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Review Article

ETHNOBOTANICAL, PHYTOCHEMICAL, AND PHARMACOLOGICAL PROPERTIES OF NEPENTHES SPECIES: A REVIEW

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ABSTRACT

The genus *Nepenthes* (Nepenthaceae) has been utilized in folk medicine for a long time in India and Southeast Asia countries. They are used in the treatment of leprosy, cholera, night blindness, gastrointestinal discomfort, dysentery, stomachache, and bed-wetting among others. This review highlights the ethnobotanical uses, phytochemicals, and pharmacological activities of both crude extracts and pure bioactive compounds of *Nepenthes* spp. The phytochemical compounds isolated from *Nepenthes* species include flavonoids, terpenoids, tannins, alkaloids, and steroids among other phytochemicals. A wide range of pharmacological activities was exhibited by the crude extracts and pure bioactive components such as antibacterial, antifungal, antimalarial antioxidant, antidiabetic, antiosteoporotic, anti-inflammatory, cytotoxicity, and hypolipidemic activities. This review revealed that many active compounds are present in *Nepenthes* spp. However, many pharmacological screenings such as anticancer, antiviral, wound healing, antihelminthic, antidiarrheal properties, among others have not been carried out yet. Therefore, more biological investigations and phytochemical screenings are required to fully explore the genus *Nepenthes* which may lead to development of new therapeutic agents.

Keywords: Nepenthes species, Ethnobotanical, Phytochemistry, Pharmacological activities.

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INTRODUCTION

Natural products have been used as alternative treatments for various diseases due to their reasonable efficacy and low toxicity [1]. Biologically active compounds from natural resources have always been of great interest to scientists working on different diseases [2]. Plants and plant-based medicines are since been used as the basis of many modern pharmaceuticals used today for the treatment of various ailments [3-6]. Despite the fact that the modern medicines are more accepted worldwide, folk medicines are still being used either as complementary or alternative medicines, especially due to their good therapeutic effects and less side effects [7,8]. The World Health Organization reported that more than 80% of global population from both developing and developed countries uses their indigenous plants for basic health care to treat various health issues [9-11]. *Nepenthes* species is from the family of Nepenthaceae, widely known as pitcher plant that is carnivorous in nature. It is the only genus in the family of Nepenthaceae from the order Nepenthales which produces unique pitcher for trapping and digestion of insect pray to acquire nutrients at habitats that are deprived of nitrogen [12]. The stem of pitcher plant is a climber, subshrubs, or herbs. The pitcher itself is as a result of modification of the leaf blade [13,14]. *Nepenthes* species consists of over 100 species distributed within southern China, northern Australia, New Caledonia, and western Pacific islands with Indonesia, Malaysia, Philippines, India, and Brunei Darussalam considered world's diversity centers of *Nepenthes* [13,15,16]. *Nepenthes* spp. have been utilized in traditional medicine system to treat and control different ailments including gastrointestinal discomfort, such as dysentery, stomachache, and bed-wetting among others [17]. A wide range of phytochemicals were identified and isolated from different species of *Nepenthes* [18-22]. The previous researches showed that *Nepenthes* spp. exhibited many pharmacological actions, including antibacterial, antifungal, antimalarial antioxidant, antidiabetic, and hypolipidemic among others [19-21,23]. The previous studies as mentioned above indicated that *Nepenthes* spp. possesses a lot of ethnobotanical, phytochemical, and pharmacological properties; however, no previous study attempted to summarize these findings. Thus, the objective of this review is to highlight the ethnobotanical use, phytochemistry and the pharmacological activities of both crude extracts and pure bioactive compounds of *Nepenthes* spp.

ETHNOBOTANICAL USE

Nepenthes species have been used in traditional medicines to treat numerous illnesses. It has been reported that the Northeast Indian herbalist prescribed the fluid contain from an unopened pitcher of *Nepenthes khasiana* for the treatment of diabetes mellitus [13]. In addition, the fluid from unopened pitcher of *N. khasiana* is prescribed to cure night blindness, conjunctivitis, ear troubles, and gynecological problems. Khasi people consume the liquid in the morning as a digestive tonic. The grinded powder of the *N. khasiana* pitcher is used to treat cholera. Garo traditional medical practitioners use *N. khasiana* to treat leprosy by applying a fine paste of the pitcher [24]. The people of Dayak Serebuang used the fluid from unopened pitcher of *Nepenthes* to cure stomachache and cough [16]. The root of *Nepenthes* is used traditionally in the treatment of bed-wetting dysentery and stomachache [17]. *Nepenthes ampullaria* and *Nepenthes gracilis* are the two most common species used in folk medicine, where the liquid contain of an unopened pitcher are administered to regulate the menstrual cycle, ease child birth, relieve asthma, treat eye inflammation, and act as a stamina booster [21]. Root decoction of *N. ampularia* was understood to be employed in asthma treatment by Orang Asli from Jakun community in Endau Romping, Johor, Malaysia [25]. The blended leaves of some *Nepenthes* spp. have been used as an astringent in Malaysia [26]. In Malaysia, the decoction of stem of *N. ampullaria* has been consumed to treat malaria [27]. In Vietnam, *Nepenthes mirabilis* is used in the treatment of gastric ulcer, jaundice, high blood pressure, ureteral stones, and hepatitis by traditional medical practitioner [28].

