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(Mini Review)

A comprehensive review on the phytoconstituents and pharmacological properties of two genoprotective Acacia species

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ABSTRACT

In the present review article, the two genoprotective species *Acacia auriculiformis* and *A. pennata*, which are native to Australia and Southeast Asia, respectively, are the subjects of the phytochemical and pharmacological investigations gathered and summarized in the current review paper. Acacia is the largest genus of the family Leguminosae with myriad valuable medicinal plants. Both of them have been employed for various ailments in traditional medicine such as headaches, rheumatism, dry cough, and fever. They possess major pharmacological activities such as antioxidant, anti-genotoxic, hepatoprotective, antiviral, and antifungal properties which were previously reported for both. *A. Auriculiformis* possessed antimalarial, cestocidal, anti-filarial, and spermicidal activities, whereas *A. pennata* showed anti-nociceptive, anti-inflammatory, and anti-transcription activity. Triterpenoid saponin and flavonoids are the primary phytochemical compounds isolated from different parts of *A. auriculiformis* and leaves of *A. pennata*, respectively. This review will increase the potential nutraceutical applications of both plants and their future anticipation in the area of clinical medicine.

Keywords: Acacia; antioxidant; genoprotective; flavonoid; saponin.

1-Introduction

The second-largest genus in the family Leguminosae is the worldwide genus Acacia, commonly known as wattles, which consists of more than 1350 species [1]. The genus is distributed in both warm tropical and temperate climates, with the majority of its species found in Australia [2]. Different Acacia species have yielded a variety of pharmacologically active compounds [3]. The highest concentration of tannin and phenolic components, including gallic acid, dicatechin, quercetin, robidandiol, *β*-amyrin, kaempferol-3 chlorogenic acid, and glucoside isoquercetin, was isolated from Acacia root, leaves, pods, and bark [3]. Recently, several studies have emphasized the biological value of medicinal plants as genoprotective agents [4]. Phytochemicals may prevent genotoxicity by interacting with ROS, but they may also serve as a protective shield by preventing ROS from accessing DNA by providing a steric hindrance for ROS[4]. Several biological studies have been carried out on the genus Acacia that confirmed its genoprotective role [5], different species have shown this effect in various test systems, anti-oxidant, anti-inflammatory, minimizing DNA strand breaks, and chromosomal aberrations were the observed mechanism of action for genoprotection [5]. *A. auriculiformis*is an Australian acacia known as earpod wattle widely cultivated in India [6]. It grows up to 30 meters in height and is of great importance in agroforestry systems as its hybrid with *A. magnum* showed more hot resistance than each individual plant [7]. *A. pennata* known as climbing wattle is a perennial woody climber that possesses bipennate leaves cultivated in regions of South and Southeast Asia including India, Bangladesh, Myanmar, Southwest China and Thailand [8]. Both plants have long been used in folk medicine for their important biological effects, *A. auriculiformis* was used in the treatment of inflammation, sore eyes, aches, malaria, and skin diseases such as rashes, allergies, and itching [9], as well as *A. pennata* has been used to treat cough, headaches, rheumatism, and fever [8]. Previous phytochemical studies on both plants reported the isolation of saponin which was found in a unique tridismoside nature in *A. auriculiformis* [10], as well as the new biologically active saponin from *A. pennata* [11] and flavonoids as auriculoside, a CNS-depressant flavan glycoside from *A. auriculiformis* [11], in addition to several reported kaempferol-, apigenin- and quercetin diglycoside, isovitexin, flavanol glycosides isorhamnetin mono-glycoside from *A. pennata* [12]. Both plants revealed various pharmacological activities including the genoprotective effects. As their phytochemistry has recently been the subject of

numerous studies.This contribution's goal is to explore and thoroughly highlight the pharmacological activities and active compounds.

2- Material and methods

The present review covers the literature available from 1966 to 2021. The information was gathered from electronic searches using a variety of databases including Reaxys, PubMed, SpringerLink, Scifinder, and Web of Science; in an effort to gather published data on the selected two species.

3-Phytochemistry

Several phytochemical investigations have been performed on both *A. auriculiformis* and *A. pennata* and have led to the isolation of secondary metabolites including flavonoids, saponins, and carbohydrates from different parts of both plants, The isolated compounds' chemical names and chemical structures are displayed in Figure 1.

