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Review article

Health-promoting compounds in *Amomum villosum* Lour and *Amomum tsao-ko*: Fruit essential oil exhibiting great potential for human health

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A R T I C L E I N F O

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A B S T R A C T

Background: The Zingiberaceae family serves as a diverse repository of bioactive phytochemicals, comprising approximately 52 genera and 1300 species of aromatic perennial herbs distinguished by their distinct creeping horizontal or tuberous rhizomes. *Amomum villosum* Lour. and *Amomum tsao-ko* Crevost & Lemaire., are the important plants of family Zingiberaceae that have been widely used in traditional medicine for the treatment of many ailments. The Amomum species are employed for their aromatic qualities and are valued as spices and flavorings. In the essential oils (EOs) of Amomum species, notable constituents include, camphor, methyl chavicol, bornyl acetate, *trans*-p-(1-butenyl) anisole, α-pinene, and β-pinene. Objective: The aim of this review is to present an overview of pharmacological studies pertaining to the extracts and secondary metabolites isolated from both species. The foremost objective of review is not only to increase the popularity of Amomum as a healthy food choice but also to enhance its status as a staple ingredient for the foreseeable future. Result: We endeavored to gather the latest information on antioxidant, antidiabetic, anticancer, antiobesity, antimicrobial, and anti-inflammatory properties of plants as well as their role in neuroprotective diseases. Research conducted through *in-vitro* studies, animal model, and compounds analysis have revealed that both plants exhibit a diverse array health promoting properties. Conclusion: the comprehensive review paper provides valuable insights into the diverse range of bioactive phytochemicals found in *A. villosum* and *A. tsao-ko*, showcasing their potential in preventing diseases and promoting overall human well-being. The compilation of information on their various health-enhancing properties contributes to the broader understanding of these plants and their potential applications in traditional medicine and beyond.

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1. Introduction

The Zingiberaceae family, commonly referred to as the ginger family, being a significant contributor to the source of dietary antioxidants. These dietary antioxidants typically comprise phenolic or thiolic compounds [1]. The Zingiberaceae family encompasses around 1300 species of aromatic, perennial herbs with distinctive creeping horizontal or tuberous rhizomes [2]. The plant from this family are found across three continents: The Asia, Africa, and Americas. Notable members of this family include turmeric (*Curcuma longa* L.), ginger (*Zingiber officinale* Roscoe), Javanese ginger (*Curcuma zanthorrhiza* Roxb.), and Thai ginger (*Alpinia galanga*) [3,4]. The genus Amomum occupies an important position in the family Zingiberaceae because of its oil, food, fibers, minerals, vitamins, soluble sugars, phytochemicals like organic acids, flavonoids, and phenolic compounds.

Amomum villosum Lour, commonly known as amomi Fructus or 砂仁(Sha Ren) in traditional Chinese medicine, is a species of aromatic spice. It is native to Southeast Asia, particularly to China, India, Bhutan, Nepal, Malaysia, Vietnam, Myanmar, and Laos [5–7]. The planting area of *Amomum villosum* in Yunnan accounted for 91%, about 66 thousand hectares. *Amomum villosum* typically thrives in tropical and subtropical climates. It prefers well-drained soil and partial shade [8]. The plant is characterized by its large, dark brown to black pods, which contain seeds used as a spice in cooking. The plant is propagated through rhizomes.

Furthermore, the ripe and dried fruits of *A. villos*um have been reported to be utilized for medical purposes [9], while its stems and leaves are always discarded. Oil of Phytochemical investigation revealed chemical components found in A. villosum stems/leaves and those found in fruits are very different. Most common are Bornyl acetate, camphor, α-cadinol, linalool, β-myrcene, D-limonene, and terpinolene [6]. The foliage and stem of *A. villosum* can be used as a medicinal remedies or dietary supplement to prevent and treat disorders caused by inflammation and oxidative stress [10]. Here is unique ability of dried fruit of *Amomum villosum* could be helpful for increasing longitudual bone growth in children with growth retardation [11].

Amomum tsao-ko, also known as Tsao-ko cardamom, or "草果" (Cao Guo) is a species of plant in the ginger family, Zingiberaceae. It is native to Southeast Asia, particularly China and Vietnam [12]. The planting area of *Amomum tsao-ko* in Yunnan accounted for 99%, about 144 thousand hectares [13]. It is also reported that planting area in Yunnan has reached 1,198,800 hm2, with a yearly yield of around 3000 tons [14]. The dried seeds of *Amomum tsao-ko* are used as a spice in various culinary applications, particularly in Chinese cuisine [15]. It's worth noting that the names and uses of spices can vary regionally, and in some cases, the same spice may be known by different names. In the case of *Amomum tsao-ko*, it is valued for its unique flavor and is an important component in the culinary traditions of the areas where it is cultivated [16]. In traditional medicine systems, dried fruit is frequently employed to alleviate abdominal pain, dyspepsia, malaria, nausea, throat infections, stomach disorders, vomiting, and diarrhea [17]. Due to their diverse pharmacological activities, including antitumor, antioxidant, and neuroprotective properties, the fruits of A. tsao-ko have garnered interest as both functional food and medicine [16]. Volatile components from *Amomum villosum* have been documented to exhibit beneficial effects such as gastrointestinal protection, hypoglycemic properties, anti-allergic actions, and antibacterial capabilities. Non-volatile elements found in plants have demonstrated anti-inflammatory and antioxidant activities [8]. Over 490 chemical compounds have been extracted and isolated from *Amomum tsao-ko*. The primary constituents in *Amomum villosum* and *Amomum tsao-ko* are diterpenes, flavonoids, and polysaccharides [7]. It is worth noting that indenoids are chemical compounds unique to A. tsao-ko that can be utilized as quality indicators [18]. Diarylheptanoids, Flavanol-fatty alcohol hybrids, and Flavanol-menthane conjugates are among the unique chemical components recovered from A. tsao-ko [19]. The novelty of this work lies in its comprehensive exploration of the diverse array of compounds present in Amomum plants, with specific emphasis on Amomum villosum and Amomum tsao-ko. While previous research has touched upon the pharmacological properties of these plants, our review delves deeper into their phytochemical composition, shedding new light on previously overlooked bioactive compounds. By focusing on these specific Amomum species, we aim to provide a more detailed understanding of their potential health benefits and therapeutic applications. Additionally, our review synthesizes the latest findings from a variety of sources, including in-vitro studies, animal experiments, and compound analysis, offering fresh insights into the multifaceted nature of these plants. Through this approach, we contribute to the advancement of knowledge in the field of phytochemistry and traditional medicine, paving the way for further exploration and utilization of Amomum plants in healthcare and beyond.

Fig. 1. Classification of both representative plants.

