

Aphananthe aspera (Thunb.) Planch.: An Unexploited Eastern Asian Species from the Center of Biodiversity

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Abstract

Aphananthe Aspera (Thunb.) Planch. is a towering woody deciduous tree and belongs to riparian forest territory. It is highly allocated to the Northern region of Eastern Asia especially Korea, China, Northern Vietnam, and Japan to be the richest countries with this species. The plants were assayed based on various types of methods including extraction. Based on folkloric usage it is important to treat acne, inflammation and cancer. Google Scholar, Web of Science, PubMed, Science Direct, and MEDLINE etc. are the electronic versions from which many bibliographic records were thoroughly explored to identify, collect, and analyze available information relevant to *A. aspera*. The extracted data were scrutinized in order to have a better understanding of the existing research on this species and to look into the plant's future potential in pharmaceutical research. This study aims to offer current knowledge on botany, distribution, ethnomedicinal applications, pharmacological actions, clinical study and reported phytochemicals of *A. aspera*. Finally, this plant is still recommended for extensive research to explore prospective novel sources of novel therapeutic agents as there are very little data available on this plant to the best of our knowledge. Extensive research on this plant can open a new horizon to discover novel therapeutics.

Key words: *Aphananthe aspera*, botany, distribution, ethnopharmacology, phytochemical, pharmacological action.

Introduction

It's inconceivable to envision the human species surviving if there were no plants on the planet. Humans' reliance on plants may be traced all the way back to the dawn of time (Devkota *et al.*, 2019). Medicine is commonly obtained from medicinal plants. Herbs have been employed for the treatment of ailments and the restoration and fortification of bodily systems in ancient medical systems such as Ayurvedic, Unani and Chinese traditional medicine. The goal of using herbs was always to achieve a beneficial interaction with the body's chemistry (Spinella, 2001). Traditional and alternative approach is very much popular to treat different disease states

across the globe (Alam *et al.*, 2021a; Chowdhury *et al.*, 2022). Over the last two decades, governments in Southeast Asia and the Western Pacific have become increasingly interested in recognizing ethnomedicinal systems as part of their healthcare strategy and include herbal medical goods as over-the-counter or necessary prescription treatments (Khandokar *et al.*, 2021; Sultana *et al.*, 2022a).

Ayurvedic and other traditional healers in South Asia employed around 1,800 distinct plant species (Mughal, 2008). Seven natural medicines or direct derivatives of natural substances were determined to be among the top-20 greatest sellers in the pharmaceutical industry. These medications brought

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in a total of \$20 billion in income per year (Martinez *et al.*, 2003). According to conservative estimates, there are over 400,000 secondary plant metabolites on the planet, with only 10,000 having been chemically separated (Islam *et al.*, 2022a; Capasso, 1998). Plants are employed in the production of 30% of all pharmaceutical formulations worldwide. Their present market capitalization is US \$60.0 billion, with predicted growth of US \$5.0 trillion by 2050 (Farooqi, 1998).

According to estimates, 20-25 % of all drugs listed in the Pharmacopeia are derived from natural sources, whether used in disease management without modification, such as vincristine from *Catharanthus roseus* and *silymarin* from *Silybum marianum*, or with minor chemical modifications, such as aspirin, a derivative of salicylic acid isolated from *Salix* spp. (Newman *et al.*, 2000.) *Aphananthe* is such a plant which have medicinal properties. The

Greek words "aphanes" means "invisible" and "anthos" means "flowers" pointing towards "small unobtrusive flowers" (Johnson and Wilson, 1989) is the origin for the name "Aphananthe", a small-scale genera comprising 5 species affiliated to Cannabaceae family, characteristically shrubs or trees (monoecious) ranging from semi-deciduous to deciduous types (pore-free seeding species) (Yang *et al.*, 2017). The trees are approximately 30 m high with 60 cm (diameter) grey-brown trunk that provides a hard and heavy type wood as its density is 510930 kg/m³ and water content is 15% (Sosef *et al.*, 1998). In this article we discussed about *A. aspera* a species belongs to this *Aphananthe* genera which are yet not highly researched (Figure 1) (Wikipedia, 2021; Wikimedia, 2012). It is also known as "Muku tree". The aim of this review work is to focus on the botany, distribution ethnomedicinal applications and reported phytochemicals of *A. aspera*.