3-1. Flavonoids

The heartwood and bark of *A. auriculiformis* have yielded some flavonoids. In the early 60's, a new flavan-3,4-diol **(1)** was isolated by paper ionophoresis from its heartwood [9], A new flavan glucoside 7,3′,5′-trihydroxy-4′-methoxyflavan 3′- glucoside (auriculoside) **(2)** had CNS depressant activity, was also isolated from the heartwood [18]. Quercetin **(3)** and epicatechin **(4)** were reported from its bark [11]. Whereas, in *A. pennata* several phytochemical studies have been carried out on its phenolic constituent in the last few years which revealed the presence of several flavonoids from its leaves, including the two new flavonoids quercetin 4'-*O*-*α*-rhamnopyranosyl-3-*O*-*β*-allopyranosyl**(5)**, apigenin 6-*C*-[2"-*O*-feruloyl-*β*-glucopyranosyl]-8-*C*-*β*-glucopyranosyl **(6)** were isolated along with the known ones isorhamnetin 3-*O*-*α*-rhamnopyranosyl **(7)**, kaempferol 3-*O*-*α*- rhamnopyranosyl-(1→4)-*β*-glucopyranosyl **(8)** and isovitexin **(9)** [12] and their anti-inflammatory effect has also been investigated. Eleven flavonoids have also been isolated, Five of which are new and identified as (2R,3S)-3,5,7-trihdyroxyflavan-3-*O*-*α*-L-rhamnopyranoside **(10)**, (2S)-5,7 dihydroxyflavan-7-*O*-glucopyranoside-(4*α*→8)-epiafzelechin-3-*O*-gallate **(11)**, (2R)-40,7-dihydroxyflavan-(4*α*→8)-(2R,3S)-3,5,7-trihdyroxyflavan-3"-*O*-*α*-rhamnopyranoside **(12)**, 5,7 dihydroxyflavone 6-*C*-b-

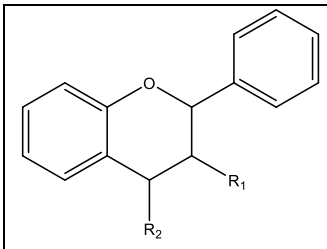
boivinopyranosyl-7-*O*-*β*-glucopyranoside **(13)** and 5,7-dihydroxyflavone 7-*O*-*β*-glucopyranosyl-8-*C*-*β*-boivinopyranoside **(14)** in addition to the known quercetin-3-*O*-*β*-glucopyranoside **(15)**, quercetin-3-*O*-*α*-rhamnopyranoside **(16)**, chrysin-7-*O*-*β*-glucopyraniside **(17)**, kaempferol 3-*O*-*α*-rhamnopyranoside **(18)**, koaburanin **(19)** and pinocembrin-7-*O*-*β*-glucopyranoside **(20)** [4]. Quercetin 3-*O*-glucopyranosyl-4-*O*-glucopyranoside **(21)** was also detected in the leaves together with four terpenoids and found to possess anti-transcriptional activity [17].

