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Review

Pharmacological activities of bioactive compounds isolated from *Acacia pennata* (L) Willd.: A comprehensive update and application of *in-silico* techniques for repurposing

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Abstract: Bioactive compounds (BACs) are naturally occurring compounds with pharmacological activities. BACs isolated from plants have significantly contributed to modern medicine. Multiple studies had reported the isolation of BACs with diverse pharmacological activities from *Acacia pennata* (L.) Willd. This review aims to compile all the available data on the pharmacological activities of the BACs that had been isolated from *A. pennata*. An online literature survey was carried out on academic databases Scopus, Science Direct, PubMed, and Google Scholar. Keywords such as '*Acacia pennata*', 'isolated compound', and 'pharmacological activity' were used alone or in combination. A total of 52 articles published between the year 1980 to 2020 that contained relevant information on *A. pennata* were identified and collected. To date, 29 compounds have been isolated from *A. pennata*. The compounds isolated from *A. pennata* belonged to secondary metabolites: triterpenoid ketone, ceramide, alkaloid, saponin, flavonoid-glycoside, and terpenoid. A total of 22 BACs had been evaluated for biological activities such as anti-Alzheimer, anti-inflammatory, antioxidant, antidiabetic, anti-obesity, antiviral, anti-nociceptive, and anticancer activities. The pharmacological activities of 7 compounds isolated from *A. pennata* remained unexplored. A total of 14 compounds isolated from *A. pennata* were also reported to be isolated from other plants. This comprehensive review provides an update on all the pharmacological works carried out on the isolated BACs of *A. pennata* to date. *In-silico* techniques may be applied to repurpose the isolated BACs of *A. pennata* before wet-lab studies.

1. Introduction

Bioactive compounds (BACs) are naturally occurring substances with pharmacological activity [1,2]. Some BACs isolated from plants such as quinine, aspirin, digoxin, reserpine, vinblastine, atropine, colchicine, artemisinin, ephedrine, morphine, pilocarpine, physostigmine, taxol, quinidine, tubocurarine, and vincristine are some examples of BACs that are currently used as pharmaceutical drugs in the modern system of medicine [3]. Notably, 1/5th of all the identified plants are employed in pharmaceutical studies and positively impact the healthcare system [4]. The medicinal value of a plant is attributed to the presence of BACs [3]. From this, it can be deciphered that the healthcare system benefits from BACs capable of eliciting the desired therapeutic actions.

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The nutritive values, vegetative values, medicinal properties, and pharmacological activities of *Acacia pennata* (L.) Willd. is well documented [5]. Studies have also reported the presence of different classes of BACs as well as the isolation of multiple BACs from *A. pennata* [5,6]. *A. pennata* is distributed in India, Myanmar, Bangladesh, Bhutan, Sri Lanka, Thailand, Vietnam, and Southwest China [5,7]. The edible parts are consumed as a vegetable in India (in Mizoram, Nagaland, and Karnataka) and Thailand. The tribe of Dimasa and Karbi utilize *A. pennata* to prepare a local tribal wine and rice beer, respectively. Studies have also reported the presence of carbohydrates, fats, proteins, free amino acids, fibre, sodium, calcium, potassium, magnesium, zinc, iron, nitrogen, phosphorus, copper, manganese, selenium, vitamin A, vitamin B_1, vitamin B_2, vitamin B_3 and vitamin C in *A. pennata* [5].

A. pennata is traditionally indicated for fever, diarrhea, bronchitis, burning urine, indigestion, skin burn, bleeding gums, a disorder of the blood, headache, haemorrhoids, eruption, oculopathy, asthma, stomach ache, strengthening of bone, wound healing, removing fowl's bone in the throat, toothache, snakebite, cholera, treating spasm, biliousness, dysentery, body pain, and flatulence. Studies have reported the antioxidant, anti-inflammatory, anti-herpes simplex virus, antidiabetic, pupicidal, larvicidal, anti-nociceptive, anticancer, anti-fungal, anthelmintic, anti-Alzheimer, anti-lice, anti-HIV activity, and anti-hyperlipidaemic activity of *A. pennata* [5,6].