Figure 1: Different parts of the *Aphananthe aspera* (Thunb.) Planch. Plant

Materials and Methods

Articles search strategy: To summarize the findings regarding the botany, distribution, ethnomedicinal applications, pharmacological actions and reported phytochemicals of *A. aspera*, a literature search was conducted using PubMed, Google Scholar, ScienceDirect, Scopus, ClinicalTrials.gov

and Wiley Online Library databases. The keywords used during the searches included "*Aphananthe aspera*", "botany", "distribution", "ethnopharmacology", "clinical study", "phytochemical", and "pharmacological action". Only peer-reviewed scientific journals were considered during the process. Of the all identified papers, after eliminating titles and abstracts for not meeting the

inclusion criteria, selected articles with matching criteria were included and reported only in this review.

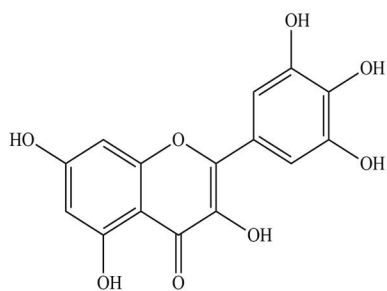
Botany: The towering woody deciduous tree *A. aspera* belongs to riparian forest territory (Yoshikawa and Kikuzawa, 2009) (Suzaki and Nakatsubo, 2001) and is renowned by different names in different localities. The Japanese, the English, and the Chinese people call this beautifully white-barked plant as muku-no-ki, muku tree, and cao ye shu respectively (Quattrocchi, 2012.). The fruits begin to come in May. There is an interesting phenomenon called gradual ripening which indicates that a part of the entire number of grains will ripe (black) at a certain time where others remain unripe (green) (Yoshikawa and Kikuzawa, 2009). The fruit is usually a drupe (radius: 10mm) characterized by a smooth endocarp that is impregnated with a folded only one round seed (radius: 6mm) (Yoshikawa and Kikuzawa, 2009). The leaf possesses 3 venations with 10 -100 micrometers trichomes and single-cell hair-like barbs (Yang *et al.*, 2017) (Sweitzer & Edward M. *et al.*, 1971). Both the flowers take birth in April-May. Fruits need two or three months to ripen (Sosef *et al.*, 1998). Birds usually eat the fruits and aid in the spreading of seeds (Yoshikawa and Kikuzawa, 2009).

Distribution: *Aphananthe*, a genus under the supervision of Ulmaceae (Cannabaceae) family rules over five species namely *Aphananthe aspera*, *Aphananthe philippinensis*, *Aphananthe monoica*, *Aphananthe cuspidate* and *Aphananthe sakalava* that are noted as evergreen shrubs or trees, are usually accustomed to tropical and temperate territories (Tanaka *et al.*, 1977) (Yang *et al.*, 2017) (Yáñez-Espinosa *et al.*, 2003). *A. aspera* is highly allocated to the Northern region of Eastern Asia. When penetrating deeper, we can see Korea, China, Northern Vietnam, and Japan to be the richest countries with this species, and thus, a clear concept is achieved. (Yang *et al.*, 2017).

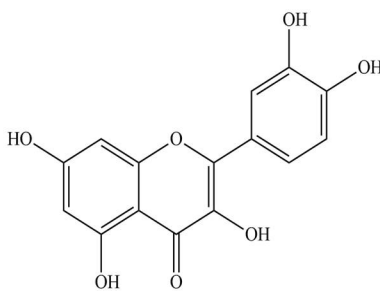
Phytochemistry: In the table 1, the noted phytochemical researches are about *A. aspera*; the