2. Distribution, Botanical description and taxonomy

Amomum villosum commonly known as 'hill cardamom. *Amomum villosum* is native to Southeast Asia, including regions in China, India, Bhutan, Nepal, Bangladesh, and Myanmar. It is often found in the hilly regions and forests, growing at higher elevations [20,21]. *Amomum tsao-ko* is commonly referred to as 'tsao-ko' or 'caoguo.' *Amomum tsao-ko* is native to China, specifically found in the southwestern provinces such as Yunnan and Guangxi. It is often found in mountainous areas and forests [22]. Both species are cultivated for various purposes, including their aromatic seeds that are used in culinary and medicinal applications. It's essential to note that the distribution of plant species can change over time due to various factors, including climate changes and human activities.

These species belong to the same genus, Amomum, within the family Zingiberaceae (Fig. 1). The Zingiberaceae family is known for including many aromatic plants, and Amomum species are particularly valued for their seeds, which are used as spices.

Plant of *A. villosum* is perennial and herbaceous in habit. Height can reach a height of 1–2 m. Leaves are large, lanceolate to elliptical, and arranged alternately along the stem. The flowers are typically borne on a spike and are pale yellow to greenish in color. The fruit is a capsule containing several seeds [Fig. 2 (a-c)]. The seeds are the valuable part used in culinary and medicinal applications. Rhizomatous root system [23].

Amomum tsao-ko is also a perennial herbaceous plant with typically grows up to 1–2 m in height. Leaves are Large, lanceolate to elliptical, arranged alternately along the stem. The flowers are often borne on a spike and may be yellow or greenish. The fruit is a capsule containing seeds, which are used for various purposes [Fig. 2 (d-f)]. It has a rhizomatous root system [24,25,26].

3. Ecology of amomum

In this study we have explored the association and differences in the original environment, chemical composition, and potential health effects of these two species. A study conducted by Bao. 2004 demonstrated the ecology of Amomum genus. Amomum is frequently observed in natural forests situated along stream banks. For the successful cultivation of Amomum, it is advisable to select sites that meet criteria. These criteria include an optimal altitude ranging from 500 to 2700 m. Additionally, the surface soil layer should be situated within the range of 30–60 m, with a suitable humidity level falling between 37 and 41 percent. Furthermore, the soil should exhibit a porosity level of no less than 70 percent, and the humus content should not be below 4.2 percent [27]. *A. villosum* Lour, is native to China and found in southern part of the country in province Guangxi and Yunnan [28]. It typically grows in mountainous regions at higher altitude [8]. Because of its shallow root, *A. villosum* is susceptible to drought [29]. With decreasing soil moisture, seedling height, biomass, leaf number and area, relative growth rate, and net assimilation rate all fell dramatically [30]. While *A. tsao-ko*, it is also native to Southeast Asia, particularly China and Yunnan, Guangxi, and Vietnam [Fig. 3 (a, b)] [12,31]. When *A. tsao-ko* was transplanted from a habitat at lower altitude to a site at higher altitude, notable changes occurred in its reproductive characteristics [32]. *A. tsao-ko* is perennial non-timber perennial forest product that grows at high elevation in southeast Asia's subtropical climate [33]. Cooler temperatures can slow down metabolic activities in plants, minimizing respiratory losses and enabling more effective photosynthesis. This may result in increased biomass accumulation of *A. tsao-ko* [34]. *Amomum* genus is susceptible to various abiotic stresses, which are primarily responsible for deprived plant health and reduced yield. The results from Gua et al., 's 2016 study indicate that A. villosum is well-suited for a moderate light environment, specifically in the range of 60–30%. This adaptability is evident through robust clonal growth and increased photosynthesis. Extreme light conditions, such as too strong (100%) or too weak (less than 15%), should be avoided when cultivating *A. villosum* in rainforests [10].

These studies indicate that for obtaining better growth and increased yields is depending on promoting cultivation under optimal

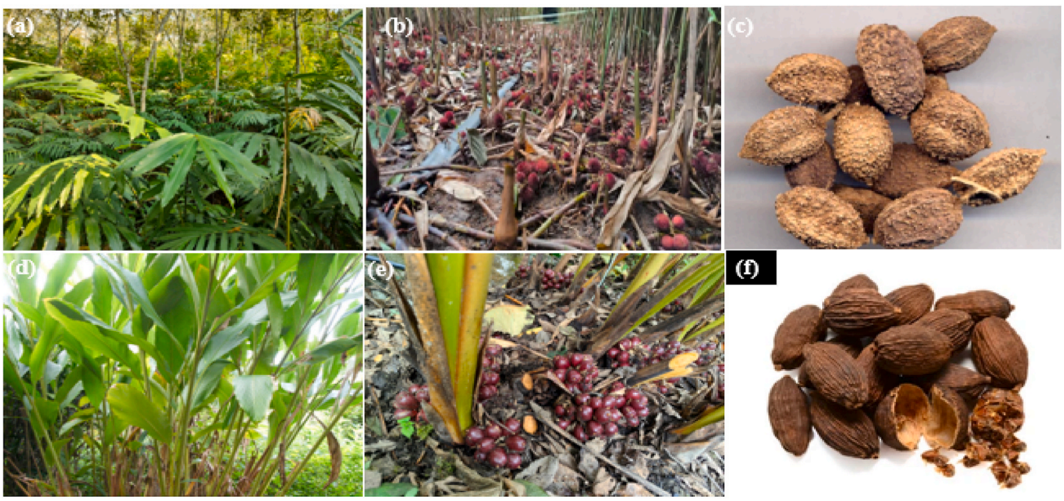

Fig. 2. (a) Plant of *Amomum villosum* (b) fresh fruit of *Amomum villosum* (c) dry fruit of *Amomum villosum* (d) plant body of *Amomum tsao-ko* (e) fresh fruit of *Amomum tsao-ko* (f) dry fruit of *Amomum tsao-ko*.

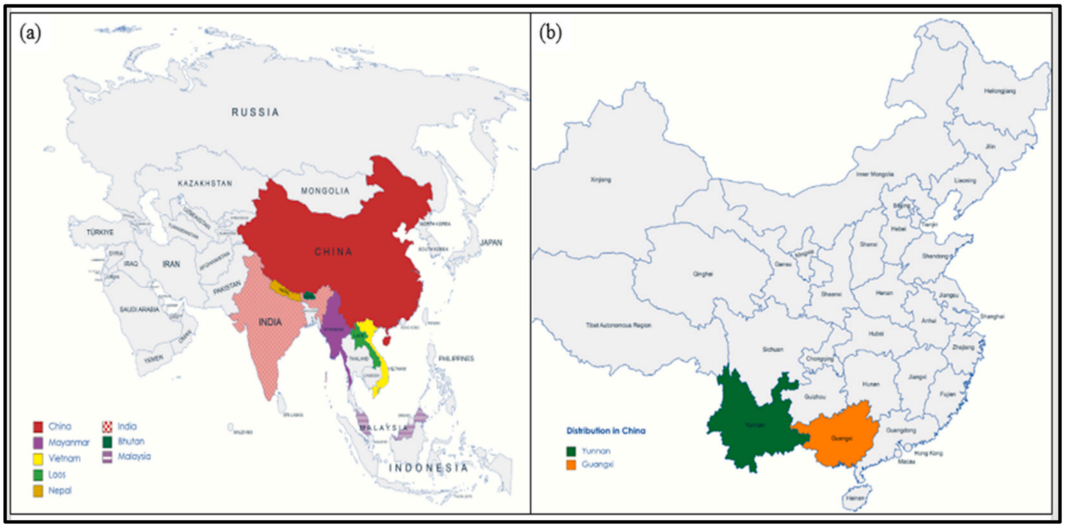

Fig. 3. (a) Distribution map of *Amomum villosum* and *Amomum tsao-ko* in world. (b) Distribution of map in China (Province Yunnan and Guangxi).

conditions of shade, light, temperature, Humidity, and moisture. It is concluded that both species exhibit a similar geographical distribution encompassing altitude, temperature, humidity, and annual rainfall. These specific environmental conditions may vary within the native range of each species. However, both *A. villosum* and *A. tsao-ko* are adapted to mountainous regions. They tend to flourish in well-drained, humid environments with moderate temperatures.