A. pennata contained different classes of plant secondary metabolites like flavonoids, glycosides, phenols, phytosterols, saponins, and terpenoids [5,6]. Interestingly, flavonoids, glycosides, phenols, phytosterols, saponins, and terpenoids were reported to exhibit different pharmacological activities [8–13]. Thus, it is safe to hypothesize that the presence of secondary metabolites may be the reason for the traditional use of *A. pennata* to treat 25 different health ailments.

Despite the available works which appraise the value of *A. pennata* as a potent medicinal plant, there is still no systematic discussion on the pharmacological activities of the compounds that had been isolated from *A. pennata*. Moreover, the status of research on the BACs separated from A. pennata is unknown. Therefore, further developments may be hindered due to the lack of a comprehensive work on the pharmacological activities of the BACs isolated from *A. pennata*. Also, there is still no attempt to identify alternate natural sources for similar compounds isolated from *A. pennata*. This justifies the necessity for an up-to-date review on the concerned topic. Therefore, the present work aims to provide a comprehensive update on the pharmacological profile of the BACs isolated from *A. pennata*.

2. Methodology for review

An online literature survey was carried out on databases like Scopus, PubMed, Science Direct, and Google Scholar. Whenever appropriate, the PubChem database was also referred to. Keywords such as '*Acacia pennata*', 'isolated compound', and 'pharmacological activity' were used alone or in combination to search relevant articles. A total of 52 articles published between 1980 and 2020 were collected as they contained significant information to our satisfaction. The chemical class of each isolated compound was identified from the collected articles or the PubChem database. Other phytochemicals that were identified as present in *A. pennata* using chromatographic-spectroscopic techniques without any information on their isolation were not included in the review. To prevent any presentation of false information on the research gaps concerning the pharmacological activity of the compounds isolated from *A. pennata*, the pharmacological activities of all the similar compounds isolated from other plants were also identified and included in the review. The chemical structures were drawn with the Marvin Sketch v20.10 software. The correctness of the chemical structures was checked using the 'Structure checker' add-in of the Marvin Sketch software. The graphical

abstract and figures were prepared with Adobe Photoshop CC 2017.Methods should be described in sufficient detail to allow others to reproduce the results. The inclusion and exclusion criteria for participant selection and statistical methods should be stated clearly.

3. Pharmacological activities of the BACs isolated from *A. pennata*

To date, a total of 29 phytocompounds (**Figure 1**) have been isolated from the twigs, stems, aerial parts, and leaves of *A. pennata*. Of these, 22 BACs isolated from *A. pennata* or similar BACs isolated from other plants had been investigated for at least one pharmacological activity. However, the pharmacological activities of a terpenoid isolated from the leaves, namely labdanolic acid (**C1**) along with the flavonoid glycosides isolated from the aerial parts such as koaburanin (**C2**); 5,7-dihydroxyflavone 7-*O*-β-D-glucopyranosyl-8-C-β-boivinopyranoside (**C3**); 5,7-dihydroxyflavone 6-C-β-boivinopyranosyl-7-*O*-β-D-glucopyranoside (**C4**); (2R)-4′,7-dihydroxyflavan-(4a→8)-(2R,3S)-3,5,7-trihdyroxyflavan-3″-*O*-α-L-rhamnopyranoside (**C5**); (2S)-5,7-dihydroxyflavan-7-*O*-β-D-glucopyranoside-(4a→8)-epiafzelechin-3-*O*-gallate (**C6**) and (2R, 3S)-3,5,7-trihdyroxyflavan-3-*O*-α-L-rhamnopyranoside (**C7**) are still not investigated for any pharmacological activity [14,15].