plants which are fetched from the Northern region of Eastern Asia; more specifically from China, Japan, and Korea. The plants were assayed based on various types of methods including extraction, paper chromatography, UV spectroscopy, co-chromatography, GLC (gas-liquid chromatography), sp gr (specific gravity) assay, acid value assay, saponification value assay, iodine value assay and unsaponifiable matter assay, UHPLC-LTQ-IT-MS/MS (ultrahigh-performance liquid chromatography linear-trap quadrupole ion-trap tandem mass spectrometry), SPE (solid-phase extraction), HPLC (high-performance liquid chromatography), 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) assay, DPPH (2,2-diphenyl-1-picrylhydrazyl radical scavenging activity assay), antioxidant activity assay, FRAP (ferric reducing ability of plasma), TPC (total phenolic contents), TFC (total flavonoid contents), HR-ESI-MS, IR, 1D, and 2D NMR, and CD spectroscopy, HMBC, NOESY, Fisher-Johns melting point apparatus, ESI-MS. In most cases, extractions were done with 95% ethanol followed by different solvents resulted in identification and isolation of several compounds (Ye *et al.*, 2007) (Sun *et al.*, 2017; Won *et al.*, 2018; Tanaka *et al.*, 1977; Giannasi, 1978; Devkota *et al.*, 2019). The structures of isolated phytochemicals have been displayed in FIGURE 2.

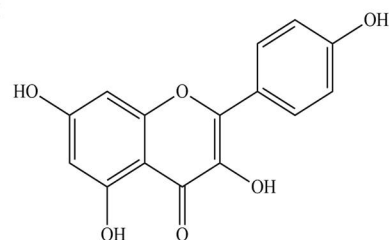
Ethnopharmacology and traditional uses: In traditional medicine, *A. aspera* is of great value as the local people of China has utilized its stem bark for the treatment of cancer (due to its anti-proliferative properties), inflammation as well as acne (Ye *et al.*, 2007; Won *et al.*, 2018). The Chinese people also utilized its root for its medicinal value (Sun *et al.*, 2017). Stem bark and root bark are known as "Zouyouju" in traditional Chinese medicine (TCM) and are used to treat inflammation, sprains, and back pain (Devkota *et al.*, 2019). In Australia, the trees are also considered as valuable source of nectar that provides energy (Klingeman *et al.*, 2017).



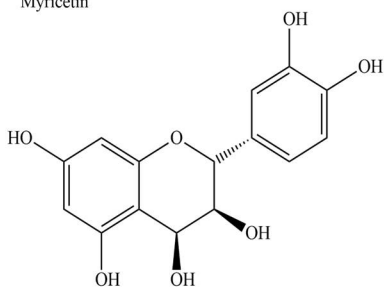
Myricetin



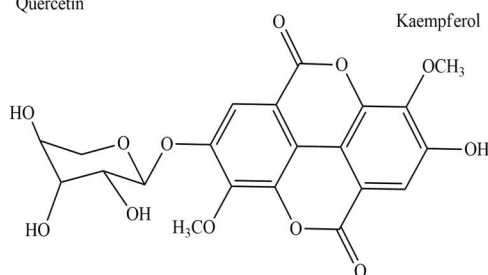
Quercetin



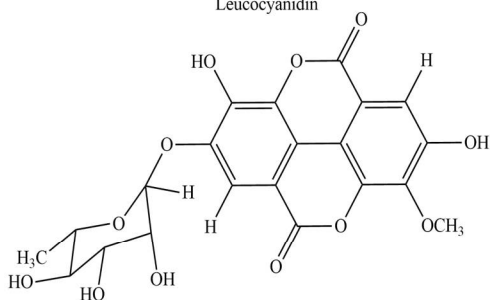
Kaempferol



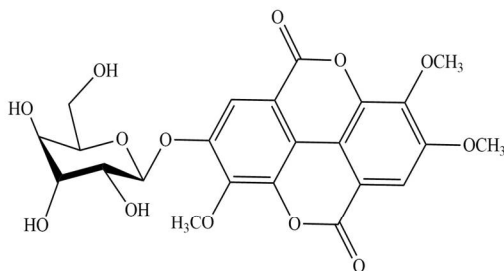
Leucocyanidin



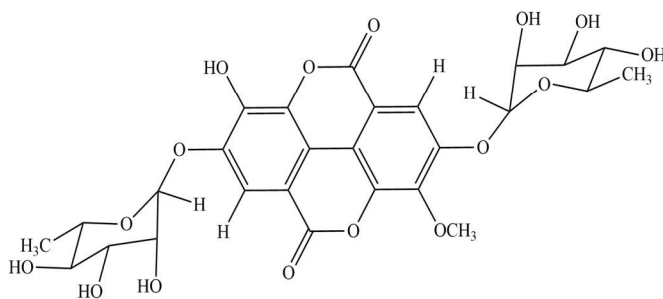
3-O-methyllellagic acid-4'-O-beta-D-xylopyranoside



