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Traditional uses, phytochemicals and pharmacological properties of *Allium tuberosum* Rottler ex spreng

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Abstract
Allium tuberosum is a lesser known plant of the *Allium* genus compared to the more known *Allium cepa* (onion) or *Allium sativum* (garlic). However, *Allium tuberosum* is now being increasingly recognized to be an important plant in its own right with diverse important pharmacological activities. This review will attempt to describe the reported phytochemicals and pharmacological activities of the plant with the objective to determine the plant's potential to be a source of lead compounds and effective new drugs.

Keywords: *Allium tuberosum*, garlic chive, amaryllidaceae

1. Introduction
From ancient periods people have been using a diverse range of medicinal plants for curing diseases. In the last 200 years, traditional systems of plant based medicines have been largely replaced with allopathic system of medicine, the latter being based on the principle of one drug-one therapy. Allopathic medicines are largely synthetic. Now the traditional way of healing is making a comeback as a large number of synthetic drugs are costly and shows adverse side-effects. Different family of plants shows effectiveness against various diseases due to presence of different phytochemicals. The genus *Allium* which belongs to Amaryllidaceae family contains approximately 700 species of plants such as *Allium cepa* (onion), *Allium sativum* (garlic), *Allium schoenoprasum* (chive), *Allium tuberosum* (garlic chive) etc. They all are important because of their commercial and nutritional value [1]. Some species of *Allium* genus have not been explored that much, which also have healing properties and *Allium tuberosum* is one of them. *Allium tuberosum* mainly grows in Asian countries. People of China, the Philippines, Korea, and Thailand consume this plant as vegetable; the plant is found largely in these countries. This plant is also considered as medicinal plant in these countries [2]. Local people of Arunachal Pradesh, India have been using the plant root, bulb, leaves and cloves for the treatment of cold and cough. It is also used for ornamental purpose because of attractive colored flowers [3]. It is a very popular spice and taken for increasing libido (sexual urge) and for the treatment of erectile dysfunction in traditional Chinese medicine. Therefore, it works as an aphrodisiac [4]. The plant is also used for lowering cholesterol as well as hair tonic locally in India [5].

2. Botanical description
Allium tuberosum is a perennial herbaceous plant which is a late season bloomer commonly found in Southeastern Asia. Because of the mild garlic flavor of leaves, the plant is also known as "garlic chive". The grey-green foliage can be 10-20" tall, bulb stays attached to the fleshy strong rhizome which produces 4-9 leaves. Bulbs are cylindrical in shape with 4-6 m length. Leaves are used in uncooked dishes for its subtle garlic like flavor.
Plant grows well in summer and in winter they dry up. Flowers bloom in late summer or early fall. It seems a bunch of butterfly is sitting on 3-2 foot-tall shoot above the foliage. Flowers are white star shaped with mild fragrance which attracts various pollinators for pollination. The plant grows by seed or by dividing clumps. Seeds can cause uncontrolled spread, so flowers should be cut off immediately after blooming. Seeds are black colored and triangular shaped, filling with a hard capsule [6, 7].

3. Synonyms of *Allium tuberosum* [8].

- *Allium angulosum* Lour.
- *Allium argyi* H. Lev
- *Allium chinense* Maxim
- *Allium roxburghii* Kunth
- *Allium clarkei* Hook.f.
- *Allium uliginosum* G.Don

4. Vernacular Names of *Allium tuberosum* [9].

- Chinese chives (English)
- Kuchai (Malaysia)
- Kucai (Indonesia)
- Kutsay, Ganda (Philippines)
- Kuichai (Thailand)

5. Taxonomic Tree

- Domain: Eukaryota
- Kingdom: Plantae
- Phylum: Spermatophyta
- Subphylum: Angiospermae
- Class: Monocotyledonae
- Order: Liliales
- Family: Amaryllidaceae
- Genus: *Allium*
- Species: *Allium tuberosum*

6. Traditional uses

Allium tuberosum is used for the treatment of asthma, abdominal pain, diarrhea, nocturnal emission and diabetes in folklore medicine [10]. The plant is highly used in China for its aphrodisiac property as well as nocturnal emission [11]. Traditionally in Manipur, North East India amongst Meitei communities the plant is known as Maroi-nakuppi and decoction of garlic chives or whole plant is taken as vegetable for curing various liver disorders as well as gastrointestinal disorders [12]. It helps in lessening blood glucose and serum cholesterol level. This plant also has anticoagulant effect. The plant has been used as an antidote for poisonous bites. Excessive bleeding can be controlled by the plant juice, bulbs contain vulnerary properties. Seeds are used for treating kidney, liver and digestive system problems [13]. Garlic chive has been used in traditional Chinese medicine for large number of purposes, which encompasses enhancing energy, and boosting good digestion and immune system. It can even cure anemia by controlling hemorrhage and also treat fatigue. This plant is also effective against intestinal parasites. According to Chinese folk traditions, there is a belief that the root of *Allium tuberosum* can prevent gastric ulcer and treat dyspepsia [14-16].

