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GENUS ALPINIA, A POTENTIAL POWERHOUSE OF BIOACTIVE: A REVIEW

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ABSTRACT: Alpinia is the largest and most taxonomically complex genus in the Zingiberaceae family. This includes about 230 species and widely spread throughout forests in tropical and subtropical Asia. Many of species are herbs and rich sources of bioactive compounds that extensively used in various purposes ranging from its use in culinary, prevention of diseases and ornamental purposes. There is no reported systematic method to differentiate many of the species within the genus particularly species used in medicinal preparations except heavily used ones. Many species in this genus could have the potentials to be utilized commercially due to valuable phytochemicals but never subjected to any kind of systematic study. Therefore, a proper morphological and physicochemical identification is a must to maintain sustainable exploration of many species of the genera. This review focuses on gathering information regarding genus Alpinia including morphological characteristics, phytochemicals, and their biological activities which provide information for further advance research work.

INTRODUCTION: From the ancient era, green plants are being used to treat many diseases. Indigenous cultures of African and Native Americans used herbs in their healing rituals, while others developed traditional medical systems such as Siddha, Ayurveda, and Unani [1]. Since then, plant sources are widely used in the preparation of medicines in traditional cultures worldwide. In the last few decades, the use of herbal medicine has increased exponentially as natural alternatives to synthetic chemicals [2]. Recently use of herbal medicine is getting popular all over the world due to its natural origin and minimum side effects.

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Green plants are an important source of bioactive compounds [3]. Zingiberaceae is one of the medicinally important plant family which many species are commercially important at present [4]. Zingiberaceae is a family of flowering plants consists of aromatic perennial herbs with rhizomes, comprising about 52 genera and more than 1300 species [5].

Considerable number of species of Zingiberaceae family have been studied for their potential biological activities. The important genera under Zingiberaceae are Curcuma, Kaempferia, Hedychium, Amomum, Zingiber, Alpinia, Elettaria and Costus [6]. Alpinia is one of the most important genera of the Zingiberaceae family. It includes about 230 species [7]. Most of the species are distributed in tropical and subtropical Asia including; India, Sri Lanka, Malaysia, China, and Japan. Few species are found in Australia and Pacific Islands [8].

Alpinia galanga, Alpinia calcarata, Alpinia nigra, Alpinia macalensis, Alpinia vittata, Alpinia purpurata, Alpinia zerumbet, Alpinia blepharocalyx, Alpinia officinarum, Alpinia nutans, Alpinia fax, Alpinia oxyphylla, Alpinia katsumadai, Alpinia mutica and *Alpinia speciosa* are some major species subjected to many studies. Alpinia and Amomum are the largest two genera that consist the highest number of endemic species of family Zingiberaceae in Sri Lanka [9]. In the genus Alpinia, *Alpinia galanga, Alpinia calcarata, Alpinia nigra* and *Alpinia macalensis* are the species commonly found in natural habitats in Sri Lanka [3]. Some species belongs to genus Alpinia is known using the same common name but consists of different notable morphological characteristics and diverse uses in traditional medicinal applications. Since, these herbs have promising potentials and are widely used, proper morphological and physicochemical identification is must but not systematically studied yet. This review intends to provide a comprehensive insight into the morphology, phytochemistry, and pharmacology of the genus Alpinia.

Studies on Genus Alpinia: Plants of genus Alpinia have been widely used for different purposes. For instance, *Alpinia galangal* Willd is an important ingredient for curries, used to preserve food and fruits and use as a flavoring agent [10], in the preparation of meats and soups in Southeast Asia and the preparation of beverages in Europe [11]; *Alpinia vittata, Alpinia purpurata, Alpinia calcarata,* and *Alpinia zerumbet* are cultivated as ornamental plants [12]; *Alpinia blepharocalyx* is a natural dye [13] and *Alpinia officinarum* used in medicinal diets [13]; wines [14]; sauces and flavorings [15]. Moreover, Alpinia plants are broadly utilized as traditional medicines in India, China, and Japan to treat many diseases such as indigestion, gastralgia, vomiting, *etc*. [16] Thus, many investigations on the phytochemicals [17, 18, 19] and bioactivities of this genus has been carried out since 1955 [7, 20, 21]. Consequently, Alpinia species were proved to have various biological activities including antibacterial [22], hypoglycemic [23], antiulcer [24], antiemetic [25], antitumor [26], cardioprotection [27], anti fungi [28], neuroprotection [29] and anti-anxiety activities [30].