PHYTOCHEMISTRY

Sterols and triterpenes including campesterol, isofuctosterol, stigmasterol, sitosterol, α-amyrin and β-amyrin were identified in free form in *Nepenthes albomarginata*. While in esterified form, campesterol,

stigmasterol, sitosterol, isofucosterol, obtusifoliol, cycloeucalenol, citrostadieno1, cycloartenol, and 24-methylenecycloartanol were identified in *N. albomarginata* [29]. Plumbagin, droserone, hydroxydroserone, and other four new quinones including nepenthone-A, nepenthone-B, nepenthone-C, and nepenthone-E were obtained from *Nepenthes rafflesiana* roots, while the fifth quinone, nepenthone-D was identified [30]. Likhitwitayawuid *et al*. isolated 2-methylnaphthazarin, droserone, isoshinanolone, octadecylcaffeate, and plumbagin from the roots of *Nepenthes thorelii* [20]. A phytochemical screening of different *Nepenthes* spp. (*Nepenthes burbidgeae, Nepenthes tentaculata*, *N. mirabilis, Nepenthes muluensis, Nepenthes rajah,* and *Nepenthes gracilis*) leaves showed that quercetin is detected in *N. burbidgea, N. mirabilis, N. muluensis, N. rajah, and N. gracilis*. Except in *N. gracilis*, Kaempferol was identified in all of the studied pitcher plants. Leucoanthocyanins such as cyanidin was present in *N. gracilis, N. mirabilis,* and *N. rajah* [22]. The compounds epishinanolone, isoshinanolone, kaempferol, plumbagin, quercetin, and shinanolone were successfully isolated from the leaves of *N. gracilis* by Aung *et al.* [26]. A study by Shin *et al.* resulted in the identification and purification of plumbagin from the extract *Nepenthes ventricosa* x maxima leaves [27]. A liquid from the pitcher of *N. khasiana* was found to contained 5-0-methyldroserone and droserone [31]. Plumbagin was isolated from the fresh leaves of *N. gracilis* [32]. A phytochemical analysis of pitcher and leaf extract of *N. khasiana* Hook showed the existence of flavonoids, glycoside, tannins, alkaloids, phytosterols, and saponins [13,23,24]. 13 active compounds including nepenthosides A, nepenthosides B, leonuriside A, koaburaside, 4-hydroxy-2,6-dimethoxyphenyl 6'-O-vanilloyl-β-D-glucopyranoside, (-)-heimiol A, phenylethyl-β-D-glucopyranoside, icariside D_1, rutinoside, syringaresinol, syringaresinol-4'-O-β-D-glucopyranoside, pinoresinol-4-O-β-D- glucopyranoside and lupeone were obtained from the leaves and branches extract of *N. mirabilis* [28]. Phytochemical such as alkaloids, flavonoids, tannins, anthraquinones, phlobatannins steroids, and terpenoids were detected in the screening of *Nepenthes bicalcarata* Hook. F. [21]. Two novel naphthoquinones, namely, nepenthones F and nepenthones G as well as five famous naphthoquinones including droserone, plumbagin, 3-methoxy-7-methyljuglone, 2-methoxy-7-methyljuglone, nepenthone C, and a well-known acetogenictetralone; cis-isoshinanolone were obtained from branches and leaves extracts of *N. mirabilis* [19]. In addition, from the leaves and branches extracts of *N. mirabilis*, five known flavonoids, namely, quercetin, quercetin 3-O-β-D-glucuronide, quercitrin, kaempferol-3-O-α-L-rhamnoside, and (-)-epicatechin were also isolated [19]. 26 biologically active compounds were isolated from *N. mirabilis* (Lour.) Rafarin, and these are identified as nepenthone F, nepenthone G, nepenthoside A, nepenthoside B, cis-isoshinanolone, droserone, plumbagin, 3-methoxy-7-methyljuglone, 2-methoxy-7-methyljuglone, nepenthone C, (–)-heimiol A, 4-hydroxy-2,6-dimethoxyphenyl 6'-O-vanilloyl-β-D-glucopyranoside, leonuriside A, koaburaside, syringaresinol, syringaresinol-4'-β-D-glucopyranoside, pinoresinol-4-O-β-D-glucopyranoside, lupeone, phenylethyl-β-D-glucopyranoside, icariside D_1, phenethylrutinoside, quercetin, quercitrin, kaempferol-3-O-α-L-rhamnoside, quercetin 3-O-β-D-glucuronide, and (–)-epicatechin [33].