An aboriginal group of people from the Zamboanga Peninsula, Philippines named Subanen (river people) use the poultice of whole plant to treat fever [17]. Some secondary metabolites of *Allium tuberosum* have been found effective against asthma, which is traditionally used in Philippines for treatment of asthma [18]. In India the plant is popular for the treatment of spermatorrhoea, which is recognized in traditional Chinese medicine as a condition of frequent involuntary ejaculation. Plant juice acts as moth repellent. Essential oil from *Allium tuberosum* possesses larvicidal activity especially against larval mosquitoes [19, 20]. For toothache, the plant seeds are largely used as an antiseptic mouthwash in Thailand and Indo-China [8].

7. Reported Phytochemicals

Different parts of *Allium tuberosum* have been reported to consist of a substantial number of phyochemicals. Leaves were reportedly found to contain sulfides, linalool and flavonoid glycosides. Methanolic extract of aerial parts of the plant was examined, which gave two new phenylpropane glycosides specified by tuberonoid A (1) and B (2). With these two, four common flavonoids named [kaempferol 3-*O*-b-sophoroside], [3-*O*-b-D-(2-*O*-feruloyl)-glucosyl-7, 40-di-*O*-b-D-glucosylkaempferol], [3-*O*-b-sophorosyl-7-*O*-b-D-(2-*O*-feruloyl)glucosylkaempferol], and [kaempferol 3,4-*O*-di-*O*-b-D-glucoside] were found [21]. Alcoholic extract of garlic chives seeds gave several chemical constituents. The compounds were identified as [nicotianoside C], [(22S)-cholest-5-ene-1 beta, 3 beta, 16 beta, 22-tetrol-1-O-alpha-L-rhamnopyranosyl-16-O-beta-D-glucopyranoside], daucosterol, adenosine, and thymidine, which were isolated for the first time from seed of this plant [22].

The seeds of *Allium tuberosum* are a rich source of steroid saponins [23]. From 1999 to 2002, thirteen steroidal saponin compounds have been identified from this plant's seeds, which were named tuberoside (A-M). In 2003, eight new steroid saponins were further reported that included four spirostanols, three furostanols and one cholesterol saponin from the seeds. These new steroid saponins were basically isolated by acid hydrolysis and comprehensive spectroscopic analysis, and named as tuberoside (N-U) with molecular formulas of $C_{45}H_{74}O_{18}$, $C_{33}H_{54}O_{10}$, $C_{39}H_{64}O_{14}$, $C_{39}H_{64}O_{15}$, $C_{39}H_{64}O_{15}$, $C_{51}H_{84}O_{22}$, $C_{51}H_{84}O_{21}$, $C_{51}H_{86}O_{22}$, respectively [24].

Methanolic extract of seeds of the plant gave three oligoglycosides; two of them were furostane-type steroidal oligoglycosides and another one was pregnane-type oligoglycoside. The structures of the compounds were determined by spectroscopic analysis. The two furostane-type steroidal oligoglycosides were [26-*O*-b-D-glucopyranosyl-(25R)-3b,22x,26-trihydroxyl-5a-furostane3-*O*-b-chacotrioside] ($C_{51}H_{86}NaO_{22}$) and [26-*O*-b-D-glucopyranosyl-(25S)-3b,5b,6a,22x,26-pentahy-droxyl-5b-furostane 3-*O*-a-L-rhamnopyranosyl-(1→4)-b-D-glucopyranoside] ($C_{45}H_{76}NaO_{20}$). The structure of the pregnane-type oligoglycoside was [3-*O*-a-L-rhamnopyranosyl-(1→4)-b-D-glucopyranosyl 3b,5b,6a,16b-tetrahydroxypregnane 16-(5-*O*-b-D-glucopyranoyl-4(S)-methyl-5-hydroxypentanoic acid) ester] with the molecular formula $C_{45}H_{76}NaO_{20}$ [25].