4. Ethnopharmacology

For centuries, Amomum species have been employed worldwide to address a variety of health issues, digestive problems [35], respiratory issues, dental issues [36], inflammation, malaria, cancer. Apart from their medicinal use, certain plants within this genus offer nutritional benefits and can be consumed. Their leaves, fruits, and flowers can also be utilized in the creation of diverse food products, with applications as spices in various countries [37]. The traditional uses of both species are detailed in Table 1.

Amomum villosum and *Amomum tsao-ko* have ethnomedicinal importance and are traditionally used in various cultures for their medicinal properties [43]. *Amomum villosum* is often used to alleviate digestive issues. It may help in reducing indigestion, bloating, and gas. The seeds are sometimes used to relieve respiratory problems, including coughs and bronchitis. The aromatic properties of cardamom are believed to have a soothing effect on the respiratory system [44]. In some traditional medicine systems, black cardamom is considered to have anti-inflammatory potential. It can be used to alleviate inflammation and related conditions [45]. Beyond medicinal uses, black cardamom is widely used as a spice in culinary applications, adding a distinctive flavor to dishes. However, *A. villosum* is extensively used in traditional Chinese medicine to treat digestive issues such as diarrhea, bloating, and abdominal distention [44].

Amomum tsao-ko is traditionally used for digestive purposes, like black cardamom. It may be used to treat indigestion and alleviate stomach discomfort. The seeds of *A. tsao-ko* are valued for their aromatic properties. They are often used to enhance the flavor of dishes in traditional cuisines [46]. In traditional Chinese medicine, *A. tsao-ko* is used for its warming properties. It is believed to help strengthen the spleen and stomach, promoting digestion [26]. Some traditional uses involve the use of Tsao-ko for its anti-inflammatory and analgesic (pain-relieving) properties [47]. It's important to note that while these plants have a history of traditional use in various cultures, scientific studies are ongoing to validate and understand the specific medicinal properties and potential health benefits.

Furthermore, *A. villosum* and *A. tsao-ko* are particularly popular among Chinese people. According to research, many ethnic subgroups utilize these plants to treat ailments (Table 2). The fruits of these plants are the principal medicinal portions, whereas other locations are rarely used medicinally. There are numerous prescriptions for *A. tsao-ko* that have considerable therapeutic effects.

5. Chemical profiles of amomum essential oils

The analysis of chemical profiles of the essential oils extracted from Amomum villosum and *Amomum tsao-ko* showed that the oils consisted of some chemical groups, including monoterpene hydrocarbons, oxygenated monoterpenes, and non-terpenes. Previous studies have explored various plant parts, including leaves, flowers, fruits, stems, seeds, pods, rhizomes, and roots [6,49,53,54]. Table 3 summarizes the major compounds found in the Amomum essential oils extracted from these different plant parts.

Oxygenated monoterpenes, which constitute another chemical class, were also identified in A. *tsao-ko.* In the fruit oils of certain A. *tsao-ko* specimen collected from Vietnam, China, and India, 1,8-cineole was identified as the predominant component [46,54]. Similarly, this compound was reported as the primary constituents in the seed and pod oils of A. tsao-ko [59]. Additionally, camphor

Table 1
Some key characteristics and uses of *Amomum villosum* and *Amomum tsao-ko*.

Characteristic	*Amomum villosum Lour*	*Amomum tsao-ko*	References
Appearance	The plant has long, lance-shaped leaves and produces large pods. The pods are dark brown to black and have a tough, dried outer shell.	a perennial herb with large, lance-shaped leaves. The seeds, which are the primary culinary part, are found in the seed pods.	[7,24,38]
Flavor and Aroma	Black cardamom has a smoky, earthy flavor with a hint of camphor. It is less sweet and more savory than green cardamom.	The seeds have a distinct and aromatic flavor. They are often described as having a warm, spicy, and slightly camphoraceous taste.	[15,24]
Culinary Uses	The seeds inside the pods are the primary culinary part. They are often used in savory dishes, particularly in Asian cuisines. Black cardamom is a key ingredient in spice blends like garam masala in Indian cuisine. It is also used in various meat dishes, soups, and stews	The ripe seeds of Amomum tsao-ko are used as a spice in various Chinese dishes. They are often included in spice blends and are particularly popular in Sichuan cuisine, where they contribute to the characteristic numbing and spicy flavor of many dishes.	[17,39]
Medicinal Uses	In traditional Chinese medicine, Amomum villosum has been used for its medicinal properties. It is believed to have digestive and stomach-soothing properties. It's also used to alleviate symptoms such as nausea and vomiting	It is believed to have digestive benefits and is sometimes used to address issues such as indigestion	[40,41]
Cultural Significance	Black cardamom is an essential spice in many Asian cuisines, and its unique flavor adds depth to dishes. It is commonly used in both savory and sweet preparations	The spice derived from Amomum tsao-ko is a staple in certain regional Chinese cuisines, contributing to the complexity of flavors in various dishes.	[15,42]

Table 2
Traditional uses of *Amomum villosum* and *Amomum tsao ko*.

Plant parts	Plant spp	Preparation/Ailments	Treatments	References
Leaves and stem	*Amomum villosum*	Fresh leaves	Animal feed, especially black goat.	[40]
Fruits	*Amomum villosum*	Dry and mature fruit	Gastrointestinal diseases, gastritis, stomachache, and digestive troubles,	[48–50]
		Xiangshaliujunzi decoction	Dyspepsia and dysentery	[51]
	Amomum tsao-ko	Decoction	Malaria-induced chills, dampness, To alleviate turbidity, flatulence in the lower abdomen, as well as symptoms like vomiting.	[15]
Seeds	*Amomum villosum*	Decoction, tea, liquor	gastritis, stomachache, and digestive troubles	[52]
	Amomum tsao-ko	Decoction	vomiting, treatment of cholera, alcohol poisoning, tonifying spleen and stomach	[18]

Table 3
Major components identified from Amomum essential oils.

