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Bioactives and pharmacology of *Selaginella doederleinii* Hieron (Family: Selaginellaceae)

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Abstract
Selaginella doederleinii Hieron is a promising species belonging to the fern family Selaginellaceae. Though it is distributed throughout the world, it stretches quite prominently from South China to the South part of Japan and Indo-China region including Guangxi province of China. Parts of *S. doederleinii* extensively used in ancient Chinese materia medica to cure many ailments. Medicinal properties of this species are related to its phytochemical diversity. This review provides in-depth information regarding various bioactive compounds and pharmacological potential of *S. doederleinii*.

Keywords: Bioactive, medicinal plant, pharmacology, *S. doederleinii*

1. Introduction
Family Selaginellaceae is a monogeneric family represented by genus *Selaginella*, having universal distribution with predominance in tropical parts of world, with small number of species reported from arctic regions of both hemispheres and represented by 750 species [1], of which America has documentation of approximately 270 species. *Selaginella* is wide ranging in parts of American, African continent and European countries, extending eastwards to Japan, New Guinea and Australia. It was also observed in Pacific East to the Hawaiian Islands. In the Americas, genus *Selaginella* stretches from Northern Alaska to Greenland and parts of Mendoza and Buenos Aires in Argentina. From Amazon area s 31 species have been documented [2]. Some species of this genus were dwelled in very harsh climatic conditions like cold alpine or Arctic Circle and in extreme dry desert [2, 3]. In Indian perspective, about 18 species were recorded from the south part of the country [4]. In Southeast Asia many species of *Selaginella* are in use for handicrafts, food, medicine, and ornaments [5]. *Selaginella doederleinii* Hieron, an important small fern grown extensively found in Guangxi province of China at low altitude and is an integral part of ancient Chinese Pharmacopoeia [6]. It is also known as immortality grass. In Indonesia, *S. doederleinii*, commonly called as “da ye cai” and “shi shang bai” [7]. In China it is known by alternative names like ‘Shishangbai’ [8]. *S. doederleinii* is quite rich in diverse arrays of phyto constituents showing antimicrobial, antiviral, anti-cancer, cytotoxic and other effects. This review elaborates on various bioactive compounds identified in *S. doederleinii* and their pharmacological potential.

2. Bioactives
Ethanol extract of *S. doederleinii* stem and leaves reported presence of tannins, alkaloids, saponin and cardiac glycosides whereas aqueous extract showed presence of tannins, alkaloids, saponins only [9]. Amongst five fractions obtained from ethanol extract of *S. doederleinii*, maximum contents of total biflavonoids (31.98±1.49 mg/g) was obtained by ethyl acetate fraction while maximum phenolic content (28.31±1.85 mg/g) were reported from methanol fraction. Phytochemical analysis of these fractions revealed that, petroleum ether fraction rich in organic acid, free steroids and free triterpenes; diethyl ether fraction showed abundance of coumarins, anthocyanins and anthraquinones; Biflavonoid and chalcones are the prime metabolites found in ethyl acetate fraction; methanol and water fraction are rich in phenolics, alkaloids and polysaccharide respectively [10]. Ethyl acetate fraction obtained from *S. doederleinii* ethanol extract evaluated using diverse arrays of chromatographic techniques gives twenty diverse compounds *viz*., myristic acid, β-Citronellol, palmitic acid, stearic acid, beta-sitosterol, physcion, 3-beta -Acetoxysitost-5-en-7-one, chrysophanol, apigenin, amentoflavone, robustaflavone 7, 4', 7"-o-trimethyl ether, heveaflavone, podocarpusflavone A, emodin, robustaflavone 4', 4"'-o-dimethyl ether, robustaflavone 4'-o-methyl ether, adenosine, ferulic acid, syringate and vanillic acid [6]. Methanolic extract of dried *S. doederleinii* yields