Phytochemical analysis of roots of garlic chives revealed three new spirostanol saponins along with three known compound from the root of the plant. The saponin compounds were named tuberosine A [(25S)-5b-spirostan-2b,3b-diol 3-*O*-b-D-glucopyranoside], tuberosine B [(25S)-5b-spirostan-2b,3b,19-triol 3-*O*-b-Dglucopyranoside] and tuberosine C [(25S)-5b-spirostan-2b,3b-diol 3-*O*-a-L-rhamnopyranoyl-(1-4)-*O*-b-D-glucopyranoside]. Molecular formulas of the three tuberosines were $C_{33}H_{54}O_9$, $C_{33}H_{54}O_{10}$, and $C_{39}H_{64}O_{13}$, respectively [26]. A new phenylpropanoidglucoside along with a new chain compound were isolated from the methanolic extract of garlic chives roots. The glucoside compound was named tuberosine D. Molecular formula of the compound was inferred to be $C_{19}H_{28}O_{12}$. The second chain compound was (*Z*)-11*R*, 12*S*, 13*S*-trihydroxy-9-octadecenoate with the molecular formula $C_{18}H_{34}O_5$ [27]. Some novel compounds were isolated from the ethanolic extract of *A. tuberosum* among which four were new pyrazines with unique flavor, one lignan and three new flavonoids. From this study, a total 40 compounds were identified including 32 known compounds. The four pyrazine compounds were colorless oil with distinguishing roasting odor and their structures were established to be (R)-2-(1-ethoxyl)-5-(2-ethoxyl)-pyrazine

($C_8H_{12}N_2O_2$), 2-methyl-3-methylol-5-ethyl-pyrazine ($C_8H_{12}N_2O$), (R)-2-(1-ethoxyl)-6-ethyl-pyridazine ($C_8H_{12}N_2O_2$), and (R)-2, 3-di-methyl-6-(1-ethoxyl)-pyridazine ($C_8H_{12}N_2O$). Three new flavonoid compounds were found from garlic chives and their structures were elucidated to be quercetin-3-*O*-(6-trans-feruloyl)-b-D-glucopyranosyl-(1/2)-bDglucopyranoside-7-*O*-b-D-glucopyranoside ($C_{43}H_{48}O_{25}$), kaempferol-3-*O*-(6-trans-feruloyl)-b-D-glucopyranosyl-(1/2)-b-D-glucopyranoside-7-*O*-b-D-glucopyranoside ($C_{43}H_{48}O_{24}$), and quercetin-3-*O*-(6-*trans*-p-coumaroyl)-b-D-glucopyranosyl-(1/2)-b-D-glucopyranoside-7-*O*-b-D-glucopyranoside ($C_{42}H_{46}O_{24}$). A new lignan compound isolated from the plant was identified as (7R, 8S)-dihydrodehydrodiconiferyl alcohol-di-9, 90-*O*-b-Dglucopyranoside ($C_{32}H_{44}O_{16}$). Some of the known compounds identified reportedly are uridine, thymine, deoxythymidine, thymidine, guanosine, adenine, adenosine, deoxyadenosine, 1-methyl-l,2,3,4-tetrahydro-carboline-3-carboxylic acid, D-tryptophan, D-phenylalanine, 2-[(1R,2R)-2-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-1-(hydroxymethyl)-ethoxy]-5-(3-hydroxypropyl)-phenyl-b-D-glucopyranoside, hydroxybenzoic acid etc [28-30].

Plants may contain an amazing number of volatile compounds, which may serve as perfumes and flavors for various purposes. These plant volatiles also have been found effective as insect repellent [31]. Different plant parts of *A. tuberosum* have been analyzed which showed that methyl and 2-propenyl (allyl) radicals are present as volatile disulfides [32].

37 essential oils have been found from *Allium tuberosum* and they comprise mainly of dimethyl disulfide (19.58%), allyl methyl disulfide (14.37%), dimethyl trisulfide (14.34%), allyl methyl trisulfide (7.24%), methyl 1-propenyl disulfide (6.07%) and diallyl disulfide (5.14%) [33]. Further investigation claimed of identifying 47 volatiles from the fresh flower of leek comprising 24 sulfur containing compounds, 4 aldehydes, 3 alcohols, 3 ketones and 9 hydrocarbons [34].