Many morphological and physiochemical studies have been reported on heavily used parts of the Alpinia plants such as rhizome [31], leaves [32], stem [33], roots [34], inflorescence/ flowers and buds [35], fruits and seeds [36]. With all pieces of evidence, leaf, fruits and rhizomes are important in obtaining different phytochemical effects as a medicine as well as in other uses.

Morphological Characteristics of Genus Alpinia: Genus Alpinia consists of evergreen herbs. Most species grow in low to mid-elevation forests and form clumps. Normally stems are 1-3 m high. But some species tend to grow much larger [37]. When defining the characters that distinguish the genus from other genera in the Alpinioideae and in classifying its species Alpinia has always been considered as a taxonomically complex genus [37]. Hence generic limits within the tribe Alpinieae are difficult to understand. But some genera can be easily recognized by their morphological characters or geographical distribution. It is hard to identify a universal character for species assigned to Alpinia [38].

The widely used *Alpinia galanga* plant is a perennial herb. It grows up to a height of about 5 feet. It has slightly aromatic tuberous roots. The rhizome is around 3.5-7.5 cm in length. The leaves are long and oblong or lanceolate in shape. Ligules are short and rounded. Flowers are greenish white and having ovate lanceolate bracts. The calyx is tubular, and corolla lobes are oblong. Claw is green in color with a pair of subulate glands at the base. The blade is white, striated with red and broadly elliptic, lobed at the apex, with a pair of subulate glands at the base of the apex. The fruit is orange-red and small in size [39].

Alpinia nigra is a biennial herb. It has leaves which protected by showy bracts and pinkish terminal inflorescences [40]. It has a leafy stem about 1.5-3 m high. Sessile or subsessile leaves are about 20-40 cm long and pointed at the end. The fruit is a berry having many seeds. The pericarp of the berry is thin and green when it is young. When it gets old, it becomes black and brittle [41].

Alpinia nutans plant has attractive glossy foliage emerge from dense stands of pseudostems. Leaves are lanceolate. The terminal inflorescence has smaller bracts with much larger, red and yellow labellums [42]. *Alpinia officinarum* is a herbaceous plant can grow up to 10 feet in height. The leaves

are lanceolate. It has white flowers with red streaks, growing from a spike at the top. Rhizomes are thin and tough and have orange flesh with a brown coating. They have an aromatic odor and a pungent flavor [43].

Alpinia zerumbet is an evergreen perennial that grows in upright clumps 8 to 10 ft. It bears funnel-formed flowers with white or pink perianths. Labella is yellow with red spots and stripes [44]. There are three stamens in this flower, but only one has pollens. There is a globose fruit with many striations [45].

During a recent study of the genus *Alpinia* Roxb. of the family Zingiberaceae in Sri Lanka and India, researchers came to notice that the Indian specimen is significantly different from the Sri Lankan species and it is rather a different species, probably a new one. *Alpinia fax* is a herb having sessile leaves and exceeding 2 m in height. Leaf lamina is broadly lanceolate with acuminate tip, attenuate base and entire margin. Inflorescence elongates with age are consisting about 60 flowers, and they are 12-18 cm in length [46].

A study on the initiation sequence of the floral organ in *Alpinia oxyphylla* [47] has been reported that it resembles the developmental pattern (sepal, petal, inner androecium, outer androecium, and gynoecial primordium) reported for *Alpinia calcarata* [48].