3-2. Saponins

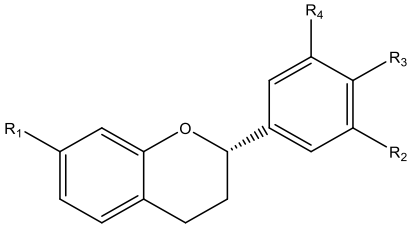
Various isolated saponins have been reported from *A. auriculiformis*. A rare new one with terminal arabinose, acacic acid lactone-3-*O*-*β*-D-glucopyranosyl(1→6)-[*α*-L-arabinopyranosyl(1→2)]-*β*-D-glucopyranoside **(22)** was isolated from the seeds [14]. Two acylated bi-glycoside saponin acaciaside A **(23)** and B **(24)** were separated from the funicles and exhibited antimicrobial and *in vitro* sperm-immobilizing activity [15-16]. A new triterpenoid saponin was isolated from the legumes and identified as 3-*O*-{[*β*-D-xylopyranosyl (1→3)-*β*-D-xylopyranosyl(1→4)-*α*-L-rhamnopyranosyl(1→2)]-[*α*-L-rhmanopyranosyl(1→4)]-*β*-D-glucopyranosyl}-3,16,21-trihydroxyolean-12-en-28-oic acid **(25)** [17]. Apart from this, a new triterpenoid saponins proacaciaside-I **(26)**, proacaciaside-II **(27),** and acaciamine **(28)** were isolated from the fruits and characterized as acacic acid lactone 3-*O*-*β*-D-glucopyranosyl (1→6)-*β*-D-glucopyranoside, acacic acid lactone 3-*O*-*α*-L-arabinopyranosyl (1→2)-*β*-D-glucopyranoside and acacic acid lactone 3-O-*α*-L-arabinopyranosyl (1→6)-2-acetamido-2-deoxy-*β*-D-glucopyranoside, respectively [18]. Whereas for *A.* pennata From the leaves, two terpenoids with anti-transcriptional activity have been discovered, and identified as taepeenin D **(29)** and (+)-drim-8-ene **(30)** [13]. Furthermore, a novel saponin known as 21***β***-*O*-[(2*E*)-6-hydroxyl-2,6-dimethyl-2,7-octadienoyl] pitheduloside G (1) **(31)** was isolated from the stem, together with the known pitheduloside G (2) **(32)** both of them exhibited anti-HIV protease activity [11].

3-3. Carbohydrates

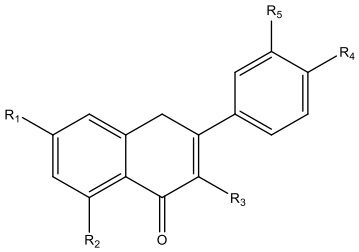
Hydrolysis of the polysaccharide isolated from *A. auriculiformis* seeds revealed the presence of D-glucuronic acid, D-galactose, D-xylose, D-glucose, and L-arabinose [23].



1 R_1=R_2=OH



2 R_1=R_2=OH, R_3=OCH_3, R_4=*O*-glc



3 R_1=R_2=R_3=R_4=R_5=OH

5 R_1=R_2=R_5=OH, R_3=*O*-glu, R_4=*O*-rha

7 R_1=R_2=R_4=OH, R_3=O-rha, R_5=OCH_3

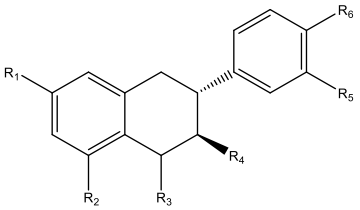
8 R_1=R_2=R_4=OH, R_3= *O*-rha(1→4)-*β*-glu, R_5=H

15 R_1=R_2=R_4=R_5=OH, R_3=*O*-glu

16 R_1=R_2=R_4=R_5=OH, R_3=*O*-rha

18 R_1=R_2=R_4=OH, R_3=*O*-rha , R_5=H

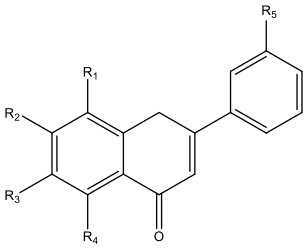
21 R_1=R_2=R_4=R_5=OH, R_3=*O*-glu(1→4)glu



4 R_1=R_2=R_4=R_5=OH, R_3=H

10 R_1=R_2=OH, R_4=*O*-rha, R_3=R_5=R_6=H

19 R_1=*O*-glu, R_2=OH, R_3=CH_2, R_4=R_5=R_6=H



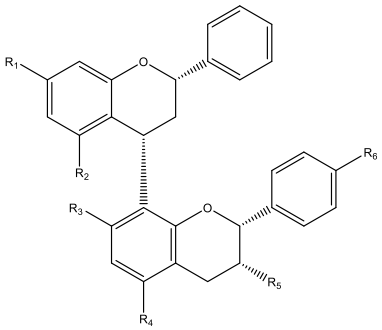
6R_1=Glc, R_2=R_4=R_5=OH, R_3=2"-*O*-feruloyl-*β*-glu