Nucleosides and nucleotides were also identified from different solvent (petroleum ether, ethyl acetate, n-butanol and water)extractof the plant. Uracil was identified as 4-pyrimidinediol, a white powder holding the molecular formula $C_4H_4N_2O_2$. The second compound was thymine, determined as 2,4-hydroxy, 5-methylpyrimidine which molecular formula was decided to be $C_5H_6N_2O_2$. Compound 3 was thymidine or thymidine deoxyriboside, determined to be 1-(2-deoxy-β-$_D$-ribofuranosyl)-5-methyluracil and its molecular formula was established to be $C_{10}H_{14}N_2O_5$. The last one was $C_{10}H_{13}N_5O_4$ which was named adenosine or adenine riboside and was identified as 9-(beta-D-ribofuranosyl)-adenine [35]. The structures of some important phytochemicals are shown in Figure 1.

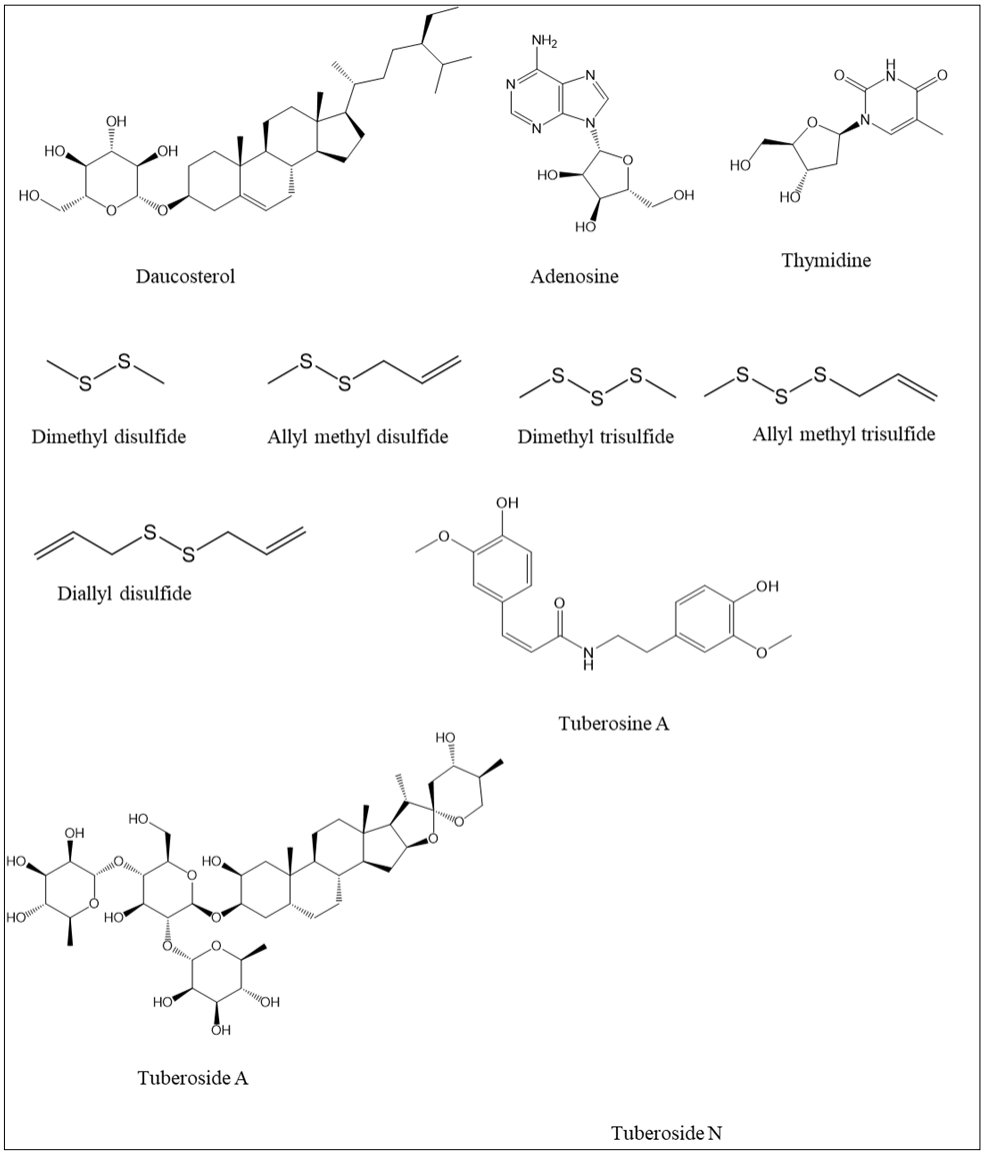

Fig 1: Some constituents isolated from various parts of *Allium tuberosum*

8. Pharmacological importance

8.1 Antidiabetic and Hepatoprotective

Garlic chives as well as its chemical constituents have various pharmacological properties including anticancer, antioxidant, aphrodisiac and nematicidal. A recent study was conducted on the antidiabetic and hepatoprotective activity of the plant. Diabetes was induced by alloxan in Wistar albino rats; rats were further given the extract of *A. tuberosum* in various doses of 100, 200, 400 mg/kg. The extract considerably reduced the blood glucose level. Some other parameters were also checked in diabetic rats. There was a substantial amount of down regulation in serum level triglyseride, total cholesterol and up regulation of high density lipoprotein (HDL). Extract of the plant significantly increased antioxidant enzyme activity in diabetic rats. Carbon tetrachloride (CCl_4) induced hepatotoxicity was studied in Swiss albino mice. The plant extract significantly reduced serum levels of aspartate amino transferase (AST), alanine amino transferase (ALT), and alkaline phosphatase (ALP), which act as liver function enzymes. The extract was also found to mitigate tumor necrosis factor alpha (TNF-α), interleukin 1b (IL-1b) and interleukin 6 (IL-6) pro-inflammatory markers [36]. Another study showed that flavonoids present in garlic chives especially allicin gave hepatoprotective and antioxidant activities. The study was performed on Wistar rats treated with doxorubicine for inducing liver injury. Test for serum glutamate pyruvate transaminase (GPT, also known as ALT) and serum glutamate