PHARMACOLOGICAL ACTIVITIES

Antioxidant

The methanolic leaf extract of *N. khasiana* displayed strong antioxidant properties with the half maximal inhibitory concentration (IC_{50}) of 23.33±0.441, 62.75±0.713, and 38.38±0.425 µg/ml in 2,2-diphenyl-1-picrylhydrazyl (DPPH), superoxide anion, and hydroxyl radical scavenging activity, respectively [24]. The methanol extract of *N. bicalcarata* leaf was investigated for it scavenging activity using DPPH and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) assays which Trolox and butylated hydroxytoluene (BHT) were used as the standards in the respective assays. The leaf extract was found to be more active than standard BHT in the DPPH assay, whereas in the ABTS assay, it was the least active when compared with both standards as indicated by its higher IC_{50} value [21]. Antioxidant properties of the pure compounds isolated from branches and leaves of *N. mirabilis* were studied for their peroxyl radical scavenging and reducing capabilities. Compounds such as nepenthones F, droserone, nepenthone C, cis-isoshinanolone, quercetin, quercetin 3-O-β-D-glucuronide, quercitrin, kaempferol-3-O-α-L-rhamnoside, and (-)-epicatechin were found to exhibited strong peroxyl radical scavenging activities in a dose-dependent manner at 1.0 and 10.0 µM concentrations [19].

Antidiabetic

A study was conducted on the hypolipidemic and hypoglycemic potential of *N. khasiana* Hook pitcher extract in insulin resistance and dexamethasone-induced hyperlipidemia in laboratory rats. At a dosage level of 250 and 500 mg/kg, methanolic extract of *N. khasiana* pitcher actively prevented the increase in the level of cholesterol, glucose, triglyceride, low density lipoprotein with progressive decreased in both high density lipoprotein, and body weight triggered by dexamethasone on tested rats [23]. Hypoglycemic property of methanolic leaf extract of *N. bicalcarata* was reported in the alloxan diabetic induced rats. A dose of 300 mg/kg body weight showed a significant decrease in blood glucose level in a time-dependent manner [21].

Antimalarial

Compounds plumbagin, 2- methylnaphthazarin, droserone, and isoshinanolone obtained from the ethanolic extract of *N. thorelii* roots was evaluated against *Plasmodium falciparum* for antimalarial activity, all the compound exhibited potent activity, especially plumbagin at 0.27 µM where 50% inhibition of response was shown (lC_{50}=0.27 µm) [20].

Antibacterial

The whole plant methanolic crude extract of *N. mirabilis* was found to be active against *Staphylococcus aureus* as assessed using disc diffusion assay [34]. The methanolic extract of *N. bicalcarata* leaf displayed antibacterial activities against gram-positive bacteria *Bacillus subtilis, Bacillus spizizenii* and *S. aureus* with minimum inhibitory concentration (MIC) values ranging from 256 to 1024 µg/ml [21]. Silver nanoparticles synthesized from the *Nepenthes* spp. exhibited a strong inhibitory activity against *S. aureus, E. coli* and *S. enterica* [35].