three unique alkaloid glycosides named as hordenine-*O*-α-L-rhamnopyranoside, N-methyltyramne-*O*-α-L-rhamnopyranoside and hordenine-O-[(6 -*O* –*trans*-cinnamoyl) -4'-*O*-β-D-glucopyranosyl-α-L-rhamnopyranoside [11]. Lignin compounds like (-)-matairesinol, (+)-syringaresinol, (+)-wikstromol, (+)-nortrachelogenin were reported from *S. doederleinii* [12, 13]. Hydro-methanolic extract of *S. doederleinii* whole plant recorded 2, 3-dihydrorobustaflavone 7, 4', 7"-trimethyl ether, 2", 3"-dihydrorobustaflavone 7, 4', 7"-trimethyl ether and 2, 3-dihydrorobustaflavone 7, 7"-dimethyl ether chemical compounds (Figure 1), of which earlier two were known while last one was a novel biflavonoid [14]. Hydro-ethanolic extract of *S. doederleinii* air dried whole plant produces four earlier undescribed biflavonoids named as compound 1-4 and delicaflavone as identified biflavonoid derivative [15]. Along with known two biflavonoids, *viz*, robustaflavone 7, 4', 7"-trimethyl ether and robustaflavone 4'-methyl ether a novel biflavonoid identified as 2, 2", 3, 3"-tetrahydrorobustaflavone 7, 4', 7"-trimethyl ether was successfully extracted from *S. doederleinii* [16]. HPLC analysis of *S. doederleinii* recorded seven biflavonoids *viz*, amentoflavone, robustaflavone, 2", 3"-dihydro-3', 3"'-biapigenin; 3', 3"'-binaringenin, delicaflavone, heveaflavone, and 7, 4', 7", 4"'-tetra-*O*-methyl-amentoflavone (Figure 2) from *S. doederleinii* [17]. Six biflavonoids identified as amentoflavone, robustaflavone, 2'', 3''-dihydro-3', 3'''-biapigenin, 3', 3'''-binaringenin, heveaflavone, and 7, 4', 7'', 4'''-tetra-O-methyl-amentoflavone were isolated from *S. doederleinii* using high-speed counter-current chromatography [18]. 7o% ethanol extract of *S. doederleinii* for 50 min at 65^0C yields maximum extraction of total flavonoids (4.414 mg/g) [19]. *S. doederleinii* ethanol extract reported total 11 phenolic compounds of which (-)-hrioresinol A, (-)-lirioresinol B, (+)-wikstromol, (-)-nortracheloside, (+)-matairesinol belongs to lignans while, 3-hydroxy-1-(3-methoxy-4-hydroxyphenyl)-propan-1 -one and 3-hydroxy-1 -(3, 5-dimethoxy-4-hydroxyphenyl)-propan-1 –one were phenyipropanones. Besides these, amentoflavone, 7, 7"-di-Omethylamentoflavone, 7, 4', 7", 4" -tetra-O-methylamentoflavone, and heveaflavone (Figure 3) are biflavonoids [20]. Total ten biflavones were extracted from hydroalcoholic extract of *S. doederleinii viz*., Ametoflavone; amentoflavone 7-methyl ether; amentoflavone 4'-methyl ether; amentoflavone 4', 7", 4'"-trimethyl ether; amentoflavone 7, 7", 4', 4'"-tetramethyl ether; amentoflavone 7, 7'-dimethyl ether; 2, 3-dihydroamentoflavone; apigenin-(3', 8")-chrysin; (2*S*)-2, 3-Dihydroametoflavone 5, 4'-dimethyl ether; and (2*S*)-5", 7"-Dihydroxy-2"-phenoxychromonyl-(4'", 3')-naringenin of which last three were novel compounds [21]. Essential oil extracted from *S. doederleinii* using HS-SPME/GC-MS reported total 58 compounds with predominance of phytone and zingerone [22]. Two fraction *viz*., Petroleum ether and ethyl acetate derived from *S. doederleinii* hydroethanolic extract revealed seven compounds *viz*., ethoxy-ferulate, 11-dien-19-oic acid, aurantiamide, 9, 16-dioxo-10, 12, 14-octadeca-trienoic acid, amentoflavone, and 4'-di-*O*-methylrobustaflavone and seladoeneolignan A (Figure 4) of which last compound is new neolignan derived for the first time [23]. Dichloromethane fraction of hydroethanolic extract of *S. doederleinii* recorded highest total flavonoid contents (340.8±1.0 mg RE/g dw) whereas n-butanol fraction reported least content (72.2±8.7 mg RE/g dw). Total sixteen flavonoid compounds (Figure 5) were also