Flowers in the ginger families possess either one fertile stamen with two anther sacs (Zingiberaceae and Costaceae) or one stamen with only one anther sac (Marantaceae and Cannaceae) [49]. Usually, all Asiatic Alpinia species consists a flower terminally on the leafy shoots [50]. These characters distinguish Alpinia from the Afro-American Renealmia. Most Afro-American Renealmia species produce inflorescences on a separate, leafless shoot from the rhizome, but some members of the Alpinieae also show this kind of inflorescences [37]. Therefore, recognizing Alpinia only by some specific characters (*e.g.*, plesiomorphic characters) is not completely successful [50].

Most Alpinias promote outcrossing by attracting large bees, birds and even bats as pollinators [51]. Flexistyly is a novel floral mechanism promoting outcrossing in several species of Alpinia which styles move up or down depending on the timing of anther dehiscence [51, 52, 53]. The lateral staminodes of the flowers in species of Alpinia are small, reduced to swellings at either side of the base of the labellum, or are absent [54]. Usually, extrafloral nectaries are absent, and the fruit is spherical and indehiscent or fleshy [49].

Karunarathne *et al.,* 2013 highlighted that it is difficult to use only vegetative characters to differentiate species in genus Alpinia for Sri Lankan species. Further, Morphological analysis revealed the segregation of Alpinia species rather depending on both vegetative and floral characters [55]. Recently, several studies have used molecular data to explore phylogenetic relationships within the family [49, 56, 57] to differentiate species in genus Alpinia, which provides more information and lead for accurate identification.

Chemical Constituents: Majority of the chemical compounds isolated from genus Alpinia has been shown multiple medical potentials and possess novel chemical structures [58, 59]. About 200 compounds have been isolated and identified from about 45 species of the genus Alpinia. Total of 143 diarylheptanoids including 66 acyclic diarylheptanoids, 11 cyclic diarylheptanoids, 50 diarylheptanoid and flavonoid conjugates, 10 dimeric diarylheptanoids and 06 other diarylheptanoids [60, 61, 62] and more than 150 terpenoids including 17 monoterpenoids [63], 55 diterpenoids [64], 132 sesquiterpenoids [65] and one triterpene named as 2, 3, 22, 23-tetrahydroxy-2, 6, 10, 15, 19, 23- hexamethyl-6, 10, 14, 18-tetracosatetraene [58] has been isolated from different parts of genus Alpinia. Moreover, 24 lignans [66], 71 flavonoids [67], 66 phenolics [68], 07 steroids [69], 08 Alkaloids [70], 06 stilbenes [71], 01 ester [72], 03 fatty acids [73] and two glycosides [2] has been isolated.

According to the reported research works, diarylheptanoids, terpenes, and flavonoids are abundant in several members in the genus. Diarylheptanoids, especially diaryl-heptane-flavonoids conjugates, are characteristic components for the genus Alpinia [65]. Rubraine, isorubraine, and sumadain C were three new monoterpene-chalcone conjugates obtained from *Alpinia katsumadai*. (E)-1-(1-terpinen-4-olyl)-3-methoxystilbene, 2α-cinnamoyl cineole, 2β-cinnamoyl cineole tonkinensis gagnep., 2a-(p-

hydroxycinnamoyl) cineole, (1S, 4R, 6R)-1,4-epidioxy-p-menth-2-ene and (1R,4S,6R)-1,4-epidioxy-p-menth-2-ene are some examples for monoterpenoids identified in genus Alpinia [74]. (E)-labda-8(17), 12-diene-15, 16-dial is widely distributed diterpenoid in Alpinia exhibited a number of bioactivities, such as antibacterial, α-glucosidase inhibition, antifungal, antiglycation, HIV-1 integrase, and neuraminidase inhibitory activities [64]. Sesquiterpenoids include trans,trans-farnesol, nerolidol and mainly caryophyllene oxide, caryophyllenol-I and caryophyllenol-II *Alpinia galanal*. Tectochrysin, chrysin, 5-hydroxy-30,40,7-trimethoxy favanone, Kaempferol-3, 40-dimethyl-ether are some flavonoids present in Alpinia [67]. Galanganal; galanganols A and B were major lignans found from rhizomes of *Alpinia galanga* (L.) Willd [66].