Quercetin 4′-*O*-α-L-rhamnopyranosyl-3-*O*-β-D-allopyranoside (**C8**) is a flavonoid-glycoside reported to be isolated from the leaves of *A. pennata*. **C8** inhibited cyclooxygenase (COX)-1 (80.4 % inhibition at 10^{-4} g/ml; IC_{50} = 11.6 µg/ml) and COX-2 (12.6 % inhibition at 10^{-4} g/ml) in a COX-1/COX-2 catalysed prostaglandin biosynthesis assay (CPBA) [16].Apigenin 6-*C*-[2″-*O*-(E)-feruloyl-β-D-glucopyranosyl]-8-*C*-β-glucopyranoside (**C9**) is a flavonoid-glycoside reported to be isolated from the leaves of *A. pennata*. **C9** inhibited COX-2 (8.6 % inhibition at 10^{-4} g/ml) in a COX-1/COX-2-CPBA [16].Isorhamnetin 3-*O*-α-L-rhamnopyranoside (**C10**) is a flavonoid-glycoside reported to be isolated from the leaves of *A. pennata*. **C10** inhibited COX-1 (74.0 % inhibition at 10^{-4} g/ml; IC_{50} = 24.4 µg/ml) in a COX-1/COX-2-CPBA [16]. Kaempferol 3-*O*-α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranoside (**C11**) is a flavonoid-glycoside reported to be isolated from the leaves of *A. pennata*. **C11** inhibited COX-1 (49.4 % inhibition at 10^{-4} g/ml; IC_{50} = 157.8 µg/ml) and COX-2 (5.0 % inhibition at 10^{-4} g/ml) in a COX-1/COX-2-CPBA [16].

Isovitexin (**C12**) is a flavonoid-glycoside reported to be isolated from the leaves of *A. pennata*. **C12** inhibited COX-1 (66.4 % inhibition at 10^{-4} g/ml; IC_{50} = 30.6 µg/ml) and COX-2 (7.4 % inhibition at 10^{-4} g/ml) in a COX-1/COX-2-CPBA [16]. **C12** inhibited the stem-like cells in hepatic carcinoma by regulating manganese superoxide dismutase and forkhead box protein M1 [17]. **C12** inhibited α-amylase, α-glucosidase, and the formation of advanced glycation end products with IC_{50} values of 0.2826, 0.0469, and 0.0252 mg/ml, respectively [18]. **C12** exerts anti-inflammatory activity against lipopolysaccharide (LPS) induced neuroinflammation in BV-2 cells and mouse primary microglia by increasing the expression of M2 microglial marker, suppressing the expression of M1 microglial marker, increasing the release of interleukin 10, and by activating the Ca^{2+} dependent protein kinase/AMP-activated protein kinase-PGC-1α signalling pathway [19]. Another study reported that **C12** inhibits the production of reactive oxygen species induced by fine airborne particles of particulate matter of fewer than 2.5 micrometres [20]. **C12** also inhibits 2,2-diphenyl-1-picrylhydrazyl (DPPH) (IC_{50} = 1.72 mg/ml), 2,2'-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) (IC_{50} = 0.94±0.01 mg/ml) and superoxide anion (IC_{50} = 0.18 mg/ml) free radicals. **C12** increases CD133 and β-catenin (stem cell markers), indicating its potential to prevent skin damage. Moreover, **C12** showed antioxidant and anti-inflammatory activity in LPS-induced acute lung injury, simulated in vitro in RAW 264.7 cells and in vivo in mice [21].