oxaloacetate transaminase (GOT, also known as AST) were performed as the indicators of liver cell injury. It was found that after treating with extract of *A. tuberosum* at a dose of 1000 mg/kg body weight, serum levels of sGPT and sGOT decreased considerably, which indicated that the plant has hepatoprotective attributes. It was concluded that the plant extract was involved in repairing mechanism of liver by decreasing the serum level of malondialdehyde (MDA) [37].

8.2 Antibacterial

Several studies have shown that *A. tuberosum* has the property to combat pathogenic bacteria. Ethanolic extract of garlic chive leaves was found effective against growth of *Klebsiella pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis*. The highest inhibition was found to be against *B. subtilis* compared with others [38]. A later study revealed that *A. tuberosum* extract gave more lethal effect against *S. aureus* and *B. subtilis*. The study even showed that *A. tuberosum* has more significant antibacterial activity than *Allium sativum* [39]. A further report exhibited that some Gram-positive bacteria such as *Salmonella typhimurium, Escherichia coli, Campylobacter jejuni, S. aureus*, and *Listeria monocytogenes* were sensitive to essential oil like diallyl disulfide from garlic chives [33, 40]. The thiosulfinates present in *A. tuberosum*, *S*-methyl methanethiosulfonate and *S*-methyl 2-propene-1-thiosulfinate gave antibacterial effect against *Escherichia coli* O-157:H7 [41].

8.3 Antifungal

Thiosulfonates of *A. tuberosum* showed antifungal activity against *Aspergillus niger*, *Aspergillus flavus* and *Aspergillus fumigatus* [42]. Allyltrisulfide, a major essential oil found in *A. tuberosum* gave inhibitory effect against *A. flavus* strains 3.2758 and 3.4408 and *Aspergillus oryzae* at the minimum concentration 250 ppm [43].

8.4 Antiparasitic

Garlic chives or *A. tuberosum* has nematicidal property against root-knot nematodes particularly against *Meloidogyne incognita* J2, a parasite that attacks vascular tissues of plant root. *In vitro* experiment with the plant extract showed significant mortality rate of the parasite [44].

8.5 Aphrodisiac

Traditionally the plant is widely used for its aphrodisiac property [45-47]. Some experimental data also demonstrated its efficacy against impotency. A study showed that n-BuOH extract of *A. tuberosum* significantly improved sexual behavior of sexually active and inactive male rats [48].