Other than above chemical constituents some glycosides [75], lignins [76], phenylpropanoids and volatile oils [77] were found in the genus Alpinia. A new katsumadain dimer named "katsumadain" has been isolated from *Alpinia katsumadai* [78]. A plant growth inhibitor named dihydro- 5, 6-dehydrokawain has been isolated from *Alpinia speciosa* leaves [79]. Moreover, polysaccharides, sito-sterol and daucosterol have also been identified [80].

Potential Medicinal and other Uses: Investigations on Alpinia species afforded a total of 544 chemical constitutes [2]. The crude extracts of Alpinia species and their chemical constituents were found to possess various biological activities. According to the researchers' point of view, *Alpinia galanga* is gaining big interest due to its biological activity [4]. 1'S-1'-acetoxychavicol acetate is the major compound so far reported with various biological activities isolated from *Alpinia galangal* [21]. Other species in genus Alpinia also have been reported many biological activities. Mainly reported were antibacterial, antioxidant, anticancer, anti-inflammatory, antiemetic, antiulcer, anti-platelet activities. Also, they also showed neuroprotective, hepatoprotective, and hypolipidemic bioactivities as well as insecticidal effects.

1. Anticancer Activity: Different experiments and assays have been carried out to determine the anti-cancer activities on species of Alpinia. One study showed that the 80% aqueous acetone extract from the *Alpinia officinarum* rhizomes can inhibit melanogenesis in theophylline-stimulated murine B16 melanoma 4A5 cells, and galangin is the representative constituent of the species. It may induce Bel 7402 cells apoptosis through the mitochondrial pathway [81]. Meanwhile, diarylheptanoids from *Alpinia officinarum* cause distinct effects on the translatome of B-Lymphoblastoid cells [82]. The diarylheptanoids isolated from the seeds of *Alpinia blepharocalyx* have exerted a pronounced antiproliferative effect against human HT-1080 fibrosarcoma and highly liver-metastatic [83]. *Alpinia katsumadai* shows significant inhibitory effects on the growth of Bel 7402 and L0-2 cells [84]. Diterpenes from *Alpinia galanga* exert significant cytotoxic activities [85]. The dried fruit methanolic extract of *Alpinia oxyphylla* has been shown to significantly contribute to the skin tumor promotion as well as ear edema in female mice [86].

2. Antioxidant Activity: The flavonoids extracted from *Alpinia officinarum* have been shown a variety of biological activities at non-toxic concentrations in organisms. Results from different studies reported that enzyme activities in cells could be modulated by galangin through antioxidative and free radical scavenging activities and also it suppresses the genotoxicity of chemicals [87]. Methanol extracts of leaves of many Alpinia species show significant anti-oxidant activities. Among them, high antioxidant activities have been shown by *Alpinia zerumbet, Alpinia zerumbetvariegata,* and *Alpinia purpurata*. The leaves and flowers of *Alpinia galanga* show highest chelating and β-carotene bleaching abilities [87]. Strong free radical scavenging activity of *Alpinia galanga* has also been observed [88].

3. Antibacterial Activity: Three diarylheptanoids isolated from *Alpinia katsumadai* revealed a significant antimycobacterial activity on EtBr accumulation and efflux. Moreover, it has been reported a synergistic effect in combination with rifampicin, which should be taken into consideration when screening lipophilic plant extracts for their antimycobacterial and modulating activities[89]. The leaf extract of *Alpinia nigra* show mild antibacterial activity compared to tetracycline, and the LC_{50} (lethal concentration 50) value of the

extract was implied a promising cytotoxic effect in the brine shrimp lethality bioassay [70].