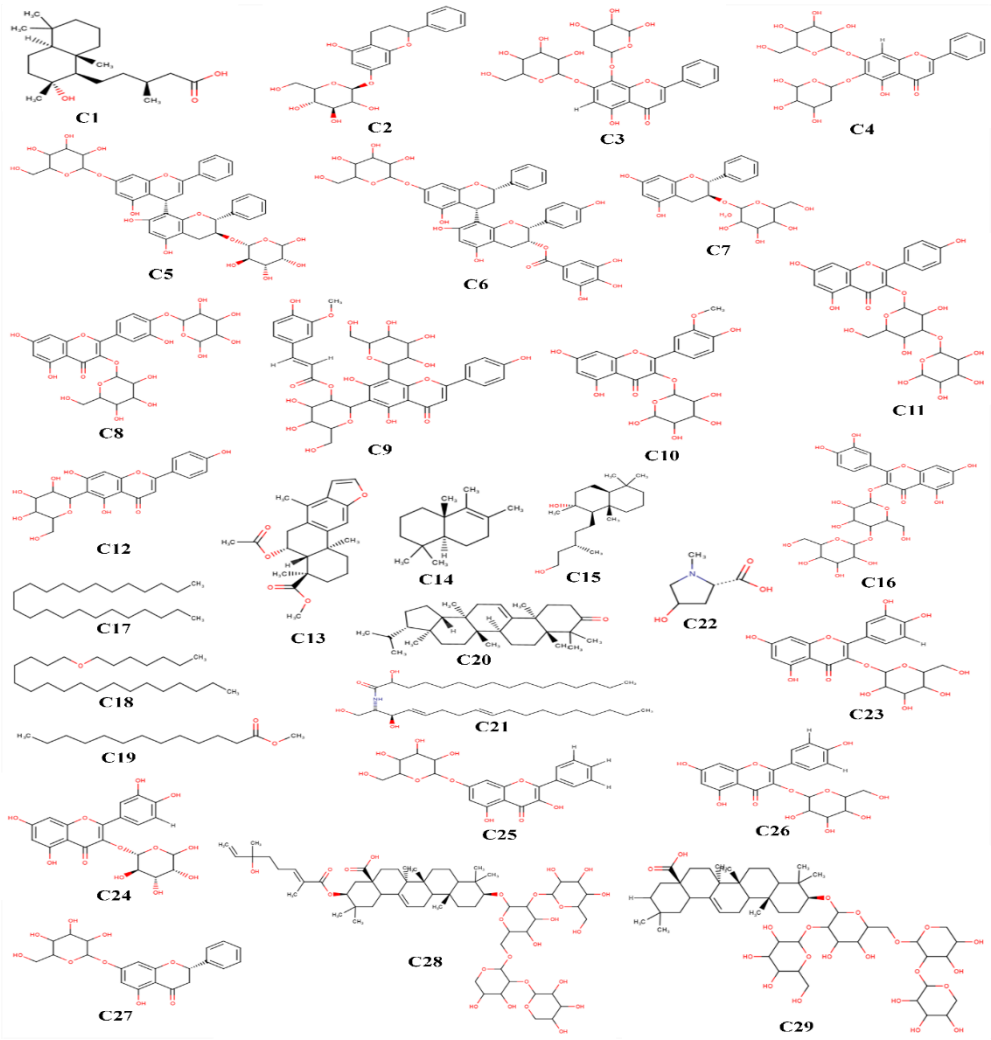

Figure 1 Chemical structures of the compounds isolated from *A. pennata*

Taepeenin D (**C13**) is a terpenoid reported to be isolated from the leaves of *A. pennata*. **C13** exhibits anticancer activity against human prostate (DU145) (IC_{50} = 3.4 μM) and pancreatic cancer cells (PANC1) (IC_{50} = 3.2 μM). Interestingly, **C13** did not exhibit toxicity against normal cells. It reduces the tumor suppressor patched one protein (PTCH) and antiapoptotic B-cell lymphoma 2 (BCL-2) protein in a dose-dependent manner. **C13** downregulates the expression of mRNA of PTCH in PANC1. This is suggestive of its inhibitory effect on the transcription of Hedgehog/glioma-associated oncogene [14]. Another study reported that Taepeenin D inhibited LPS-induced nitric oxide (NO) and tumor necrosis factor (TNF)-α production in RAW 264.7 cell lines with IC_{50} values of 8.2 and 38.8 μM, respectively [22]. (+)-drim-8-ene (**C14**) is a terpenoid reported to be isolated from the leaves of *A. pennata*. **C14** exhibits anti-cancer activity against DU145 (IC_{50} = 23.2 μM) and PANC1 (IC_{50} = 15.1 μM). Interestingly, **C14** remains non-toxic to normal cells. (+)-drim-8-ene was reported to reduce the level of the tumor suppressor PTCH and antiapoptotic BCL-2 protein in a dose-dependent manner [14].

8,15-labdanediol (**C15**) is a terpenoid reported to be isolated from the leaves of *A. pennata* [14]. 8,15-labdanediol inhibited LPS-induced NO synthase and prostaglandin E_2 production in a LPS treated RAW 264.7 macrophages cell line with IC_{50} values of 15±1.1 and 25±3.2 μM, respectively [23]. Quercetin 3-*O*-β-D-glucopyranosyl-4-*O*-β- D-glucopyranoside (**C16**) is a flavonoid-glycoside reported to be isolated from the leaves of *A. pennata*. **C16** showed anti-cancer activity against DU145 (IC_{50} = 30.0 μM) and PANC1 (IC_{50} = 26.6

μM). Interestingly, **C16** remains non-toxic to normal cells. **C16** reduces the PTCH and BCL-2 protein levels in a dose-dependent manner [14].