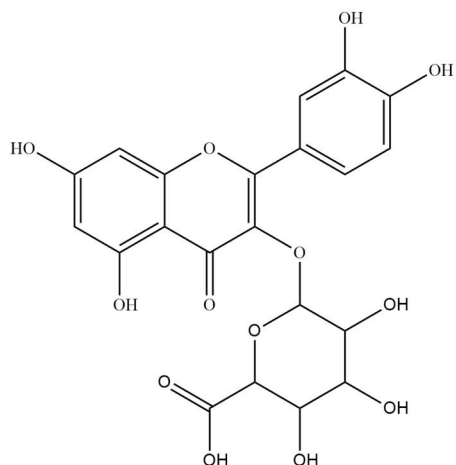
3-O-methyllellagic acid-4'-O-alpha-L-rhamnopyranoside



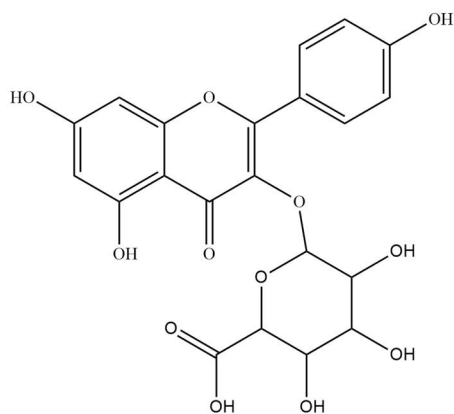
3, 3', 4'-tri-O-methyllellagic acid-4'-O-beta-D-xylopyranoside



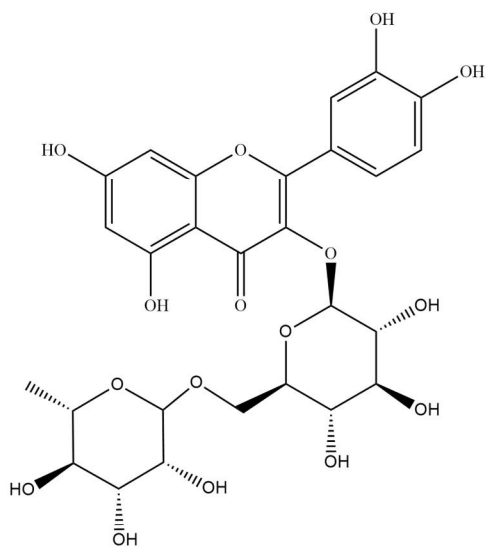
3, 3'-di-O-methyllellagic acid-4'-O-alpha-L-rhamnopyranoside



