45, 46]. *P. longifolia* extract contains clerodane diterpene, 16-oxo-cleroda-3,13(14)E-dien-15-oic acid (polyalthialdoic acid) (22) [47, 48]. They play a major role in the inhibition of antiprotozoal, noncytotoxic, and antileishmanial activities for the prolongation of the treatment to over six months [49].

The mechanism of antileishmanial activity of bioactive compounds against leishmaniasis involves significant effects on the parasites, particularly on the integrity of their plasma membranes, leading to membrane rupture. This breakdown of the plasma membrane is a hallmark of apoptosis. Bioactive compounds, such as clioquinol, not only reduce parasite cell volume but also impact mitochondrial membrane potential, contributing to their antileishmanial effects [50]. A study by Shang *et al.* [51] and Liu *et al.* [52] has revealed that *P. bullata* contains a significant quantity of clioquinol.

Various research studies have found that mitochondria play a crucial role in the death process of trypanosomatids. Because this sensory organ is specific to these protozoa, the breakdown of the mitochondrial membrane potential is recognized as one of the parasites' characteristic metabolic processes of cell death. It was reported by Misra *et al.* [53] that 16α-hydroxycleroda-3,13Z-dien-15,16-olide (20) from *P. longifolia* contributes as an active antileishmanial agent and suggests that this compound has potential therapeutic effects against leishmaniasis. This highlights the importance of natural products in drug discovery and the potential of *Polyalthia* spp. in developing treatments for parasitic infections.

Sexual Treatment

The common symptoms of male hypogonadism requiring therapy include male infertility and sexual dysfunction. These symptoms are really what distinguish this condition from others [54]. Many herbal therapies for male sexual dysfunction are commonly used in India, Borneo, and Indonesia [54, 56]. Low levels of testosterone in the blood are considered abnormal, and several forms of testosterone replacement therapy are used to address the condition [57, 58]. *P. bullata*, an aphrodisiac and tonic for men and women, is used in Southeast Asian countries to treat abnormal levels of testosterone in the blood. Ingesting the *P. bullata* plant has significant effects on sexual enhancement, by decreasing epididymis weight and increasing blood testosterone production [59]. The extracts of *P. bullata* also played an important role in increasing blood testosterone levels following treatment [60].

Low testosterone levels in the blood are also referred to as late-onset hypogonadism and androgen deficiency. In most cases, males over the age of 40 are associated with a variety of factors, including decreased quality of life [61], cardiovascular disease [62], obesity [63], type-2 diabetes [64], and depressive illness [65]. Regardless of the lack of strong evidence that herbal supplements increase testosterone levels in males, there are really plausible mechanisms of action. Factors such as the antioxidant and anti-inflammatory activities of various herbs, including *P. bullata*, may reduce primary testosterone counterregulatory hormones like cortisol [66-68] and alter the efficiency of major enzymes involved in testosterone synthesis [66, 68-70]. For instance, several human and animal investigations have shown that oxidative stress and inflammatory stress have an opposite relationship with testosterone levels [63, 71]. Antioxidant and anti-inflammatory compounds play a major role in increasing the testosterone level, as numbers researchers have demontrsated that *P. bullata* is a rich source of these compounds [70-72].

Anti-diabetic Activity

Diabetes mellitus is a severe, multifactorial condition marked by hypoglycemia (excessive glucose levels) and glucose intolerance. Diabetes is among the top contributors to death rates in Malaysia and all over the world. There are reports of various adverse effects caused by synthetic diabetes medications, particularly insulin, such as hypoglycemia, weight gain, and cognitive impairment. *P. bullata* is an effective medicinal natural product for anti-diabetic treatment, in which it can control blood glucose levels [74]. The extract of aerial parts of *P. longifolia* at doses of around 300 mg/kg showed hypoglycemic activity when used on rats with alloxan-induced diabetes [38]. In another study on *P. longifolia* extracts as an anti-diabetic, findings demonstrated that glucose uptake using the L6 cells and HepG2 was more than in control cells [75,76]. On the other hand, there is no statistically significant difference between the positive control and L6 cells.