4. Antifungal Activity: During the screening for phytochemical potentiators with antibiotic action, an antimicrobial diterpene has been isolated from *Alpinia galangal.* Researchers have been suggested that the antifungal activity of this compound is due to a change in membrane permeability arising from membrane lipid alternation [90]. Good antifungal activities against *Trichophyton longifusus* found to possess in ethanolic extracts of *Alpinia galangal* [91]. A Diterpene compound extracted from *Alpinia galanga* enhanced the antifungal activity of quercetin and chalcone against *Candida albicans*. 21 strong antifungal activities of *Alpinia galanga* has been demonstrated by the zone of inhibition assay [21].

5. Antiviral Activity: Despite several therapeutic advancements, there is an urgent need to develop a new therapeutic method for human immunodeficiency virus (HIV). Currently, AIDS remains a major global health issue and an investigation hotspot. 1'S -1'-acetoxychavicol acetate (ACA), which was isolated from *Alpinia galanga,* has been shown that it can be a blocker in HIV-1 replication in peripheral blood mononuclear cells[92]. Not only for HIV, but Alpinia species have also been shown inhibitory effects toward other viruses too. Out of ten, two diarylheptanoids isolated from *Alpinia officinarum* have been reported potential anti-viral activity against influenza virus A/PR/8/34 (H1N1) *in-vitro* [93].

6. Anti-Inflammatory and Analgesic Activity: The ethanolic extract and three pure components from *Alpinia katsumadai* seeds possess anti-inflammatory activities which have been investigated for the production of inflammatory mediators and some potential underlying mechanisms in lipopolysaccharide-induced inflammation RAW264.7 cells [94]. *Alpinia katsumadai* extract has remarkable analgesic effects too [95].

7. Antidiabetic Activity: The powdered rhizome and its methanol and aqueous extracts of *Alpinia galanga* show hypoglycemic activity on blood glucose levels by significantly lowering the blood glucose level of normal rabbits [96]. Methanolic extract of aerial parts of *Alpinia galanga* was effective in controlling blood glucose level and improve lipid profile in euglycemic as well as diabetic rats [97]. The methanolic extracts of *Alpinia galanga* show a considerable inhibition of the hemoglobin glycosylation via α -amylase and α-glucosidase activities [98].

8. Antitumor Activity: Active compounds such as 1′-acetoxychavicol acetate and 1′-acetoxyeugenol acetate from *Alpinia galanga* were isolated as antitumor principles against Sarcoma 180 ascites in mice [99]. The high dose of methanolic extract of *Alpinia galanga* treated albino mice showed no estrogenic activity [100]. Two isolated compounds from the rhizomes *Alpinia galanga,* 1,7-bis (4-hydroxyphenyl)-1,4,6-heptatrien-3-one and bisdemethoxycurcumin were examined for their effectivenesses on the human melanoma A2058 and showed that it could significantly inhibit the proliferation of melanoma cells in the cell viability assay [101].

9. Antiulcer Activity: A significant antisecretory and cytoprotective action of *Alpinia galanga* ethanolic extract which responsible for its antiulcer activity have been reported on experimentally induced gastric ulcers in rats [24]. The methanol and ether extract of *Alpinia officinarum* showed obvious effects against mice on ulcer induced by water-immersion stress method [102].

10. Antiallergic Activity: *Alpinia galanga* was found to be effective in the treatment of allergy. The isolated compounds could inhibit the release of antigen IgE mediated in passive cutaneous anaphylaxis reactions in mice [81].

11. The Digestive System Protection: The volatile oil of *Alpinia villosum* exhibits inhibition effects, but non-volatile compounds exhibit promotion effects as a kind of traditional herbal medicine in China [103]. Two compounds that have been isolated from *Alpinia katsumadai* showed antiemetic activities on copper sulfate induced emesis in young chicks [10].

12. The Cardiovascular System Protection: Some compounds of the Alpinia species have been proven to exhibit cardiovascular system protection. 5, 6-dehydrokawain, isolated from *Alpinia mutica*, showed strong inhibition on platelet aggregation induced by arachidonic acid with very lower

concentrations in IC_{50} values [104]. Intravenous treatment with the essential oil of *Alpinia zerumbet* decreases blood pressure in conscious deoxy-corticosterone-acetate-salt hypertensive rats, and this action is significant when compared with uninephrectomized controls [105].