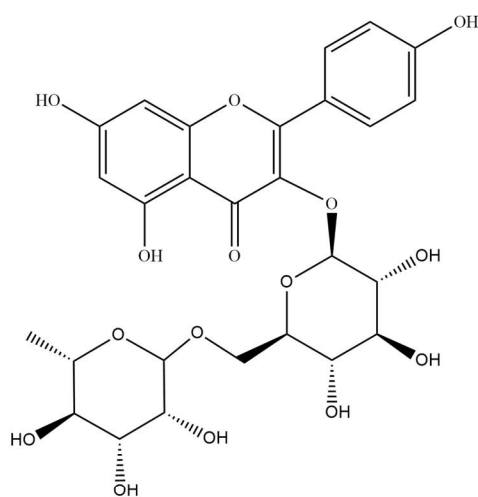
Quercetin 3-O-beta-glucopyranoside



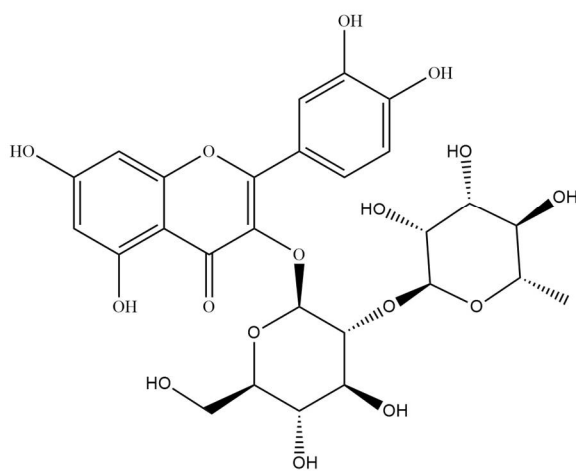
Kaempferol 3-O-beta-glucopyranoside



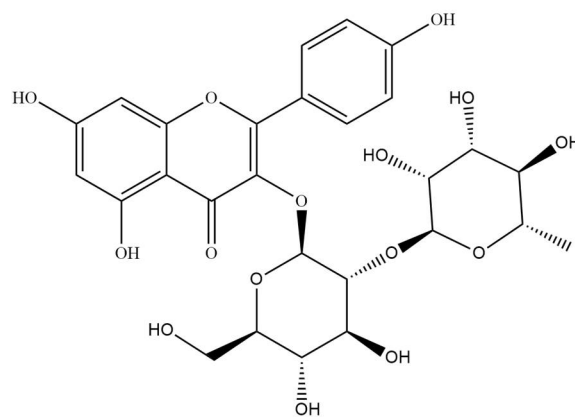
Quercetin 3-O-rutinoside



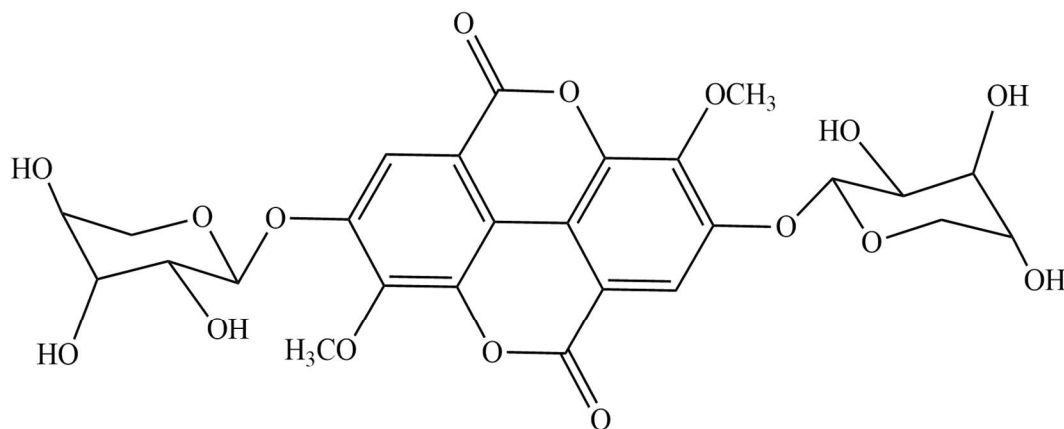
Kaempferol 3-O-rutinoside



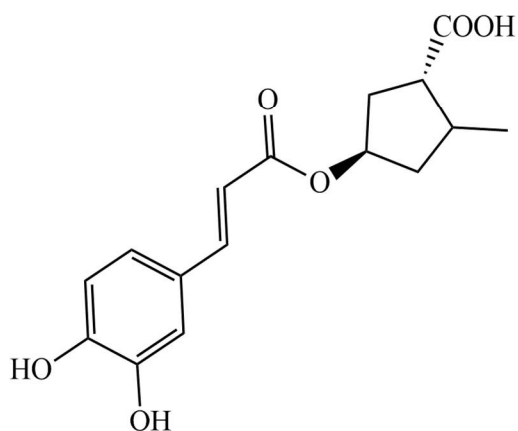
Quercetin 3-neohesperidoside



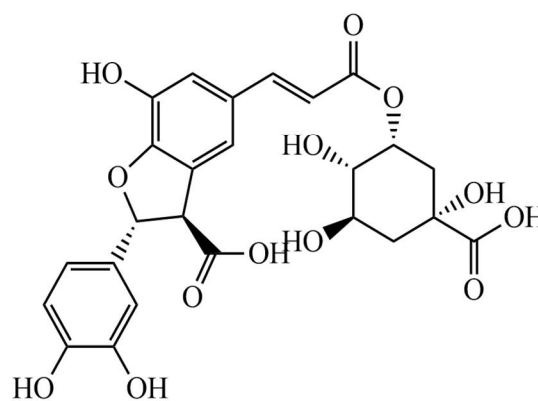
Kaempferol 3-neohesperidoside



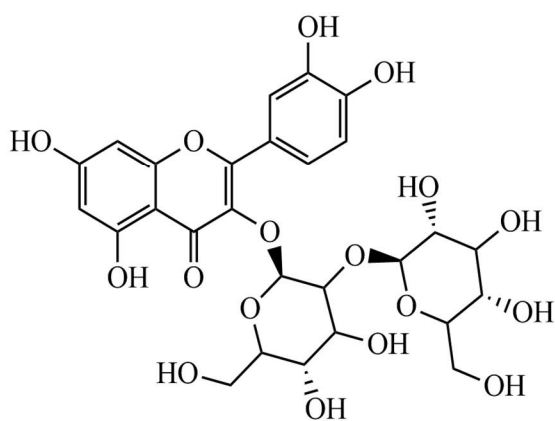
3, 3'-di-O-methylsuccinic acid-4'-O-beta -D-xylopyranoside



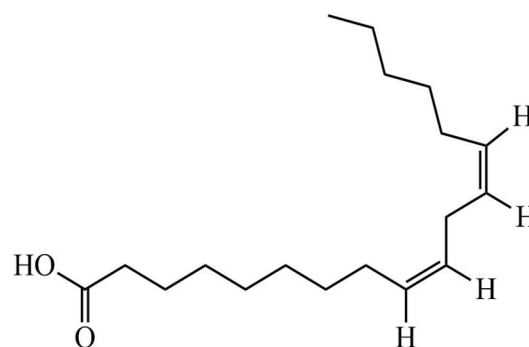
(2S,4R)-2-carboxy-4-(E)-p-caffeoyl-1-methyl-hydroxyproline



5-O-caffeoyl quinic acid-(7'R,8'S,7''E)-3',4',3''-dihydroxy-4'',7'-epoxy-8',5''-neolign-7'-ene-9- carboxyl



Quercetin 3-sophoroside



Linoleic acid

Figure 2. Chemical structures of isolated phytochemicals from *Aphananthe aspera*.

Table 1. Phytochemicals isolated from *Aphananthe aspera*.

Species	Site of collection	Studied organ	Compounds	Methods of study	Reference