9 R_1=H, R_2=R_4=R_5=OH, R_3=glu

13 R_1=R_5=H, R_2=*O*-glu, R_3=rha, R_4=OH

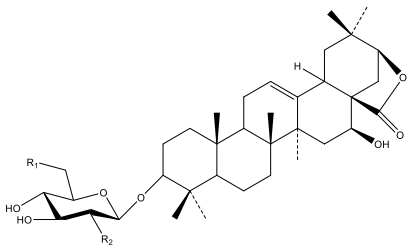
14 R_1=Boiv, R_2=*O*-glu, R_3=R_5=H, R_4=OH

17 R_1=R_3=R_5=H, R_2=*O*-glu, R_4=OH



11 R_1=*O*-glu, R_2=R_3=R_4=R_6=OH, R_5=*O*-gall

12 R_1=*O*-glu, R_2=R_3=R_4=OH, R_5=*O*-rha, R_6=H



22 R_1=*O*-glu, R_2=*O*-arab
26 R_1=*O*-glu, R_2=H
27 R_1=H, R_2=*O*-arab
28 R_1= *O*-arab, R_2=NHAc

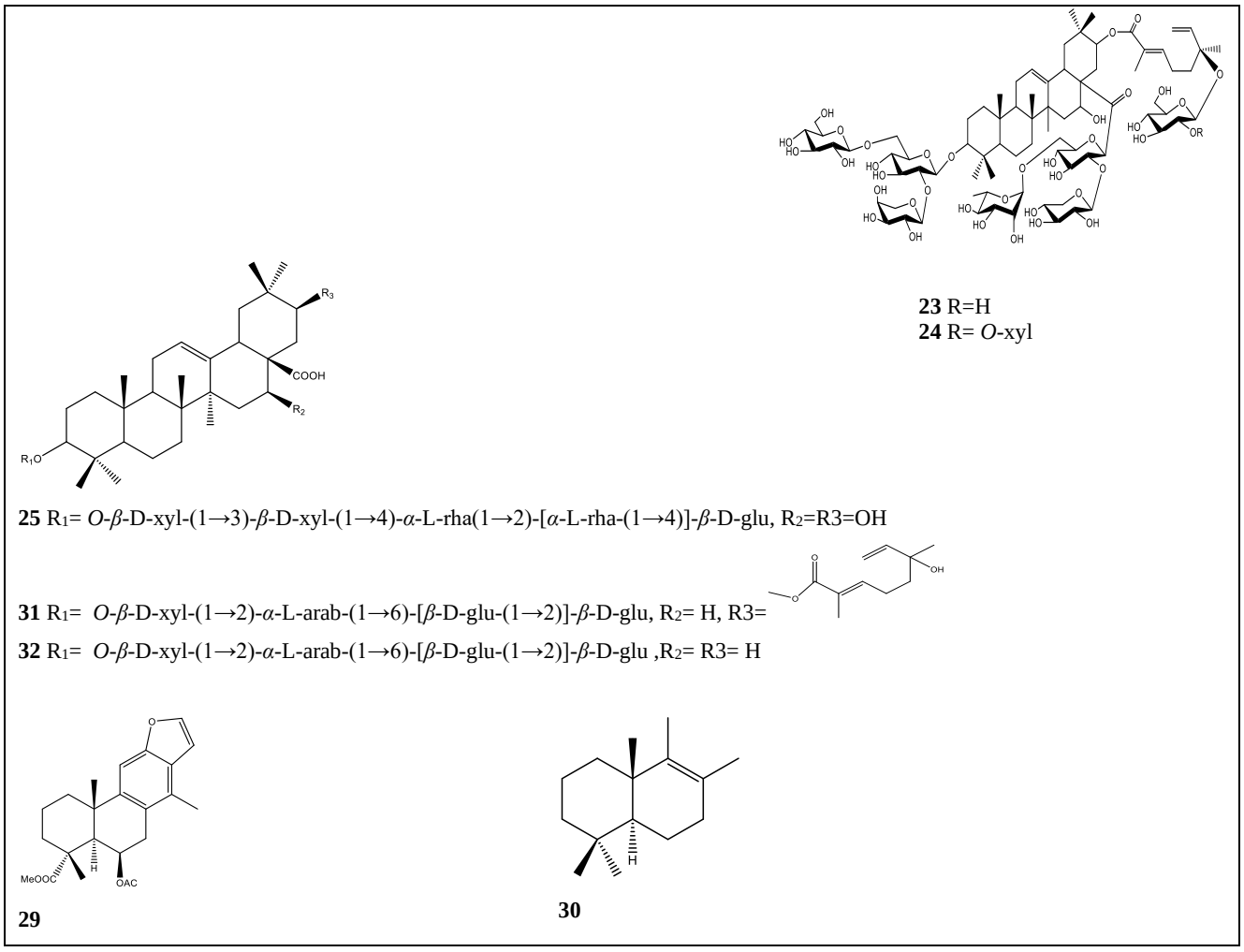


Figure 1. Compounds isolated from *A. auriculiformis* and *A. pennata*

4- Pharmacological activities

Reviewing the available literature several biological activities have been reported for both *A. auriculiformis* and *A. pennata*. The following section introduces their reported pharmacological effect together with their biologically active isolated compounds.

4-1. Antioxidant and radical scavenging activities

The methanolic heartwood extract of *A. auriculiformis* was found to possess an antioxidant effect by using the DPPH radical scavenging activity method which was equivalent to that of *A. mangium* [3]. By using DPPH, non-site specific deoxyribose scavenging, chelating power, site-specific deoxyribose scavenging, and lipid peroxidation assays to determine the antioxidant and free radical scavenging activity of different fractions of the ethyl acetate bark

extract, the percent of inhibitions were 83.37%, 75.63%, 73.66%, 72.92%, and 71.2%, respectively, generally the fractions exhibited more potent scavenging activity as compared to the crude extract [24]. However, Using the DPPH assay, an ethanolic extract of flowers and foliage leaves showed a weak anti-oxidant activity (IC_{50} value of 152 and 161 µg/mL, respectively) [25]. The ethyl acetate fraction of the bark had the strongest DPPH scavenging assay activity, with an IC_{50} value of 7.80 g/mL, as opposed to the methanol leave extract (IC_{50} value of 7.95 g/mL), according to a comparative antioxidant investigation on the leaves and the bark extract. Whereas, the *n*-hexane root fraction was found to possess higher nitrogen oxide scavenging activity than that of the leaves' ethyl acetate fraction [26]. With the aid of *in vitro* techniques like the DPPH assay, reducing power assay, hydroxyl radical assay, ABTS assay, linoleic acid emulsion system