13. Hepatotoxicity and as an Immunomodulator: The crude extract of *Alpinia galanga* at 200 and 400 mg kg^{-1} has been shown the hepatoprotective effect on hepatotoxicity in rats [106]. Hot water polysaccharide extracts of *Alpinia galanga* (L.) Willd. Shows marked stimulating effect on the reticuloendothelial system and increased the number of peritoneal exudate cells and spleen cells of mice [107].

14. Insecticidal Effect: Two sesquiterpenoids; Epinootkatol and nootkatone in fruits of *Alpinia oxyphylla* Miq. shown insecticidal activities against larvae and adults of *Drosophila melanogaster* with IC_{50} values of 11.5 mM and 96 mg per adult, respectively [108]. Sukhirun *et al.,* 2010 reported that hexane crude extract of *Alpinia galanga* gave the highest control efficiency compared to dichloromethane, ethyl acetate, and 95% ethanol to adult *Bactrocera dorsalis.* Thus, this extract can be used as an alternative for control this insect pest in the future. A strong repellency against *L. serricorne* adults was exhibited by essential oil and eucalyptol from Alpinia [109].

Abdullah *et al.,* 2015 reported that essential oil from *Alpinia galanga* and 1,8-cineol poses antifeedant, repellent and toxicity activity against Asian subterranean termites *Coptotermes gestroi* and *Coptotermes curvignathus.* Further, studies have shown that *Alpinia galangal* can also use to control *Plutella xylostella, Callosobruchus chinensis, Sitophilus zeamais, Tribolium castaneum,* and two parasitoids[110, 111]. Seed extracts showed mortality against *Tyrophagus putrescentiae* and *Dermatophagoides pteronyssinus* due to the effect of acaricides present in *Alpinia galangal* [112].

15. As a Natural Dye: Some species in genus Alpinia has been used to extract natural dyes. Wang *et al.,* 2013 reported that natural dyes were extracted from the leaves and stems of *Alpinia blepharocalyx* K. Schum and the experiment revealed that optimal amount of dye could be obtained when extraction was performed at 80 °C for 4 h under 20 min ultrasound, in the presence of 10g/l sodium hydroxide, with extraction at a plant/water ratio of 1:20. In addition, *Alpinia purpurata* is also an important source of raw material in natural dye production [113]. Roots and stalks of *Alpinia galanga* Willd. can be used as sources of coloring agents in calico printing and it is a major dye yielding plant in India [114]. Galangin is the major chemical compound acting as the coloring agent in *Alpinia galanga* [115].

CONCLUSION: According to the review, genus Alpinia is a potential powerhouse with several lead molecules which are responsible for numerous bioactivities. Hence, isolation and identification of those important molecules are needed for the opening of a new window in therapeutics. Although there are about 230 species for the genus Alpinia, only 35 were investigated for their chemical constituents and bioactivities.

Most of these compounds have been isolated from the rhizomes, seeds, leaves or fruits. Therefore, the other parts of the plants of the genus Alpinia should be of interest to researchers to discover more therapeutic compounds in the field of natural product research. Also, much attention should be paid to Alpinia species on further phytochemical and pharmacological studies, which would produce structurally interesting and biologically active compounds with potential use in agricultural and medicinal applications.

Since, Alpinia is the largest, most widespread, and most taxonomically complex genus in Zingiberaceae, still there is no systematic method to differentiate the species within the genera. But the molecular approach is important for a better understanding of the generic boundaries and relationships between species and the evolution of the Zingiberaceae as a whole. Ecological and biological studies should be considered thoroughly because of pollination and dispersal biology are unknown in the majority of species, even the fruits and seeds of many species are unknown.

Finally, it can be concluded that researchers have vast field of research to be discovered than exists at present on medicinally important other Alpinia species which will be more useful in therapeutic

alternatives for treating many diseases as well as other ecological remedies.

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