<i>Aphananthe aspera</i>	China	Leaf	Myricetin, Quercetin, Kaempferol; Leucocyanidin	PC, UV, CC	Giannasi, 1978
		Stem bark	3-O-methylellagic acid-4'-O α -L-rhamnopyranoside, 3-O-methylellagic acid-4'-O β -D-xylopyranoside, 3,3'-di-O-methylellagic acid-4'-O β -D-xylopyranoside,, 3,3', 4-tri-O-methylellagic acid-4'-O β -D-glucopyranoside, 3,3'-di-O-methylellagic acid-4'-O α -L-rhamnopyranoside	HR-ESIMS, UV, IR, 1H NMR	Ye et al., 2007
		leaf	(2S,4R)-2-carboxy-4-(E)-p-ca \square eoyl-1-methyl-hydroxyproline, 5-O-ca \square eoyl quinic acid-(7'R,8'S,7''E)-3',4',3''-dihydroxy-4'',7'-epoxy-8',5''-neolign-7'-ene-9-carboxyl	UV, HPLC, HR-ESI-MS, IR, 1D and 2D NMR	Sun et al., 2017
	Korea	leaf	quercetin, kaempferol, and isorhamnetin O-glucosides (quercetin O-sophoroside)	UHPLC-LTQ-IT-MS/MS, SPE, HPLC,	Won et al., 1977
	Japan	Fruit	Linoleic acid	GLC, UV	Tanaka et al., 1977
	Japan	leaf	3-O- β -glucopyranoside, Kaempferol 3-O- β -glucopyranoside, quercetin 3-O-rutinoside, kaempferol 3-O-rutinoside, quercetin 3-O-neohesperidoside, kaempferol 3-O-neohesperidoside	NMR	Devkota et al., 2019