8.6 Anticancer

Park and others isolated two thiosulfinates named S-methyl methanethiosulfonate and S-methyl 2-propene-1-thiosulfinate from the crude thiosulfinates of *A. tuberosum*, which were investigated against different cancer cells. The compounds along with crude thiosulfinates were found to induce cell death in human breast cancer cells MCF-7 [49]. *A. tuberosum* can prove to be an outstanding drug source for colon cancer. The crucial active compounds of the plant are thiosulfinates, which has been studied on human colon cancer cells HT-29. The compounds significantly inhibited the proliferation of cancer cells in dose and time dependent manner. Thiosulphonates initiated this apoptotic pathway by activating the initiator caspase-8, and -9, and the effector caspase-3. Thiosulfinates were also found to enhance the expression of apoptosis inducing factor (AIF), which is a caspase-independent mitochondrial apoptosis factor [50]. Further study showed that thiosulfinates from the plant were involved in lessening the expression of antiapoptotic protein Bcl-2 and enhancing the expression of pro-apoptotic protein Bax as well. This was the mechanism behind thiosulfinates-induced inhibition of human prostate cancer cells RC-58T/h/#4 [51]. Another investigation revealed that thiosulfinates inhibited human prostate cells PC-3 by increasing the expression of AIF [52]. Seeds of the plant contain a phytochemical named tuberoside M which was studied on human promyelocytic leukemia cell line (HL-60). It showed inhibitory effect on the growth of the cell line [53].

8.7 Hypolipidemic

A preliminary study on hypolipidemic action of garlic chives showed that feeding *A. tuberosum* whole plant along with fermented *A. tuberosum* and processed sulfur ameliorated liver dysfunction and reduced serum LDL level and intra-abdominal fat [54].

8.8 Pesticidal

A comprehensive study was done by Gao and others on the repellent action of extract (essential oil) of garlic chives against *Plutella xylostella* larvae. It showed satisfactory result by inhibiting glutathione S-transferase and carboxylesterase in extract treated larvae [55].

8.9 Renoprotective

Besides other protective aspects, the plant *A. tuberosum* also possesses renoprotective activity. A current report revealed that polysaccharides from garlic chives significantly reduced the area of renal pathogenic damage induced by adenine in mice. The result was found to be dose dependent and at a dose of 200mg/kg/day, it gave 59.2% reduction of damaged area

and also decreased the serum level creatinine and blood urea nitrogen by 23.9% and 34.7% compared to control [56].

8.10 Promotion of hair growth
Testing hair growth promoting activity with different solvent extracts of *A. tuberosum* (AT), n-butanol extract of AT was found the most effective on hair growth in mice. Extract was applied to the dorsal skin area of mice which augmented the hair follicles number by stimulating the expression of insulin like growth factor-1 (IGF-1) [57].

8.11 Anticoagulant
Ethanolic extract of *A. tuberosum* leaves when extracted with water gave water soluble substances like amino-styrene-acrylic acids and their glycosides, which gave strong anticoagulant effect [58].

8.12 Regulate hormonal balance
Experimental study showed that four different solvent extracts of *A. tuberosum* increased serum testosterone (a hormone that regulates male sexual function) level and nitric oxide (NO) level, which is a major factor for the penile psychogenic erection. By increasing the level of testosterone and NO, the study showed that the plant can form a potential treatment of these hormonal imbalances [35].

8.13 Mediate sensory perception
The transient receptor potential or TRP channels mostly belong to the cation channel family comprising seven subfamilies TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystin), TRPN (NOMPC-like), and TRPV (vanilloid), which arbitrate various sensory functions like nociception, temperature sensation, taste transduction, pheromone signaling, vision etc. Different phytochemicals can activate individual TRP. *A. tuberosum* contains allicin derived sulfur compounds, which activates TRPA1 and TRPV1, two temperature-activated ion channel responsible for pain sensation in mouth [59, 60].

9. Conclusion
A. tuberosum (garlic chive), although not so well known as *A. cepa* (onion) and *A. sativum* (garlic), still is considered an important medicinal plant in the traditional medicinal systems of a number of countries. The plant contains a number of phytochemicals, which can prove important in the discovery of lead compounds or new drugs for treatment of cancer, hepatic disorders, and impotency.

10. Competing interests: The authors declare that they have no competing interests.

11. Author's contributions
KJ wrote the first draft of the manuscript. TR drew the structures of the various phytochemicals. MR wrote the final draft of the manuscript. All authors edited the manuscript and read and approved the final manuscript.

12. Data availability and funding
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