Plants	Plant parts	Compounds	References
Amomum villosum	Fruit	Bornyl acetate (52.5%),Camphor 19.17%, Camphene(8.9%), D-limonene(17.8%),	[6,55]
	Leaves	Bornyl acetate (8.48%), β-pinene(53%), α-pinene (22.1%) Camphor 3.18%, γ-terpinene (1.2%)Limonene(4.2%), α-humalene (2%)	[56]
	Seed	Bornyl acetate (40.4%) Camphor14.82%, esters (52.5%),	[57]
	Stem	α-pinene (18.5%), Sabinene(19.2%), β-pinene(38.8%), β-caryophyllene(2.2%), γ-terpinene (1.8%)Limonene (3.9%)	[53,58]
	Peels	Bornyl acetate (3.87%) Camphor 6.90%, esters (42.1%)	[58]
	Rhizomes	B-pinene(19%), α-pinene (9%),Bornyl acetate (18.3%) Camphor (2.49%), Sabinene(16%),fenchyle acetate (17%),camphene(5.4%)	[58]
Amomum tsao-ko	Pod	Geranial(7.8%),1,8-cineole(22.6%), Geraniol(7%),(2E)-decenal(6.1%)	[22]
	Entire plant	1,8-cineole(34.6%), geraniol(4.8%), α-terpineol(4%), α-phellandrene(5.8%), β-pinene(3.3%)	[47]
	Fruit	1,8cineole(45.24%),Geraniol(5.11%),Geranial(4.52%), α-terpineol(3.59%), α-phellandrene(3.07%)	[46,54]
	Seed	1,8-cineole(30.6%), limaneon (22.77%), 2-decanal(17.3%), neral(7%), geranial(10.6%), α-terpineol(4.3%)	[59]

was detected as the most abundant compound in the essential oils of A. villosum, with this compound representing the second-highest proportion in the oils derived from A. villosum fruits [6]. Bornyl acetate was the richest compounds in the seed oil of the A. villosum from China [49].

Monoterpene hydrocarbons represent the most prevalent components found in the A. villosum essential oils. β-Pinene has been identified as the predominant component in the essential oils extracted from various Amomum species, with notably higher proportions observed in the stem, roots, leaves, and rhizomes of A. villosum [53,56,60]. Additionally, it was reported that the seed shell of *A. villosum* contains five compounds, including quercetin, vanillic acid, β-sitosterol, protocatechuic acid and sitosterol-β-D-glucoside [61,57]. Decenal, a novel non-terpene chemical, was discovered in the essential oils of the pods extracted from *A. tsao-ko* [22]. Overall study reported that more than 300 compounds have been found in A. tsao-ko, with at least 209 of them isolated and named. Terpenoids, phenylpropanoids and other substances can be classed based on their core structural properties. Overall, there are 32 terpenoids, 157 phenylpropanoids, 19 organic acids, and 1 pyrrole. Tsaoko Fructus possesses an aromatic and spicy odor, making it volatile oil, referred to as essential oil (EO), has received significant interest and attention [24,22,46,47]. The essential oil (EO) of A. tsao ko comprises terpenoids, phenolic acids, and organic acids among its chemical constituents [22]. Similarly, in the case of *A. villosum* flowers, the aroma is attributed to a combination of glandular secretions and petals, resulting in a total of 22 volatile components. Among these, 13 are terpenoids and 7 are aromatics. However, over time, 7 chemical compounds were depleted (isopymyristate, diethylphthalate, nonanal, tridecane, bicyclogermacrene, 2,3-dihydro-4-methyl-,α-farnesene), while 5 decreased (ɑ-pinene, γ-elemene, β-phellandrene, D-limonene, 2-undecanone). Conversely, 3 new chemical compounds emerged (2-methyl-5-(1-methyllethylene)-2-cyclohexen-1-ketone, 3,7-dimethyl- 1,6-octadien-3ol, and 4-methylene-1-(1-methylethyl)-bicyclo- hexane), while 4 increased (benzoic acid hexyl ester, β-myrcene, butylatedhydroxytoluene, and undecane, 4,7-dimethyl-) after pollination [62]. In addition to the volatile components listed above, 30 other types of nonvolatile components have been identified in *A. villosum*. Among these polysaccharide, Quercetin -8-*O*-α-L [rhamnopyranosyl]-3-*O*-α-L-[rhamnopyranosyl-(1′-2″)-β-D-particularyly abundant [57]. For instance, among 19 different types of different chemicals, six components (epicatechin, catechin, isoquercitrin, polydatin, vanillic acid, and quercitrin) were newly discovered in the water extraction of A. Fructus [6]. Additionally, the total flavonoids contents of *A. villosum* seeds, fruit, and peels were measured as 0.884, 0.772, and 0.01 mg/g, respectively [63].

6. Health benefit

Some of the pharmacological effects of *Amomum villosum* and *Amomum tsao-ko* are presented Fig. 4.

6.1. Antiobesity activity

Obesity is the most common disease marked by excessive deposition of body fat. It has emerged as the fifth most prevalent cause of death. It is caused by number of factors include genetic, lifestyle, diet, and environmental factors. It has been the fifth most common cause of mortality worldwide during the last 20 years due to its severe implications [58]. According to the World Health Organization, 13% of adults worldwide, 11% of men and 15% of women are classified as obese [64].

A study concluded that Extract of *A. villosum* has shown potential to prevent high-fat diet (HFD)-induced obesity in mouse. The suggested mechanisms involve the expressions and modifications of lipogenesis-related genes, such as ACC and FAS, in the liver. In addition, may influence lipid metabolism in a way that counters the negative impacts of a high-fat diet [65]. *A. villosum* water extract treatment has promising anti-obesity effects by influencing adipose tissue, hepatic triglycerides, and key molecular pathways involved in adipogenesis. AVE treatment significantly increased the expression of adiponectin in adipocytes. Adiponectin is a protein hormone that play crucial role in various metabolic processes, including regulation of glucose and fatty acid metabolism [66]. Another suggests that the mixtures of *A. villosum* (AV) and *Atractylodes macrocephala* (AM) extracts exhibit hypolipidemic (cholesterol-lowering) and anti-obesity effects in a (HFD)-induced obesity model. The findings are promising and suggest a potential avenue for developing therapeutic or preventive agents for obesity using these extract mixtures [67]. Treatment with *A. villosum* extract resulted in a significant increase in mRNA expression levels for key genes involved in lipid metabolism, such as the LDL receptor, sterol regulatory element-binding protein 2, and HMG-CoA reductase [68]. *A. tsao-ko* exhibit an anti-obesity effect. This effect is attributed to the inhibition of adipogenic transcription factors, and the suppression of genes associated with adipocyte development in 3T3-L1 cells. The inhibitory effect was linked to the down-regulation of adipogenic transcriptional factors, such as peroxisome proliferator-activated receptor γ and CCAAT-enhancer-binding protein α [69]. Four bioactive compounds were identified from the ethanol extract of *A. tsao-ko* fruits, including two phenolic compounds, a fatty acid, and a sesquiterpenes alcohol. The anti-adipogenic effect was noted to be dose-dependent manner, indicating that higher concentrations of the compounds were associated with stronger inhibition of lipid accumulation [70,71].