The presence of bioactive compounds, such as flavanols, terpenoids, flavonoids, and phenolic compounds, demonstrated that glucose was generated from the liver for enhancing glucose uptake in hepatic cells and thus regulating the intracellular signaling pathway [77]. Additionally, the most popular method for preparing an extract of naturally occurring plant-based bioactive chemicals is to use solvents like methanol, ethyl acetate, and hexane to extract the phytochemical compounds, flavonoids, phenolics, and oils. Various plant parts, such as flowers and leaves, are used in the extraction procedures [74, 78, 79]. A study by Huang *et al.* [79] reported that *P. macropoda* contains bioactive compounds that significantly contribute to controlling hypoglycemia by inhibiting dipeptidyl peptidase (DPP-4). This mechanism of action suggests that these compounds have potential as antidiabetic agents, helping to manage blood sugar levels effectively. It was reported by Chen *et al.* [80] that *Polyalthia* spp contain a high amount of bioactive compounds, including azafluorene 5-hydroxy-6-methoxyonychine (isoursuline), polycerasoidol, anonaine, bidebiline E, (+)-stepharine, 23-(2-furyl)tricosa-5,7-diynoic acid, liriodenine, lanuginosine (oxoxylopine), N-trans-feruloyltyramine, oxostephanosine, and lysicamine.

Gastro-protective Activity

Bismuth cholinergics, sucralfate, histamine H2-antagonists, and proton pump inhibitors are currently the main medications used to treat gastric ulcers. These medications also provide acid-independent therapy [81].

Table 1 The phytochemical constituents of *P. bullata*, *P. macropoda* and *P. longifolia.*

Sources	Structure number	Class of compounds	Name of constituent	Pharmacological activity	Plant part	References
P. bullata King			Bisdehydroaporphine	Sexual treatment and anti-diabetic activity	sb	[94]
	(1)	Alkaloid	7,7-bisdehydro-O-methyl isopiline			
	(2)	Alkaloid	7 dehydronornuciferine-7'dehydro- O-methyl isopiline			
	(3)	Alkaloid	Urabaine			
P. macropoda King			7-Substituted aporphine	Antileishmanial activity and gastro-	sb	[95,97]
(Monoon borneenes)	(4)	Alkaloid	Oliveroline N-oxide	protective activity		
	(5)	Alkaloid	Oliveroline			
			Oxoaporphine			[99]
	(6)	Alkaloid	Liriodenine			
			Benzylisoquinoline			[97]
	(7)	Alkaloid	Coclaurine			
			Tetrahydroprotoberberine			[95]
	(8)	Alkaloid	Thaipetaline			
			Labdane diterpene ester			[39]
	(9)	Diterpene	(4S,9R,10R) methyl 18- carboxy-labda-8,13E-dien-15-oate			
P. longifolia			7-Substituted aporphine	Anti-diabetic activity	sb	
	(10)	Alkaloid	Noroliveroline			
	(4)	Alkaloid	Oliveroline N-oxide		b	
	(5)	Alkaloid	Oliveroline		sb	[97,98]
	(11)	Alkaloid	Ushinsunine		L	
	(6)	Alkaloid	Oxoaporphine		st & sb	[10]
			Liriodenine		L	
			Proaporphine		b	[10, 101]