assay, metal chelation, and antihemolytic activity assays, antioxidant activities of *A. auriculiformis*, *A. ferruginea*, and *Cajanus cajan* seed extracts were compared. In DPPH, reducing power, and hydroxyl radical assays, all extracts were discovered to be dose-dependently active [27]. The methanol fruit extract exhibited a potent antioxidant effect by using the DPPH assay [28] which was further used to assess the antioxidant potential of different leaves extracts at the concentrations of 25-150 µg/mL and revealed that the most potent antioxidant effect was exhibited by the ethanol extract [29]. However, using different assays including DPPH, ABTS, FRAP, and metal chelation to evaluate the antioxidant effect *A. pennata* acetone and methanol bark extracts revealed that the acetone extract was more potent [30].

4-2. Genoprotective activity

Both *A. auriculiformis* and *A. pennata* 70% methanolic extracts led to potent genoprotective activities. The genoprotective activities were assessed against CCl_4- and acetaminophen-induced genotoxicity in male rats. *A. auriculiformis* significantly protects DNA against apoptotic fragmentation and damage, it possesses the ability to down-regulate CYP450 and Hsp70-genotoxicity-related genes. *A. pennata* significantly down-regulated mdr1b and p53-genotoxicity-related genes and protected hepatic cells from oxidative stress [30-32].

4-3. Antifungal activity

The acylated bisglycoside saponins acaciaside A and B isolated from the funicles of *A. auriculiformis* possessed an antifungal effect, They suppressed *Curvularia lunata* and *Aspergillus ochraceous* fungal stains at a concentration of 300 µg/mL or less[33], moreover, the

antifungal effect of the heartwood extract *A. auriculiformis* was found to be greater than that of *A. mangium* in a comparative study performed, Both species contain 3,4',7,8-tetrahydroxyflavanone and teracacidin that showed significant antifungal activity and their levels were higher in *A. auriculiformis* suggesting that these compounds may play a key role in its antifungal effect [3]. Whereas the methanol extract of *A. pennata* leaves showed a strong antimicrobial effect by using a serial dilution assay, the effect was particularly against *Candida albicans* and *Kluyeromyces polysporus* [34].