Tetracosane (**C17**) is a straight-chain alkane reported to be isolated from the twigs of *A. pennata* [24,25]. At 100 μM, **C17** effectively inhibits the aggregation of β-amyloid (% inhibition = 65.0±1.8; IC_{50} = 0.4 μM). At 100 μg/ml, **C17** weakly inhibits acetylcholinesterase (% inhibition = 14.8±0.7). At 1 mg/ml, **C17** weakly inhibits DPPH free radicals (% inhibition = 5.8±1.4) [24]. **C17** also exhibits anti-cancer activity against HT-29 colon cancer cells, estrogen-dependent breast cancer (MDA-MB-231) cells, and gastric cancer cells (AGS) with IC_{50} values of 128.7, +250, and +250 μM respectively [26].

1-(heptyloxy)-octadecane (**C18**) is a straight-chain alkane reported to be isolated from the twigs of *A. pennata* (Lomarat et al. 2015; PubChem 2020b) [24,27]. At 100 μM, **C18** effectively inhibits the aggregation of β-amyloid (% inhibition = 58.9±1.8; IC_{50} = 12.3 μM) [24]. Methyl tridecanoate (**C19**) is a fatty acid methyl ester reported to be isolated from the twigs of *A. pennata* [24,28]. At 100 μM, **C19** moderately inhibits the aggregation of β-amyloid (% inhibition = 32.2±2.7). At 100 μg/ml, **C19** weakly inhibits acetylcholinesterase (% inhibition = 20.7±1.1) [24].

Arborinone (**C20**) is a triterpenoid ketone reported to be isolated from the twigs of *A. pennata* [24,29]. At 100 μM, **C20** moderately inhibits the aggregation of β-amyloid (% inhibition = 47.8±1.6). At 1 mg/ml, **C20** weakly inhibits DPPH free radicals (% inhibition = 5.5±0.3) [24]. Confertamide A (**C21**) is a ceramide reported to be isolated from the twigs of *A. pennata* [2430]. At 1 mg/ml, **C21** weakly inhibits DPPH free radicals (% inhibition = 1.2±0.4) [24]. 4-hydroxy-1-methyl-pyrrolidin-2-carboxylic acid (**C22**) is an alkaloid reported to be isolated from the twigs of *A. pennata* [24,31]. At 100 μM, **C22** moderately inhibits the aggregation of β-amyloid (% inhibition = 32.1±6.0). At 100 μg/ml, **C22** weakly inhibits acetylcholine esterase (% inhibition = 14.1±0.8). At 1 mg/ml, **C22** weakly inhibits DPPH free radicals (% inhibition = 7.7±0.4) [24].

Quercetin-3-*O*-β-D-glucopyranoside (**C23**) is a flavonoid-glycoside reported to be isolated from the aerial parts of *A. pennata* [15]. **C23** showed *in vitro* (EC_{50} = 5.3 μM; EC_{90} = 9.3 μM) and *in vivo* (BALB/c or C57BL/6 mice model) inhibitory activity against the *Ebola* virus [32]. **C23** showed weak antimicrobial activity against various gram-positive bacteria, gram-negative bacteria, and fungi (minimum inhibitory concentration and IC_{50} value against different microbes ranged from 100 to >400 μg/ml and from 99.72 to 167.61 μg/ml, respectively). With IC_{50} values of 82.55 and 97.52 μg/ml, **C23** showed antioxidant activities against DPPH free radicals and β-carotene bleaching respectively [33].