6.2. Neuroprotective activity

Zhang et al. (2014) discovered that flavonoids in *A. tsao-ko* had the potential of reducing H2O2-induced apoptosis in PC-12 cells [72,73]. Two new diphenylheptanes, namely 2,3-dihydro-2-(4′-hydroxy-phenylethyl)-6-[(3″,4″-dihydroxy-5″-methoxy) phenyl]-4-pyrone (CG-A) and 4-dihydro-2-(4′-hydroxy-phenylmethyl)-6-[(3″,4″-dihydroxy-5″-methoxyphenyl) methylene]-pyran-3,5-dione (CG-B), were extracted from the fruits of *A. tsao-ko*, and Explored their potential protective effects against H2O2-induced nerve

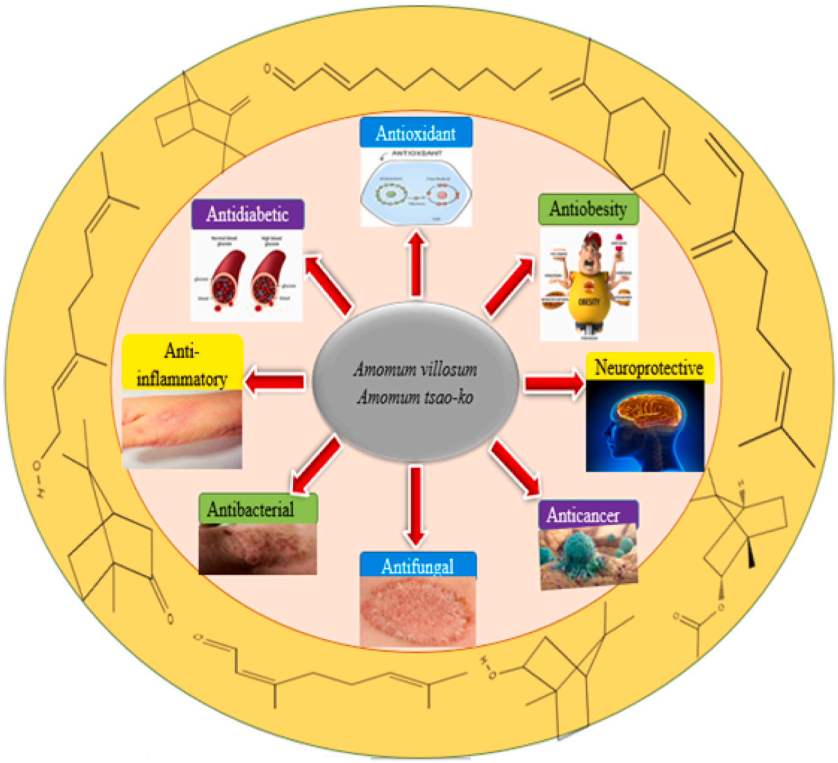

Fig. 4. The chemical makeup and pharmacological effects of *Amomum villosum* and *Amomum tsao-ko*.

injury. These results imply that both compounds play a crucial role as nutritional components responsible for the health benefits associated with neuroprotection and anti-inflammatory properties of *A. tsao-ko* [41]. The administration of EE-ATF (ethanolic fraction of *A. tsao-ko* fruit) considerably reduced the onset and duration of convulsions, suppress seizure severity, and lowered mortality in animals induced with PTZ (pentylenetetrazol). Treatment with EE-ATF also significantly improved the changes in GABA, glutamate, and dopamine levels, as well as the activities of Ca2+ ATPase and Na + K + ATPase in the brain tissues induced by PTZ. These findings suggest a potential therapeutic effect of EE-ATF in mitigating seizures and modulating neurotransmitter levels and enzyme activities associated with PTZ-induced convulsions [74]. Tsaokoic acid, a novel bicyclic nonene, was extracted from the fruits of *A. tsao-ko*, along with three known compounds: tsaokoin, vanillin, and tsaokoarylone. In silico molecular docking simulations indicated potential inhibitory activity of all compounds against acetylcholinesterase (AChE). Subsequent in vitro assays confirmed their moderate inhibitory activity, with IC50 values of 32.78 μM, 41.70 μM, 39.25 μM, and 31.13 μM, respectively. These results suggest the potential of these compounds, particularly tsaokoic acid, as inhibitors of AChE, which could have implications for neurological health and therapeutic development [75]. In the Morris water maze experiment, the *A. villosum* extract (AMV) extract group greatly inhibited the scopolamine-induced memory deficit in mice. According to the findings, AMV extract could be effective in the treatment and prevention of Alzheimer's disease [76].

6.3. Antidiabetics activity

Tsaokols A and B, classified as flavanol-monoterpenoid hybrids, were identified in the fruits of *A. tsao-ko*. Both compounds demonstrated noteworthy α-glucosidase inhibitory activity, showcasing IC50 values of 18.8 and 38.6 μmol/L, respectively, in comparison to acarbose with an IC50 value of 213 μmol/L it is suggested the potential of Tsaokols A and B as effective inhibitors of α-glucosidase, indicating their possible utility in managing conditions related to glucose metabolism and diabetes [18]. In a separate investigation, eight distinct compounds were isolated from the fruit extract of *A. tsao-ko*. These compounds exhibited significant α-glucosidase inhibitory activity, displaying IC50 values ranging from 59.4 to 116.5 μM, surpassing the inhibitory activity of acarbose (IC50: 219.0 μM). Enzyme kinetic analysis revealed that the 2,6-epoxy diarylheptanoids acted as noncompetitive inhibitors of α-glucosidase, with Ki values of 539.6 and 385.2 μM. These findings offer novel insights into the potential use of *A. tsao-ko* and highlight 2,6-epoxydiarylheptanoids as promising candidates for anti-diabetic applications [77]. A recent investigation proved that fifty bioactive compounds were discovered across five distinct fractions of *A. tsao-ko*, comprising 11 phenolic acids and derivatives, 18 flavonoids and derivatives, 14 proanthocyanidins, 2 organic acids, and 5 other compounds. Particularly, the ethyl acetate fraction (EF) displayed outstanding anti-α-glucosidase activity (IC_{50} = 20.14 μg/mL) and demonstrated antioxidant properties. Moreover, EF exhibited the ability to improve fasting blood glucose levels and glucose tolerance in diabetic mice. In summary, EF emerges as a promising candidate for potential development in preventing or treating conditions associated with oxidative stress and diabetes [78]. Administering *A. tsao-ko* extract at a dose of 100 mg freeze-dried powder per kg body weight for a period of 6 weeks resulted in a significant improvement in impaired glucose tolerance. This treatment also led to a decrease in levels of fasting blood glucose (FBG), insulin, and malondialdehyde (MDA), while increasing the superoxide dismutase (SOD) level. Histopathological analysis indicated that the A. tsao-ko extract maintained the structural integrity and functionality of the pancreas. In summary, the flavonoids present in A. tsao-ko exhibited remarkable antioxidant and antidiabetic properties, as demonstrated in both laboratory experiments and animal studies. This suggests that *A. tsao-ko* holds promise as a novel natural material and could be developed for use in functional foods and medicines related to the management of Type 2 Diabetes Mellitus (T2DM) [79]. *A. villosum* extract demonstrated a concentration-dependent inhibitory effect against rat α-glucosidase. At concentrations of 1, 3, and 5 mg/mL, AVE inhibited α-glucosidase activity by 31.99%, 48.85%, and 62.58%, respectively [68].