4-4. Antibacterial activity

Besides the antifungal potential of acaciaside A and B, their antibacterial activity was similarly moderate, their mixture inhibited *Pseudomonas aeruginosa*, *Salmonella typhimurium,* and *Bacillus megaterium*at 700 μg/mL or higher concentrations [33]. The flower and leaves with 75% ethanolic extract of *A. auriculiformis* exhibited mild antimicrobial activity, they showed potent activity against gram-positive bacteria but were found to be inactive against gram-negative [25]. Moreover, its ethanolic bark extract showed significant antimicrobial activity against the three tested bacterial strains *S. aureus, P. aeruginosa, B. subtilis*, the highest activity was exhibited against the *P. aeruginosa* [31]. The synthesized silver nanoparticle of pod aqueous extract showed a significant effect against both gram-positive *(B. cereus* and *Staphylococcus* sps.) and Gram-negative bacteria with a more potent effect on gram-negative [36]. The antimicrobial effect of methanolic and ethanolic seed pod extracts was examined against thirteen strains of Gram-positive and Gram-negative bacteria, the ethanolic extract was observed to be more potent, they inhibited most of the examined bacteria except *K. pneumonia*, *Listeria monocytogenes, Acinetobacter boumanii* and *P. aeruginosa* which were found to be resistant at 20 μg/ mL [37].

4-5. Antimalarial activity

The 70% ethanolic extract of *A. auriculiformis* leaves revealed a significant antiplasmodial activity as compared to the standard drug chloroquine at the dose of 350-1,050 mg/kg/day (5 mg/kg/day) by using suppressive schizonticidal activity method to determine its *in vivo* antimalarial activity in infected mice. The findings revealed considerable activity ($P<0.05$), supporting its conventional use in the treatment of malaria [38].

4-6. Cestocidal activity

The funicles 70% ethanolic extract of *A. auriculiformis* as well as the isolated acaciaside A and B possessed a cestocidal activity. Oral inoculations of two groups of 10 rats each with a single *Hymenolepis diminuta* cysticercoid were performed. Within 5 and 3 days, respectively, the adult worms were ejected following treatment with the extract and saponins [39].

4-7. Antifilarial activity

Using an *in vitro* experiment, isolated Acaciaside A and B killed 100% of adult worms in 35 minutes and 97% of *Setariacervi* microfilaria in 100 minutes at a dosage of 4 mg/mL, both of which had no harmful effects on rats [40]. Moreover, When pariah dogs naturally infected with *Dirofilariaimmitis* were given the funicles ethanolic extract of *A. auriculiformis* at the dose of 150 mg/kg/day for 45 days, there was a 98–99% reduction in microfilarial density [41].

4-8. CNS depressant activity

The effectiveness of the butanol extract fraction of aerial portions of *A. auriculiformis* was assessed using a barbiturate potentiation test in mice, it was discovered that auriculoside, which is soluble in ethyl acetate, accounts for 80% of the CNS depressing activity [14, 42].

4-9. Alzheimer's disease

Following oral administration of two doses of *A. auriculiformis* leaves 95% ethanolic extract (200 mg/kg and 400 mg/kg), which resulted in a significant dose-dependent improvement in the memory score and the percentage of correct responses as well as a significant dose-dependent inhibition of brain cholinesterase activity, rats' learning and memory were evaluated using the passive avoidance paradigm and the rewarded alternation test (T-maze) [43]. Alzheimer's illness was also discovered to be significantly impacted by *A. pennata* twigs. Six compounds were isolated from their active fractions because they were found to be a potent inhibitor of β-amyloid aggregation. Tetracosane was the most potent inhibitor, followed by 1-(heptyloxy)-octadecane, while methyl tri-decanoate, arborinone, and 4-hydroxy-1-methyl-pyrrolidin-2-carboxylic acid were found to be moderate inhibitors [44].