Quercetin-3-*O*-α-L-rhamnopyranoside (**C24**) is a flavonoid-glycoside isolated from the aerial parts of *A. pennata* [15]. **C24** showed strong inhibition of human recombinant aldose reductase *in vitro* (IC_{50} = 11.5±0.05). **C24** significantly reduces sorbitol accumulation in the rat lens [34]. **C24** showed an immunomodulatory activity against the H1N1 virus [35,36]. **C24** non-competitively inhibits the pancreatic lipase (IC_{50} = 100.56 μM) hinting at its anti-obesity potential [37]. **C24** showed significant antioxidant activity in the human umbilical vein endothelial cells model by increasing the activities of enzymatic antioxidants (superoxide dismutase and glutathione) and by inhibiting hydrogen peroxide (H_2O_2) induced apoptosis. **C24** reduces the production of free radicals and deoxyribonucleic acid fragments mediated by H_2O_2 [38].

Chrysin-7-*O*-β-D-glucopyranoside (**C25**) is a flavonoid-glycoside reported to be isolated from the aerial parts of *A. pennata* [15]. **C25** showed weak antimicrobial activity against various gram-positive bacteria, gram-negative bacteria, and fungi (minimum inhibitory concentration and IC_{50} value against different microbes ranged from 150 to >400 μg/ml and from 109.27 to 293.67 μg/ml, respectively). With IC_{50} values of 102.35

and 140.48 µg/ml, **C25** showed an antioxidant activity against DPPH free radicals and β-carotene bleaching, respectively [33]. **C25** exhibits hypotensive and diuretic activities. **C25** increases the α-transcriptional action in MCF-7 cells. **C25** inhibits the growth of *Acinetobacter baumannii* by 10 mm at 0.001 mg/ml. **C25** inhibits α-glucosidase activity by 70% and 90% at 0.05 and 0.1 mg/ml respectively [39]. A molecular docking simulation study showed the potential to inhibit nicotinamide phosphor ribosyl transferase in human colon cancer cells [40].

Kaempferol 3-*O*-α-L-rhamnopyranoside (**C26**) is a flavonoid-glycoside reported to be isolated from the aerial parts of *A. pennata* [15]. **C26** inhibits DPPH free radicals with an SC_{50} value of 12.45 µg/ml [41]. Pinocembrin-7-*O*-β-D-glucopyranoside (**C27**) is a flavonoid-glycoside isolated from the aerial parts of *A. pennata* [15]. **C27** exhibits significant hepatoprotective activity in rats [42]. 21β-*O*-[(2*E*)-6-hydroxyl-2,6-dimethyl-2,7-octadienoyl] pitheduloside G (**C28**) is a saponin reported to be isolated from the stem of *A. pennata*. **C28** was reported to inhibit the human immunodeficiency virus (HIV)-1 protease (PR) *in vitro* (IC_{50} = 2.0 ± 0.2 µM) [7]. Pitheduloside G (**C29**) is a saponin reported to be isolated from the stem of *A. pennata*. **C29** was reported to inhibit the HIV-1 PR *in vitro* (IC_{50} = 18 ± 0.5 µM) [7].

4. Alternate natural sources of BACs isolated from *A. pennata*

Taepeenin D was also reported to be isolated from the roots of *Caesalpinia mimosoides* [22]. Labdanolic acid was also reported to be isolated from *Psiadia arguta* leaves and *Cistus palinhae*. Other compounds isolated from P. arguta were tested for their antiplasmodial activity, but labdanolic acid was not tested for its antiplasmodial activity [43,44]. 8,15-labdanediol was also isolated from *C. palinhae* and *Oxylobus glanduliferus* [23,44]. Tetracosane was also reported to be isolated from the aerial parts of *Acrostichum aureum* L [26]. Arborinone was also reported to be isolated from the powder coating of *Lingnania chungii* MCCLURE [29]. Confertamide A was also reported to be isolated from *Sinularia conferta* [30]. 4-hydroxy-1-methyl-pyrrolidin-2-carboxylic acid was also isolated from the leaves and stem of *Toddalia aculeate* [31].

Quercetin-3-*O*-β-D-glucopyranoside was also reported to be isolated from the leaves of *Azadirachta indica*. At 500 µg/disc, the ethyl acetate extract of *A. indica* showed a zone of inhibition ranging from 06–10 mm against various gram-positive bacteria, gram-negative bacteria, and fungi. Hexane, butanol, and ethyl acetate extract of *A. indica* showed cytotoxicity against *Artemia salina* (shrimp in simulated brine water) with IC_{50} values of 1.3, 10.2, and 0.61 µM, respectively. Even though Quercetin-3-*O*-β-D-glucopyranoside was reported to be isolated from *A. indica*, it was not explicitly investigated for its antimicrobial or anticancer activity [45]. As other phytocompounds could also induce antimicrobial and anticancer activity, these activities were not considered for review.