Continue Table 1

(12)	Alkaloid	O-methyl bulbo-capnine ß-N-oxide			
(13)	Alkaloid	O-methyl bulbo-capnine a-N-oxide		st & sb	
(14)	Alkaloid	N-methyl nandigerine ß-N-oxide		st & sb	
		Tetrahydroprotoberberine		b, sb & L	[95]
(15)	Alkaloid	Stepholidine			
		Azafluorene	Anti-inflammatory and cytotoxic activity	b	[101]
(16)	Alkaloid	Darienine			
(17)	Alkaloid	Polyfothine	Anti-microbial	sb & L	[10]
(18)	Alkaloid	Isoncodine			
(19)	Alkaloid	Onychine			
		Clerodane diterpene	Antileishmanial and antioxidant activity	L	[102,103]
(20)	Diterpene	16α-hydroxylcleroda-3,13Z-dien-16,15-olide			
(21)	Diterpene	4β,16α-dihydroxycleroda-13(14)Z-dien-15,16-olide		sb	
(22)	Diterpene	16-oxo-cleroda-3,13(14)E-dien-15-oic acid (Polyalthialdoic acid)		sb	
(23)	Diterpene	Kolavenic acid		sb	[105]
(24)	Diterpene	3,13E-kolavadien-15-oic acid			
(25)	Diterpene	16-hydroxycleroda-3,13(14)E-dien-15-oic acid		sb & L	
(26)	Diterpene	16-hydroxycleroda-4(18)13-dien-15,16-olide		sb	
(27)	Diterpene	Cleroda-6(18)13E-diene-15-oic acid			
(28)	Diterpene	Halimane diterpene 16-hydroxy-ent-halima-5(10)13-dien-15,16-olide			
(29)	Diterpene	Ent-halima-5(10)13E-dien-15-oic acid			[104]
(30)	Diterpene	Ent-halima-1(10)13E-dien-15-oic acid			
(31)	Styryllactone	Tetrahydrohydrofuro[2,3]pyran-5-one (Altholactone)			[106]
		Flavonoid		L	[107]
(32)	Flavonoid	Rutin			
(33)	Flavonoid	Quercetin			
(34)	Flavonoid	Hyperoside			

*sb: stem bark, L: leave, b: bark, st: stem

However, gastric-illness therapy has a huge downside nowadays because most medications on the market are frequently accompanied by adverse effects. Overall, gastro-protective therapy seems to dramatically diminish gastric aggressive factors by reducing gastric secretion and acidity while improving cytoprotective factors by improving the stomach mucosal barrier [82].

P. macropoda contains many bioactive compounds, including diterpene (4S, 9R, 10R) methyl-18-carboxy-labda-8,13(E)-diene-15-oate (9), which are present in the stem bark [38]. It is the main compound for the production of amide derivatives, which have excellent gastro-protective properties and have low basal cytotoxicity [24, 83-85].

Anti-inflammatory and Cytotoxic Activity

P. longifolia extracts contain diterpenoids, including 16α-hydroxylcleroda-3,13Z-dien-15,16-olide (20), which showed a significant difference in terms of cytotoxicity against hepatoma cell lines (G2 and 3B) [12, 24, 86]. *P. longifolia* extracts play a significant role in inhibiting cancer activity following therapy, particularly in human nasopharyngeal carcinoma and human gastric cancer cell lines [12]. Phytochemical compounds identified in *P. longifolia* extracts possessed chemoprevention, anti-inflammatory, and antioxidant activities [24] as shown in Table 1. These compounds are present in the *P. bullata*, *P. macropoda*, and *P. longfolia.* Diterpenoid 16-oxo-cleroda-3,13-(14)E-dien-15-oic acid (22) plays a major role in the IKBα kinase inhibition with an IC_{50} of 14.9 μM [12,38]. 5-Hydroxy-2 (5H)-furanone isolated from *P. longifolia* has a safe redox potential in the rat sub-brain parts [86]. These compounds' anti-inflammatory mechanism involves inhibiting inflammation by activating the MAP_K, NF-B, and Nrf_2/ARE signaling pathways [86]. In normal physiological responses and inflammatory processes, the $PI3_K$-Akt/NF-B signaling pathways perform distinct functions [87-89].

Antimicrobial Activity

The sensitivity of bacterial strains depends on bacterial types (gram-positive and gram-negative bacteria) to the bioactive compounds. Many researchers discovered that bioactive compounds seemed to have a greater effect on gram-positive bacteria than gram-negative bacteria [90].