Antifungal

The hexane extract from *N. gracilis* showed antifungal activity with the MIC and minimum fungicidal concentration of 20 µg/ml against *Candida albicans*, *Issatchenkia orientalis*, and *Trichophyton mentagrophytes*. The compound plumbagin isolated showed strong antifungal activity with the MIC values between 2 and 31 µg/ml against all of the tested fungi [32]. The pitcher liquid extract of *N. khasiana* contained droserone, 5-0-methyldroserone, and purified naphthoquinones which exhibited antifungal activities when tested against *Aspergillus* sp. and *Candida* sp. [31]. The antifungal activity of 3:1 droserone: medroserone mixture tested against *C. albicans, Candida glabrata, Candida krusei,* and *Aspergillus fumigatus* showed MICs of 63, 125, 63, and 250 µg/ml, respectively [31]. The crude hexane extract of *Nepenthes ventricosa* x maxima leaf showed strong antifungal activity against plant fungal pathogens screened, namely, *Alternaria alternata, Aspergillus niger, Bipolaris oryzae, Fusarium oxysporum, Phytophthora capsici, Rhizopus stolonifera* var. *stolonifera*, *Rhizoetonia solani, Sclerotinia sclerotiorum*, of which *R. solani* was the most sensitive [27]. A bioactive compound, plumbagin identified, and purified from the leaves extract of *N. ventrieosa* x maxima showed MIC values between 4.8 and 56.6 µg/ml when screened for antifungal activities against *A. niger, A. alternata, F. oxysporum, P. capsid, R. solani, R. stolonifera, B. oryzae,* and *Sclerotinia scierotiorum* [18]. The methanol extract of *N. bicalcarata* leaf exhibited good activity against non-filamentous fungi *Saccharomyces cerevisiae* and *C. albicans* with MIC ranged from 256 to 1024 µg/ml [21].

CYTOTOXICITY

The brine shrimp lethality toxicity at 50% (LC_{50}) methanolic leaf extract of *N. bicalcarata* was determined through probit analysis, and it was estimated to be 73.3 µg/ml which may be considered as mildly

toxic according to Meyer *et al.* said that high toxicity is indicated by a LC_{50}<30 µg/ml [21,36]. The viability of LLC-MK2 cells treated with different plumbagin concentrations were measured by NRU assay. Moreover, a 50% cytotoxicity concentration of plumbagin at 0.60 µg/ml was observed [32]. Acute cytotoxicity study showed that the *N. khasiana* methanolic extract of leaf neither demonstrated any toxicity nor mortality at a 3000 mg/kg bw dose level in rats [13].

HEPATOPROTECTIVE

Hepatoprotective activity of *N. khasiana* against alcoholic induced liver damage in adult Wistar albino rats was reported. The administration of methanolic extract reversed the damage effect due to alcohol on liver as showed from histopathological investigations of the liver. Thus, exhibited a potent hepatoprotective effect [24].

ANTIOSTEOPOROTIC

The inhibitory effects of compounds isolated from branches and leaves methanolic extract of *N. mirabilis* on osteoclast differentiation were examined by measuring the suppression of excessive bone resorption by osteoclasts. These compounds including plumbagin, 2-methoxy-7-methyljuglone, cis-isoshinanolone, quercetin 3-O-β-D-glucuronide, and kaempferol-3-O-α-L-rhamnoside significantly decreased TRAP activity in multinucleated osteoclast cells at concentration of 10.0 µM compared with positive control (genistein). Consequently, the findings demonstrated that *N. mirabilis* is a good source of biologically active compound for the osteoporosis treatment [19].

ANTI-INFLAMMATORY

Some compounds isolated from branches and leaves methanolic extract of *N. mirabilis* showed anti-inflammatory activities. 2-methoxy-7-methyljuglone inhibited the production of interleukin (IL-12) p40, IL-6, and tumor necrosis factor (TNF-α) (IC_{50}=0.17±0.02, 0.46±0.01, and 8.28±0.21 µM, respectively). The active compound, nepenthoside B exhibited strong inhibition of IL-12 p40, and IL-6 production (IC_{50}=1.17±0.01 and 2.15±0.04 µM). Likewise, the inhibition of IL- 12 p40 by naphthalene derivatives (nepenthoside A, nepenthoside B, nepenthone C, nepenthone F, nepenthone G, cis-isoshinanolone, droserone, 2-methoxy-7-methyljuglone, and plumbagin), phenolic compounds ((–)-heimiol A, 4-hydroxy-2,6-dimethoxyphenyl 6`-O- vanilloyl-β-D-glucopyranoside, koaburaside, leonuriside A, and syringaresinol), lupeone, and flavonoids (quercetin, (–)-epicatechin, quercetin 3-O-β-D- and glucuronide) was more effective than positive control. However, these bioactive compounds showed no or little inhibitory properties on TNF-α production in lipopolysaccharide-stimulated bone marrow-derived dendritic cells [33].

CONCLUSION

This study revealed that *Nepenthes* spp. is an essential medicinal plant with broad pharmacological spectrum. Many species of *Nepenthes* show the presence of various phytochemical constituents responsible for various pharmacological and ethnomedicinal properties. Further study on the available information is crucial in developing novel clinical therapeutics out of *Nepenthes* spp. This review will proffer a remarkable opportunity for future research as it compiled the information related to various aspects of this medicinal plant genus.

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