Quercetin-3-*O*-β-D-glucopyranoside was also reported to be isolated from *Halostachys caspica* C. A. Mey aerial parts; leaves of *Euphorbia heterophylla* L. and leaves of *Loranthus kaoi* (Chao) Kiu [33,46,47]. Quercetin-3-*O*-α-L-rhamnopyranoside was also reported to be isolated from *Chamaecyparis obtuse* leaves [34], *Rapanea melanophloeos (L.) [35], Euphorbia heterophylla* L. leaves [46], *Polygonum aviculare* L. [37], Bronowicka Ostra (a variety of hot pepper) [48], *Lindera aggregata* (Sims) Kosterm [38], and *Mimosa pigra* L. leaves [49].

Chrysin-7-*O*-β-D-glucopyranoside was also reported to be isolated from *Calycotome villosa* subsp. *Intermedia* flowers and leaves [50], *Halostachys caspica* C. A. Mey aerial parts [33], and *Calicotome villosa* stems [39]. Kaempferol 3-*O*-α-L-rhamnopyranoside was also reported to be isolated from *Raphanus raphanistrum* L. aerial parts. The extract of *R. raphanistrum* was evaluated for *in vitro* cytotoxic activity.

However, Kaempferol 3-*O*-α-L-rhamnopyranoside was not investigated explicitly for its cytotoxic activity [51]. Thus, this activity was not included in the review. Kaempferol 3-*O*-α-L-rhamnopyranoside was also reported to be isolated from *Chenopodium ambrosioides L.* leaves [41] and *Dennstaedtia scandens* (BLUME) MOORE fronds [52].

Pinocembrin-7-*O*-β-D-glucopyranoside was also reported to be isolated from *Penthorum chinense* Pursh aerial parts [42], *Viscum articulatum* whole dried plants [53], leaves of *Loranthus kaoi* (Chao) Kiu [47] and *Elytranthe parasitica* (L.) Danser (EP) [54]. Though pinocembrin-enriched fractions of *E. parasitica* showed potential anticancer activity, Pinocembrin-7-*O*-β-D-glucopyranoside was never specifically investigated for its anticancer activity [54]. Thus, this activity was not included in the review. Pitheduloside G was also reported to be isolated from the seeds of *Pithecellobium dulce* [55].

5. *In-silico* techniques for repurposing BACs isolated from *A. pennata*

In-silico techniques have been increasingly used in the field of pharmaceutical research. Computational approaches such as molecular docking, molecular dynamics (MD) simulations, calculation of binding free energies with molecular mechanics (MM)- generalized born surface area (GBSA)/Poisson Boltzmann surface area (PBSA) approaches are popularly used to study the binding affinity, molecular interactions, and molecular mechanisms of chemicals against drug targets [56,57]. Computational techniques can also be combined with *in-vitro* and *in-vivo* studies [58,59]. However, there should be some similarities in the models used for the *in-silico* and wet lab studies. For example, in the case of antidiabetic evaluation, α-amylase may be used for *in-silico* and *in-vitro* studies [58]. Also, in the case of cerebroprotective studies of chemicals, biomarkers such as interleukins or tumor necrosis factors may be used for *in-vivo* and *in-silico* studies [59,60]. It is considered illogical to randomly apply *in-silico* models that do not correlate with *in-vitro* or *in-vivo* models.