6.4. Antimicrobial activity

The microwave-assisted hydro distilled oil from fruit of *Amomum villosum* yielded the highest quantities of bornyl acetate, borneol, and camphor. Additionally, the essential oil samples exhibited antimicrobial activity, inhibiting the growth of *Enterococcus faecalis, Staphylococcus aureus, Bacillus cereus, and Pseudomonas aeruginosa,* with minimum inhibitory concentrations (MIC) ranging from 100 to 200 μg/mL. Notably, the hydrodistilled oil demonstrated superior antimicrobial potential [80]. Furthermore, the total flavonoids of *A. villosum* extract demonstrated inhibitory effects on both *E. coli* and *B. subtilis*, with a more pronounced impact on *E. coli*. In conclusion, these findings lay the groundwork for further exploration of bioactive compounds in *A. villosum* Lour. and their effective utilization. This research contributes to the understanding of its potential applications in deep processing, as well as its development and utilization as a fundamental ingredient in the food industry [42]. One hundred and thirty-eight bioactive components have been identified in essential oil extracts obtained from the seeds and husks of *A. villosum* Lour. The primary components of the essential oil were bornyl acetate, camphor, borneol, also including α-pinene, β-pinene, α-copalene, neophytadiene, globulol, and bicyclogermacrene, etc. The essential oil demonstrated significant inhibitory effects against *Trichophyton rubrum, Trichophyton mentagrophyton, Microsporum gypseum, Staphylococcus aureus*, and *Enterococcus faecalis,* based on the results of the study on its antimicrobial properties. This suggests the potential of the essential oil as an effective agent against these bacteria and fungi, which could have applications in various fields such as medicine, agriculture, or cosmetics where controlling the growth of microorganisms is crucial [81,82]. Seventy-three bioactive compounds were identified in the essential oil extracted from the fruit of *A. tsao-ko*. The key constituents included 1,8-cineole, geraniol, geranial, α-terpineol, and α-phellandrene. Notably, the essential oil exhibited a wide-ranging spectrum of antimicrobial activity, effectively inhibiting various microorganisms, encompassing both bacteria, as well as fungi. Noteworthy it has potent bactericidal effect against *Staphylococcus aureus* with the minimum inhibitory concentration and minimum bactericidal concentration of 0.20 g L−1 [46]. Essential oil of *A. tsao-ko* exhibited significant antimicrobial efficacy, displaying a moderate to potent spectrum of activity against all tested strains. This included 5 g-positive and 2 g-negative bacteria, with minimum inhibitory concentrations (MIC) ranging from 2.94 to 5.86 mg/mL. These finding are due to predominant bioactive components geraniol, 1.8-cineole, and α-phellendrene [47] (see Table 4). Another study revealed that 1,8-cineole isolated from essential oil of *A. tsao-ko*, demonstrated a weak inhibitory effect on bacteria and proved to be ineffective against fungi. The essential oil exhibited varying degrees of antimicrobial activity against bacteria, with the order of effectiveness being *Bacillus subtilis* > *Staphylococcus albus* > *Escherichia coli*. Regarding fungi, the essential oil displayed inhibitory activity in the following order: *Aspergillus oryzae* > Rhizopus sp. > Penicillium sp [12]. Another investigation showed that the *A. tsao-ko* extracts had a minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of 1.25 mg/mL against B. subtilis and L. monocytogenes. Bacterial growth curves illustrated a distinct antibacterial effect of *A. tsao-ko* extracts on *Bacillus subtilis* and *L. monocytogenes*. Moreover, the mechanism of action of *A. tsao-ko* was assessed by examining its impact on cell membrane integrity and cell morphology. The leakage of alkaline phosphatase (AKP) provided confirmation that the *A. tsao-ko* extracts inflicted significant damage to the cell wall structure of both *B. subtilis* and *L. monocytogenes*. This suggests a potential disruption of bacterial cell integrity as part of the antimicrobial activity of *A. tsao-ko* extracts [83]. According to Tang et al.'s analysis, the mechanism of action of *Amomum villosum* Lour's essential oils against methicillin-resistant *S. aureus* (MRSA) involves diminishing the bacterial adherence to inert surfaces. They conducted the first proteome analysis of A. villosum Lour EO's mode of action against MRSA and demonstrated that the inhibitory effect is temperature- and dose-dependent [83]. Another study indicated that citral and geraniol induced rapid and substantial reactive oxygen species (ROS) production in Aspergillus flavus. This finding is consistent with an earlier report which demonstrated that citral and carvacrol induced oxidative damage in *Escherichia coli* as well [84,85].

6.5. Anticancer activity

The polysaccharides from *A. villosum* extract displayed dose-dependent anticancer activity in the concentration range of 50–500 μg/mL [50]. Volatile oil and flavonoids extract from *A. villosum* effectively inhibited the growth of MFC cells. Flow cytometry analysis further confirmed that treatment with these extracts induced apoptosis in MFC cells. This apoptotic effect was mediated through the reactive oxygen species (ROS)-mediated mitochondrial pathway, evidenced by increased endogenous ROS levels and the collapse of mitochondrial membrane potential. In conclusion, the findings suggest that FNAV holds promise as a potential candidate for the development of new drugs for the treatment of gastric cancer [43,89]. Crude extracts obtained from *A. villosum* demonstrated cytotoxic effects, with IC50 values ranging from 100 to 500 μg/mL [93]. Four distinct compounds names, isotsaokoin (I), hannokinol (II), 2, 3-dihydro-2-(4′-hydroxy-phenylethyl)-6-[(3″,4″-dihydroxy-5″-methoxy)phenyl]-4-pyrone (compound III) and 4-dihydro-2-(4′-hydroxy-phenylmethyl)-6-[(3″,4″-dihydroxy-5″-methoxyphenyl)methylene] pyran-3,5 dione (IV) have been isolated from extract of *A. tsao-ko*. Compounds III and IV displayed notable antioxidant activity. Additionally, Compound II, III, and IV exhibited significant anti-tumor activity against tested tumor cell lines (HepG-2, SMMC-7721, HeLa, and A549). The robust antioxidant and anti-tumor activities observed. Result suggested that they merit further investigation as potential effective nutraceutical compounds and candidates for chemotherapeutic drugs [94,95]. The crude methanol extract obtained from the fruits of *A. tsao-ko* demonstrated cytotoxic

Table 4
Chemical profiles of essential oils of *Amomum villosum* and *Amomum tsao ko*.