P. longifolia root bark, stem bark, leaves, and flowers are considered excellent sources of compounds with antifungal and antibacterial activities. Previous literature reviews have described diterpenoid compounds in *P. bullata*, *P. macropoda*, and *P. longfolia*, as shown in Table 1. In particular, 16α-hydroxylcleroda-3,13Z- dien-15,16-olide (20), 4β-16α-dihydroxycleroda-13(14)Z-dien-15,16-olide (21), and 16-hydroxycleroda-4(18)13-dien-15,16-olide (26), have activity against bacteria. The highest antibacterial activity was shown by diterpenoid 16α-hydroxylcleroda-3,13Z-dien-15,16-olide (20) [38]. The diterpenoid 16-hydroxylcleroda-3,13Z-dien-15,16-olide (20) had a positive effect on human ovarian cancer cells and also showed antibacterial activity [90]. The mechanisms of action of bioactive substances were related to the deactivation of cellular enzymes, which depended on the degree of penetration of the compound into the cell or were induced by changes in membrane permeability. The antibacterial activity of bioactive compounds was found to be related to their phenolic structure in all the literatures. The structure of gram-negative bacteria is more complex than that of gram-positive bacteria; thus, gram-negative bacteria are more resistant to bioactive compounds [90].

Antioxidant Activity

Herbs and plants have recently been suggested as a potential natural source of antioxidantsm, such as hydroxycinnamate esters, tannins, and flavonoids [91, 92]. The antioxidant compounds have a significant positive impact on human health [42, 90, 93]. They reduce the free radicals. *P. longifolia* extracts contain diterpenoids, especially clerodane diterpenoids and 16-hydroxycleroda-3,13(14)E-dien-15-oic acid (25), which have excellent antioxidant activities. They inhibit anion production and esterase release in formyl-l-methionyl-l-leucy-l-phenylalanine-activated human neutrophils. This is conclusive evidence of its excellent antioxidant activity on human neutrophil respiratory burst and formation of apoptotic bodies. These are effective for inhibiting p38 signaling, kinase B, and calcium metabolism [12]. These mechanisms allow the molecules to function as singlet oxygen quenchers, metal chelators, reducing agents, and hydrogen donors. This multifaceted redox activity contributes to the antioxidant activity [92, 95].

Opportunities and Challenges

Plant-derived bioactive compounds have gained popularity due to their wide availability and low cost. Moreover, many people believe in their efficacy. However, several scientific, technological, and cultural challenges are hampering their development. First, pharmaceutical companies often resist the development of low-cost medicinal products. Secondly, the appropriate dosages of plant-derived bioactive compounds are still not well established, which could have deleterious effects on human health. Third, some plant-based products contain high concentrations of bioactive compounds, which may pose risks to both human and animal health. Furthermore, additional research on *Polyalthia* spp. is necessary to explore their potential medicinal applications, particularly as antioxidants, antidiabetic, and anticancer agents, given the current limitations in understanding their full therapeutic potential and the mechanisms of action of their bioactive compounds.

Conclusions and Future Research Needs

Many Southeast Asian countries utilized *Polyalthia* species as traditional medicine, including *P. bullata*, *P. longifolia* and *P. macropoda*. Most *Polyalthia* extracts are rich in phytochemical compounds, including alkaloids and clerodane diterpenoids. Current research showed that extracts of *P. bullata*, *P. longifolia* and *P. macropoda* are good sources of terpenes and alkaloids and have potential as anticancer, anti-inflammatory, antimicrobial, and anti-diabetic agents. *P. macropoda* has anti-lishmanial activity, while *P. bullata* has antidiabetic activity and is also used for sexual treatment. *P. longifolia* extracts have greater effectiveness in terms of pharmacological activity than the other species. Further investigation is needed to explore the potential medical applications of these plants based on their phytochemical and pharmacological properties. Additional research is essential to evaluate their efficacy, safety, and potential side effects, aiming to develop them as modern pharmaceuticals for enhancing human health.

Conflicts of Interest

The authors confirm that they have no conflicting interests.

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