isolated [24]. Involvenflavone E, involvenflavone F, unciflavone F, 3-[5, 7-dihydroxy-2-(4-methoxy-phenyl)-4-oxo-4*H*-chromen-8-yl]-4-methoxy- benzoic acid, naringenin, and eriodictyol were the recognized flavonoids extracted from *S. doederleinii* petroleum ether and the ethyl acetate fractions. Along with these compounds three novel flavonoids *viz*., seladoeflavones G, seladoeflavones H and seladoeflavones I (Figure 6), were also isolated from these fractions [25]. Ethyl acetate fraction of *S. doederleinii* recorded 12 compound belonging to various groups and some of them were mentioned as 2-trans, 6-trans-Farnesal, Syringic acid, 5-hydroxy-ferulic acid methyl ester, Affinisine, Frutinone A, and Valeroidine [26]. Novel biflavone was identified from *S. doederleinii* and is identified as Robustaflavone, 4'-O-methyl ether [27]. Ethyl acetate extract of *S. doederleinii* reported 11 components belonging to class of flavonoids and phenolic acids and they were identified as, asamentoflavone; robustafavone 4'-methyl ether; 5, 5″, 7, 7″, 4', 4‴-hexahydroxy-(2', 8″)-biflavone; 7, 4', 7″, 4‴- tetra -O-amentoflavone; 5, 5″, 7, 7″, 4', 4‴-hexahydroxy-(2', 6″)-biflavone; ginkgetin; isoginkgetin; quercetin -3-O-α-D-arabinfuranosi; nobiletin; gallic acid; and shikimic acid. Besides this n-butanol extract recorded two alkaloids, and they were identified as berberine and palmatine [28]. 8, 4′-oxyneolignans [(-)-erythro-(7′E)-4, 9-dihydroxy-3, 3′, 5′-trimethoxy-8, 4′-oxyneolign-7′-en-9′-al; (-)-erythro-guaiacylglycerol-β-O-4′-sinapyl ether; and (7′E)-3, 5, 3′, 5′-tetramethoxy-8, 4′-oxyneolign-7′-ene-4, 9, 9′-triol were the three lignans along with(+)-（7R, 8S）-5-methoxy dihydro dehydrodiconiferyl alcohol as a benzofuran and syringaresinol as a furofuran were extracted from *S. doederleinii* and first four compounds extracted for the first time [29]. UPLC-Q-TOF-MS investigation of *S. doederleinii* biflavonoid-rich extract reported total twelve known biflavonoid [30]. Six biflavones *viz*., amentoflavone, robustaflavone 7, 4', 7"-o-trimethyl ether, heveaflavone, podocarpusflavone A, robustaflavone 4', 4"'-o-dimethyl ether and robustaflavone 4'-o-methyl ether (Figure 7) were extracted from ethyl acetate fraction obtained from *S. doederleinii* ethanol extract [31]. Six novel flavonoids, nomenclature as seladoeflavones A–F along with earlier identified flavonoids 3'-phenol-apigenin (Figure 8) were derived from hydroethanolic extract of *S. doederleinii* [32]. Selagintriflavonoids A-H were the eight triflavonoids (Figure 9) compounds successfully isolated from hydroethanolic extract of *S. doederleinii*. Structurally three naringenin units constitutes selagintriflavonoids A-C whereas, apigenin and two naringenin components comprised selagintriflavonoids D-H [33]. Hydroethanolic extract of *S. doederleinii* yielded two novel apigenin derivatives, doederflavones A and B (Figure 10) along with ten other known components *viz*., unciflavones E, unciflavone D, unciflavone F, 6-(2-hydroxy-5-carboxyphenyl)-apigenin, apigenin, kaempferol, isoschaftoside, schaftoside, chromone, 2, 6, 8-trimethylchromone [34]. 75% ethanol extract of *S. doederleinii* whole plant two novel biflavonoids were isolated and they were nomenclature as (2R, 2"R)-2, 3, 2", 3"-tetrahydrorobustaflavone and 7-O-methyl-2, 3, 2", 3"-tetrahydro-3', 3"'-biapigenin. In addition to this eight earlier recognised biflavonoids *viz*., 3', 3"'-binaringenin; robustaflavone; 7-O-methylrobustaflavone; 7"-O-methylrobustaflavone; 4'-O-methylrobustaflavone; 4'-di-O-methylrobustaflavone; 7", 4"'-tetra-O-methylrobustaflavone and 3-dihydrorobustaflavone were also recovered [35].