Drug repurposing is investigating a compound for other therapeutic purposes than what it was initially intended for [61]. Researchers have used *in-silico* techniques to repurpose phytochemicals that are present in Indian spices as inhibitors of the main protease (Mpro) and papain-like protease of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [62]. Food and Drug Administration-approved drugs were also repurposed for a popular drug target of Plasmodium falciparum, dihydrofolate reductase thymidylate synthase (*Pf*DHFR-TS) [63]. Molecular docking and MD simulations were used to screen phytocompounds for their potential application in treating cancer [64,65]. The phytochemicals in antiviral medicinal plants such as *Baccaurea ramiflora* and *Bergenia ciliata* have been studied with molecular docking, MD simulations, MM-GBSA calculations, and density functional theory studies to investigate their inhibitory potential against SARS-CoV-2 Mpro [66]. Bioactive molecules of a traditional Ayurvedic herbal formulation were repurposed to inhibit SARS-CoV-2 Mpro [67]. Many researchers are applying *in-silico* techniques to discover new molecules for therapeutic applications.

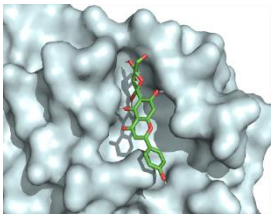

Figure 2 Binding pose of isovitexin at the active binding site of SARS-CoV-2 Mpro (reproduced with permission from Zothantluanga et al. 2022, http://dx.doi.org/10.1186/s43094-021-00348-7)

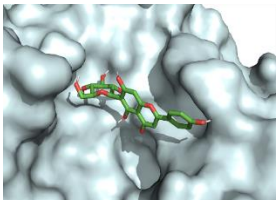

Figure 3 Binding pose of isovitexin at the active binding site of SARS-CoV-2 Mpro (reproduced with permission from Zothantluanga et al. 2021, http://dx.doi.org/10.1186/s43094-021-00348-7)

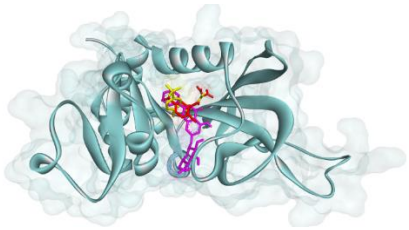

Figure 4 Binding pose of pinocembrin-7-O-β-D-glucopyranoside at the active binding site of *Pf*DHFR-TS. RJ1 (yellow color) of the original co-crystallized complex, RJ1 (red color) re-docked with PyRx 0.8 tool, and **C27** (purple color) docked with PyRx0.8 tool (reproduced with permission from Zothantluanga et al. 2022, http://dx.doi.org/10.33263/BRIAC124.48714887)

Of all the phytocompounds present in *A. pennata*, isovitexin was found as the most promising phytochemical, with the potential to inhibit the viral replication of SARS-CoV-2 as well as to prevent the cellular entry of SARS-CoV-2 by binding to active binding sites of SARS-CoV-2 Mpro (Figure 2) and furin (Figure 3). *In-silico* ADMET screening was executed, and it computed isovitexin as a safe, bioavailable, and non-toxic phytocompound [68]. In another study, the flavonoid phytocompounds of *A. pennata* were studied for their potential antimalarial activity by targeting the *Pf*DHFR-TS of *P. falciparum*. Molecular docking with two different virtual screening tools, *in-silico* ADMET screening and bioactivity prediction, revealed pinocembrin-7-O-β-D-glucopyranoside as a promising lead compound for inhibiting *Pf*DHFR-TS (Figure 4) [69]. These *in-silico* studies support the claim that computational techniques can be used to repurpose the isolated BACs of *A. pennata* for other health ailments. *In-silico* techniques can also be used to study the molecular interactions, hypothesize the molecular mechanisms, and determine the inhibitory potential of the isolated BACs against multiple drug targets.

6. Conclusions

A. pennata is a Southeast Asian medicinal plant with a diverse range of biologically active compounds. This explains the traditional use of *A. pennata* for 25 different health ailments. The biological activity of 7 phytocompounds that remains unexplored may be investigated in the future. *In-silico* techniques can be applied to investigate the potential activity of the 7 phytocompounds whose activity remained unexplored. Moreover, the 22 BACs may also be repurposed for other health ailments. Before wet-lab studies are carried out for repurposing, the potential activities of the 22 BACs may also be investigated with *in-silico* techniques. This comprehensive review provides an update on all the pharmacological works carried out on the isolated BACs of *A. pennata* to date. This review will benefit researchers working in the field of natural products.

Supplementary Material

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Conflict of Interest

Declare any conflict of interest.

Data Availability

Not applicable.

Authors contribution

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