CC: co-chromatography, GLC: Gas Liquid Chromatography, HPLC: High Performance Liquid Chromatography, HR-ESIMS: High-Resolution Electrospray Ionisation Mass Spectrometry, IR: Infrared spectroscopy, NMR: Nuclear Magnetic Resonance, PC: Paper chromatography, SPE: Solid-Phase Extraction, UHPLC-LTQ-IT-MS/MS: Ultrahigh-performance liquid chromatography linear-trap quadrupole ion-trap tandem mass spectrometry, UV: Ultraviolet spectroscopy.

Biological activities of plant extract: In China, it is seen that the leaf extract of *Aphananthe aspera* containing eight compounds exhibits anticancer (anti-proliferative) actions in case of breast cancer and extinguishes MDA-MB-231 cells and MCF-7 cells (Sun et al., 2017).

Biological activities of bioactive phytochemicals: Two newly discovered compounds namely (2S,4R)-2-carboxy-4-(E)-p-ca \square eoyl-1-methyl-hydroxyproline and 5-O-ca \square eoyl quinic acid-(7'R,8'S,7''E)-3',4',3''-dihydroxy-4'',7'-epoxy-8',5''-neolign-7'-ene-9-carboxyl extracted from the leaf of *Aphananthe aspera* (collected from China) revealed

antiproliferative activity (Sun et al., 2017). The same plant, collected from Korea was sampled and analyzed to scavenge new bioactive compounds. This research came to the light when quercetin O-sophoroside, a bioactive compound was identified as the primary antioxidant revealing antioxidant activity (Won et al., 2018).

Other prospective phytochemicals and their pharmacological actions: Phytochemicals are major sources of novel therapeutics as well as the driving forces of plants to exert their pharmacological actions (Alam et al., 2020; Emon et al., 2021a; Alam et al., 2022). Thus, nowadays several phytochemicals have

been evaluated to validate their pharmacological potentials in order to launch new drugs actions (Alam et al., 2021a; Alam et al., 2021b; Emon et al., 2021b). Their pharmacological activities and respective mechanism of actions are established through various experimental approaches such as *in*

vitro, *in vivo*, *in silico* studies etc. (Emon et al., 2020a; Islam et al., 2022b; Chakrabarti et al., 2022; Ashrafi et al., 2022; Sultana et al., 2022). Few important phytochemicals from this plant and their mode of actions have been presented in figure 3.