Species	Plant parts	Chemical constituents	Medicinal properties	References
Amomum villosum	Roots & leaves	B–pinene, α–pinene	Anti-inflammatory	[56,86–88]
	Stem	B-pinene, α–pinene	Antioxidant	
	Fruit	Bornyl acetate, β-pinene,	Anticancer	
		A–pinene camphor, bornyl acetate, D–limonene,	Neuroprotective	
		Camphene, borneol,	Antiobesity	
		B–myrcene, limonene,	Antimicrobial	
		Dl–camphor, isobornyl formate		
	Essential oil	Bornyl acetate		
		Methylarctigenin		
		Aniba-dimer-C, cardamomin,		
		5,7 dimethoxyflavanone		
Amomum Tsao ko	Whole pod	Geranial, 1,8–cineole, geraniol,	Anti-inflammatory	[54,89,90–92]
		Trans-2,3,3a,	Neuroprotective	
		7a-tetrahydro-1H-indene-4-carbaldehyde, (2E)–decenal	Antioxidants	
	Fruit	1,8-cineole, geraniol, 2-*iso*-propylbenzaldehyde, nerol,	Anticancer	
		A–methyl cinnamaldehyde 3–heptylacrolein, citral,	Antiobesity	
		A–phellendrene,	Antimicrobial	
		A–terpineol, limonene		
		2–isopropyltoluene		
		Undecane,		
		P–propylbenzaldehyde		
	Seed	1,8-cineole, 2-decenal, geranial, neral		
	Essential oil of fruit	Amotsaokonal B and Amotsaokonal C		

activity. Through bioactivity-guided separation, a diarylheptanoid named tsaokoarylone was isolated. Tsaokoarylone exhibited cytotoxic effects with IC50 values of 4.9 μg/mL and 11.4 μg/mL against human non-small cell lung cancer A549 and human melanoma SK-Mel-2, respectively, as determined by the SRB colorimetric method [96]. In a recent study, it is demonstrated that the ethanol extract from *A. tsao-ko* possesses inhibitory effects on ovarian cancer and reduces angiogenesis in vivo. At-EE did not directly affect vascular endothelial cells but rather reduced the secretion of IL-6 and VEGF by ovarian cancer cells, thereby inhibiting angiogenesis through the suppression of p-STAT3 and NF-kB activation. *A. tsao-ko* has been observed to exhibit an antitumor effect on liver cancer cells; however, the specific mechanism underlying this effect is not yet clear [97,98].

6.6. Antioxidant activity

Amomum genus constituent; catechins and catechol have showed antioxidant activity. Eleven compounds were isolated from the fruit ethyl acetate-soluble fraction of *Amomum tsao-ko*. The catechins and derivatives of catechol demonstrated significant efficacy in both the DPPH radical scavenging activity and antioxidant activity assays [99]. The essential oil derived from *A. tsao-ko* demonstrated cytotoxicity across various cell types and induced cytotoxic activity specifically in HepG2 cells through an apoptosis-related mechanism. Additionally, it exhibited weak antioxidant properties. The data indicates that the essential oil derived from *A. tsao-ko* holds promise as a potential medicinal resource due to presence active constituents of the oil, particularly aldehydes [100]. The distinct polar fractions of the ethanol extract from fruit of *A. tsao-ko* exhibited specific in vitro antioxidant capabilities. Notably, the ethyl acetate fraction demonstrated the most potent scavenging effect on DPPH radicals, while the n-butanol fraction exhibited the strongest ability to scavenge superoxide anion radicals and reduce $Fe3+$ [97]. *A. tsao-ko*. The findings revealed that the extract exhibited robust scavenging abilities against DPPH (IC50, 0.044 mg/mL) and ABTS free radicals (IC50, 0.040 mg/mL). Another study on *A. villosum* reported that the quantitative components in gas chromatography (GC) ranged from 0.858 to 0.879, while those in high-performance liquid chromatography (HPLC) ranged from 0.817 to 0.902. This suggests that both the volatile and non-volatile components of AMV contribute significantly to antioxidant activity [79]. Six bioactive compounds have been isolated from stem and leaves extract of *A. villosum* namely, pahangensin B, 16-oxo-8,12(E)-labdadien-15-oic acid, 3,7-dihydroxyhumula- 4,8,10(E)-triene, cardamomin, 5-hydroxy-7-methoxydihydroflavone, and phenylpropionic acid. A preliminary examination of the structure–activity relationship indicated that kavapyrone compounds exhibited varied anti-inflammatory and antioxidant effects, likely attributed to their distinct stereo configurations. Additionally, the presence of the C-16 aldehyde group emerged as a potential key factor influencing the antioxidant activities of labdane diterpenoids. In conclusion, findings propose that the leaves and stems of *A. villosum* Lour. have the potential to be developed into a new functional food or drug for the prevention and treatment of oxidative stress [8]. Polysaccharides from seed of *A. villosum* demonstrated strong scavenging activities against superoxide radicals, hydroxyl radicals, and DPPH radicals. In terms of antioxidant activity in vivo, crude ASP significantly mitigated the elevation of serum ALT and AST levels, decreased the formation of MDA (Malondialdehyde), and boosted the activities of SOD (Superoxide Dismutase) and GSH-Px (Glutathione Peroxidase) in mice with carbon tetrachloride-induced liver injury. These comprehensive results suggest that ASP represents a novel and promising source of natural antioxidants due to presence of glucose, arabinose, sulfuric radical, galactose, mannose, protein, and uronic acid [50]. The fruit of *A. villosum* exhibited the highest concentration of total flavonoids content (TFC) and demonstrated the most effective antioxidant activity [101]. The GC-MS analysis revealed the occurrence of 15 components in the fruit n-hexane extract of *A. villosum*, collectively constituting over 50% of the total peak area. The predominant constituents identified were (E)-nerolidol and linalool. Notably, (E)-nerolidol is recognized for its antioxidant, antinociceptive, and antiulcer activities [102]. Another result reported that the flavonoids from crude extract of *A. villosum* Lour. exhibited superior antioxidant capability compared to vitamin C at equivalent concentrations [42].