4-10. Antimutagenic and chemopreventive activity

The antimutagenic and chemopreventive properties of the bark acetone extract of *A.auriculiformis* were investigated by using the Ames antimutagenicity assay, the acetone extract

showed potent results suggesting that it possibly possesses active chemopreventive compounds [45].

4-11. Anti-transcriptional activity

The Hedgehog signaling pathway was discovered to be inhibited by the compounds quercetin 3-*O*-D-glucopyranosyl-4-*O*-D-glucopyranoside and taepeenin D, (+)-drim-8-ene, which were isolated from the leaves of *A. pennata*, overexpression of the target gene in this pathway leads to the formation of cancer. The three isolated compounds were discovered to have specific cytotoxicity against human prostate (DU145) and pancreatic (PANC1) cancer cells, but not against normal cells [17].

4-12. Antidiabetic activity

A. auriculiformis bark and empty pod extract revealed a dual inhibitory effect on both α-amylase and α-glucosidase enzymes [10]. Their anti-diabetic effect was further evaluated in alloxan-induced diabetic rats, the elevated levels of blood glucose returned to desirable levels as compared to standard drug glibenclamide [35]. Thus, they can both be used as a nutraceutical supplement in anti-diabetic formulations.

4-13. Hepatoprotective activity

Comparing *A. auriculiformis* bark and pod acetone extracts to the standard silymarin for their hepatoprotective effect against paracetamol-induced liver injury, the results showed that the extracts restored the liver function markers (alanine transaminase, aspartate transaminase, alkaline phosphatase, total bilirubin, and total protein) [35].

4-14. Wound healing activity

When the wound-healing properties of an ointment containing ethanolic and aqueous bark extract from *A. auriculiformis* were compared, the ethanolic extract showed greater activity than the aqueous extract in terms of promoting wound contraction, shortening the epithelialization period, and increasing tensile strength [46].

4-15. Spermicidal activity

Acaciaside A and B isolated from *A. auriculiformis* exhibited *in vitro* sperm-immobilizing activity, their activity was found to be more potent when compared to the standard

Triton X-100[16]. Moreover in acaciaside B enriched fraction *in vitro* sperm immobilizing activity with no mutagenicity was observed [47].

4-16. Anti-inflammatory activity

The two new flavonoids quercetin 4'-*O*-*α*-rhamnopyranosyl-3-*O*-*β*-allopyranosyl and apigenin 6-*C*-[2"-*O*-feruloyl-*β*-glucopyranosyl]-8-*C*-*β*-glucopyranosyl isolated from the leaves of *A. pennata*along with isorhamnetin 3-*O*-*α*-rhamnopyranosyl, kaempferol 3-*O*-*α*-rhamnopyranosyl-(1→4)-*β*-glucopyranosyl and isovitexin were tested for their cox-1 and cox-2 inhibitory effect, the butanol extract was most potent inhibitor of cox-1 followed by the isolated compounds whereas isorhamnetin 3-*O*-*α*-rhamnopyranosyl was found to be in active [16].

4-17. Anti-HIV-1 Protease activity

A novel saponin termed 21*β*-*O*-[(2E)-6-hydroxyl-2,6-dimethyl-2,7-octadienoyl] pitheduloside G **(1)** and the known saponin pitheduloside G **(2)** isolated from *A. pennata* ethanolic were tested for their inhibitory effects on human immunodeficiency virus type 1 (HIV-1) protease (PR). The findings showed that the novel saponin had strong anti-HIV-1 PR activity, with an IC_{50} value of 2.0 ± 0.2 M, while pitheduloside G **(2)** showed substantially less inhibition, with an IC_{50} value of 18 ± 0.5 M. When used against HIV-1 PR, both compounds demonstrated no potential harm in human embryonic kidney 293T cells [11].

5- Conclusion

Both *A. auriculiformis* and *A. pennata* have been widely used in various traditional ailments in several Asian countries due to the presence of bioactive phytoconstituents which are responsible for their pharmacological activities. Further pharmacological studies on both plants with the possible mechanisms of action are required to establish their future use in the medicinal field.

- **Conflict of Interest**

The authors declare that no conflict of interest

6. References

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