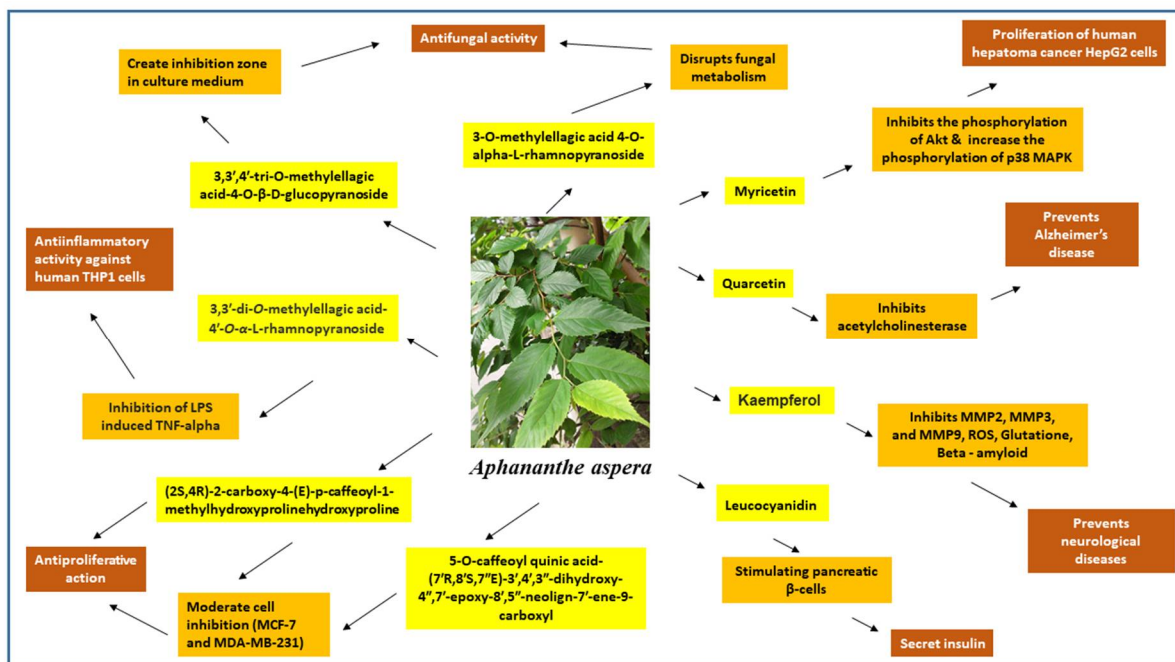


Figure 3. Pharmacological potential of important phytochemicals reported from *Aphananthe aspera*.

Clinical Study: A study on the diet of raccoon dogs was performed in Japan to ensure the availability of sugar content in foods of the raccoon dogs so that they can maintain an appropriate amount of body fat throughout the winter season. It was found that 25.6% of food (sugar) had come from the seeds of *A. aspera* by fecal analysis (Enomoto et al., 2018).

Discussion

Plants are always important sources of drug moieties (Emon et al., 2021c, Rudra et al., 2020; Kabir et al., 2021; Asad et al., 2022). Traditional or folkloric usage of a plant can be underlying hints of a plant for its extensive exploration to unveil novel therapeutics (Sultana et al., 2022b; Obonti et al.,

2021; Emon et al., 2020b, Alam et al., 2021c). Here, *A. aspera* is an asset of Northern region of Eastern Asia. It is such a useful medicinal plant that had been used since the past decades in Korea, China, Northern Vietnam, and Japan for its medicinal value (Yang et al., 2017). A few research had been carried out only. The leaf extract of *A. phananthe aspera* is useful against breast cancer as it can destroy MDA-MB-231 cells as well as MCF-7 cells (Sun et al., 2017). Two newly discovered compounds namely (2S,4R)-2-carboxy-4-(E)-p-caffeoyl-1-methylhydroxyproline and 5-O-caffeoyl quinic acid-(7'R,8'S,7''E)-3',4',3'''-dihydroxy-4'',7'-epoxy-8',5''-neolign-7'-ene-9-carboxyl extracted from its leaves have shown antiproliferative activity that can be targeted to treat cancer (Won et al., 2018). A compound quercetin O-sophoroside acts as an

antioxidant. Its stem bark works against inflammation and acne (Ye *et al.*, 2007; Won *et al.*, 2018). Therefore, this long woody deciduous tree adds a great value to the riparian forest territory. These findings are very much prospective and potential in medical and pharmaceutical sciences as it has created scopes to perform more researches that may lead to discovery and development of novel therapeutics against several disorders though till date very few research works have been conducted to explore this rich source of biomedicine.

Conclusion

A. aspera showed a wide classes of phytochemicals though very few *in vitro*, *in vitro* and clinical studies have been conducted on this plant extract and/or their phytochemicals. Folkloric use of this plant also provides clue of its ethnopharmacological importance. Thus, further study on this plant is highly recommended to isolate bioactive phytochemicals and ascertain their pharmacological actions and exact mode of actions. This includes concentrating on its anticancer properties in the quest for new medicines to combat the growing of cancer incidence based on their folkloric use.

Declarations

The manuscript was read and approved for submission by all concerned authors. No part of the manuscript has been previously published, and no part of it is currently being considered for publication in any journal.

Acknowledgment

The authors are expressing their heartfelt gratitude to all the folkloric practitioners for providing subtle hints for the further researches to discover novel therapeutics.

Conflict of interest

The authors declared no conflict of interest regarding the preparation and publication of the manuscript.

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