6.7. Anti-inflammatory activity

The inflammatory potential of *A. villosum* was recently discovered. Amomum genus is a good sources of anti-inflammatory compounds. Aniba-dimer-C, cardamomin, 5,7 dimethoxyflavanone and methylarctigenin are the compounds have been isolated from stem and leaves of *A. villosum*, which exhibit the potent anti-inflammatory activity [8]. AVLP-2, a new acidic polysaccharide identified and purified from *A. villosum* Lour. AVLP-2 influenced the levels of various inflammatory markers: MPO (myeloperoxidase) levels were reduced, Levels of pro-inflammatory factors, such as IL-1β and NF-κB p65, were downregulated. As resultant, Anti-inflammatory IL-10 levels were increased. TNF-α levels were upregulated by AVLP-2 treatment. These effects collectively suggest that AVLP-2 has a protective impact on the gastric mucosa by mitigating oxidative stress and inflammation induced by alcohol and LPS [103,104]. Another study concluded that water extract and volatile oils from *A. villosum* have a multifaceted impact on the immune and inflammatory processes in the context of IBD in rat. The regulation of inflammatory cytokines, modulation of $CD4^{+}CD25+FOXP3+$ T cells, and support for intestinal micro ecological balance all contribute to the observed anti-inflammatory effects [49]. In preclinical studied, it was reported that Bornyl acetate is a natural compound found in essential oil of *A. villosum* and it has been studied for its pharmacological effects, including anti-inflammatory and analgesic properties. The result showed the ability to lighten the pain caused by the hot-plate. Bornyl acetate demonstrated both analgesic and anti-inflammatory effects as evidenced by its ability to suppress ear swelling caused by dimethylbenzene [45]. Ulcerative colitis (UC) is a prominent example within the spectrum of inflammatory bowel diseases (IBD). This chronic condition primarily affects the colon and rectum, characterized by persistent inflammation, abdominal pain, bloody diarrhea, weight loss, fatigue, and an urgent need for bowel movements [105]. The administration of AVLP (presumed to be *A. villosum* polysaccharides) demonstrated significant positive effects in a mouse model of colitis. The findings suggest that the intake of AVLP could be considered a promising nutritional strategy for managing inflammatory bowel diseases. The observed effects on body weight, colon parameters, inflammatory markers, and intestinal barrier function, coupled with the significant impact on the composition of gut microbiota, highlight the potential therapeutic benefits of AVLP in the context of colitis [106]. Another study reported that Volatile oil of *A. villosum* exhibited efficient control over the intestinal microflora, ameliorated chronic low-grade inflammation by enhancing the expressions of ZO-1 and occludin proteins, and suppressed the TLR4/NF-κB signaling pathway [107,108]. Amotsaokonal B and Amotsaokonal C are compounds isolated from ethanol extract of *A. tsao-ko*. The isolates were assessed for their capacity to inhibit NO production in RAW264.7 cells induced by LPS. Compounds demonstrated inhibitory effects, with IC50 values measured at 94.8 and 61.2 μM, respectively [17]. Two novel bicycle nonanes along with eleven known compounds have been isolated from methanolic extract of *A. tsao-ko* fruit. All compounds exhibited noteworthy inhibitory effects on NO production in lipopolysaccharide-stimulated BV2 microglia showing efficacy across concentrations ranging from 1 μM to 100 mM [109]. Methanolic extract of *A. tsao-ko* robustly inhibits nitric oxide (NO) production induced by lipopolysaccharide (LPS). This inhibition is attributed to the activation of the ROS/MAPKs/Nrf2-mediated heme oxygenase-1 (HO-1) signaling pathway. These results provide support for the pharmacological efficacy of AOM in addressing inflammatory diseases [110].

7. Deployment in culinary industry

Numerous plants within the genus Amomum are utilized as spices and collectively known as 'cardamom' [4,22]. Spices are essential food requirements that enhance flavor, and their trade has played a significant role in the development of human civilization and the histories of various nations [111–113]. The primary applications of *A. villosum* and *A. tsao-ko* were predominantly in the food industry, with usage as a food additive accounting for over 90% of their utilization. Conversely, their utilization as a Chinese patent medicine represented less than 5% of their overall applications. This underscores the significant role of these plants as food additives, highlighting their widespread use in culinary. *A. tsao-ko* is widely utilized in the food sector as a flavoring and aromatizing ingredient, mostly dried fruits, powders [72]. *Amomi Fructus* is used as a raw material of 355 Chinese patent drug and 1082 prescription as well as 65 health food in China. *A. tsao-ko* is a commercially important spice renowned with a potent aroma commonly available in the Southeast Asian market; it has a 1000-year cultivation and application history [88]. *A. villosum* and *A. tsao-ko*, with a rich history of use in China, are renowned as a premium flavoring agents. It has been a traditional choice in cooking condiments and widely adopted as a flavor-enhancing spice for various culinary applications, including hotpot, diverse dishes, and meat preparation. Its role in elevating taste and neutralizing unpleasant aromas contributes to an enhanced culinary experience. Importantly, plants not only impart a unique flavor to dishes but also retain their medicinal properties. In the markets of South-East Asia, *A. tsao-ko* holds considerable commercial significance as a spice [Fig. 5 (a-d)]. Due to its notable economic value, there is a practice of blending *A. tsao-ko* with other fruits in the same genus, serving as adulterants [114]. The ripe fruit of *A. villosum* Lour is usually referred to as Fructus Amomi (FA). However, FAL is always substantially more expensive due to its superior market quality [6].

Based on a survey report, the total output value of A. Tsao-ko amounted to 350 million in 2018. The annual national consumption of A. Tsao-ko and dried fruit was estimated at approximately 12,550 tons, with a similar global total output. These findings suggest a market scenario marked by a shortage in supply. Nujiang prefecture sees *A. tsao-ko* as a core industry for assisting peasants in increasing their income, assisting the impoverished in increasing their per capita income by more than 2700 yuan [19].

In conclusion, the cultivation of *A. villosum* and *A. tsao-ko* is very important, and the expansion of spice and TCM cultivation can boost the income of China's western regions and support economic development.

a. Fuit harvesting & marketing b. Product development c. Grain production d. Public awareness

Fig. 5. Product development and commercialization of *Amomum villosum* and *Amomum tsao-ko*.

8. Conclusions

This review summarizes the continual development of health promoting compounds and their pharmacological application of common flavoring substances the *A. tsao-ko and A. villosum*. In this review discusses the chemical makeup and pharmacological effects of *A. villosum*, *A. tsao-ko*, emphasizing the prevalence of flavonoids, terpenes, and diarylheptanoids. Flavonoids constitute the largest portion at 30.4%, with a focus on activities related to diabetes, cardiovascular, and cerebrovascular disorders. Diarylheptanoids, found in *A. tsao-ko*, exhibit anti-inflammatory, antitumor, anti-complementary, and anti-diabetic properties. While terpenes are fewer than flavonoids, they demonstrate heightened antioxidant, anti-inflammatory, antimicrobial, and antitumor activities, particularly within the subgroup of monoterpenes. The passage underscores the need to better connect foundational studies with practical applications of plants proposing a comprehensive approach to quality markers based on chemical composition, pharmacological impacts, and clinical effectiveness. Despite indications of minimal toxicity in current research, the passage highlights a gap in understanding the connection between identified toxicities and the spice's clinical application. In conclusion, both *A. villosum* and *A. tsao-ko* have extensive historical clinical use in treating various disorders. Recent studies have unveiled their rich chemical composition consisting of hundreds of compounds and their diverse biological activities. These findings pave the way for the promising potential of these plants as natural sources for the development of next-generation medications. Furthermore, they provide a groundwork for future exploration into the therapeutic mechanisms and the intricate relationship between chemical composition, pharmacological activity and clinical application, of *A. villosum* and *A. tsao-ko* in the future.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

CRediT authorship contribution statement

Sehrish Imran: Data curation. **Yamin Bibi:** Software, Resources. **Li-E Yang:** Software, Methodology. **Abdul Qayyum:** Writing – review & editing. **Wei He:** Data curation, Conceptualization. **Jiazhen Yang:** Software, Resources, Conceptualization. **Xiaomeng Yang:** Supervision, Software. **Xiaoying Pu:** Visualization, Validation. **Xia Li:** Validation, Resources. **Yawen Zeng:** Writing – original draft, Visualization, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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