3. Pharmacology

3.1 Antibacterial activity

Petroleum ether fraction of ethanol extract of *S. doederleinii* revealed strongest activity against microbes like *B. subtilis*, *S, aureus*, *E. coli* and *Pseudomonas* with 12.2±0.5, 13.1±0.4, 13.5±0.6, and 11.7±0.5 mm Zone of inhibition respectively [10]. *S. doederleinii* ethanolic extract recorded no inhibitory action against tested bacteria using disc diffusion method, however, in agar dilution method, MIC of the extract revealed detectable inhibition of studied microbes with MIC range of 10-20 mg/ml [9].

3.2 Antioxidant efficacy

In ABTS, DPPH, and Ferric chelation power assays, amongst five fraction obtained from ethanol extract of *S. doederleinii*, ethyl acetate extract proved superior that on the other fractions in terms of activity whereas in case of reducing power assay methanol fraction supersedes others [10]. In DPPH assay, out of microwave supported extraction ionic liquids, microwave supported extraction and Soxhlet extraction methods; microwave assisted extraction ionic liquids extracts revealed strongest antioxidant action with IC_{50} value of 56.17±2.21whereas Soxhlet extract recorded weakest activity with IC_{50} value of 81.09±3.92 [36]. 7o% *S. doederleinii* ethanol extract revealed antioxidant potential in a range of 20.22 to 46.64 mg/ml in DPPH assay [19]. Ethyl acetate fraction of *S. doederleinii* hydroethanolic extract revealed strongest antioxidant activity in DPPH assay with IC_{50} = 82.1±1.1 µg/ml while, in FRAP assay dichloromethane fraction recorded strongest reducing activity with 0.9±0.1 mmol Fe^{2+}/g [24]. *S. doederleinii* polysaccharide at 120 µg/mL concentration recorded strongest antioxidant potential in DPPH (39.35%), ABTS (43.25%) and ferrous ions (48.63%) assays [37]. Ethyl acetate fraction of *S. doederleinii* ethanol extract reported strongest radical scavenging activity in DPPH assay with IC_{50} value of 12.5±1.6 µg/ml while least action was shown by petroleum ether fraction having IC_{50} value of 53.1±0.8 µg/ml [38]. Microwave-assisted extractions of volatile oil derived from *S. doederleinii* collected from ten different locations of China were evaluated for determination of antioxidant potential. For $ABTS^{+}$ assay, Volatile from No.6 habitat recorded strongest antioxidant action (IC_{50} =69.87±7.11 µg/mL), In case of DPPH assay, oil obtained from habitat No.5 had highest radical scavenging activity (IC_{50} =66.67±5.09 µg/mL), regarding reducing power determination, sample from habitat No.4 had strongest activity (EC_{50} =70.34±6.13 µg/mL) and in FRAP assay, No.5 habitat volatile oil showed highest reducing potential (IC_{50} = 8597.31±250.08 µg/mL−1) [39, 40].

3.3 Anti- Pulmonary hypertension effect

Triflavones obtained from *S. doederleinii* revealed encouraging safeguard agent against pulmonary hypertension pertaining to their hampering action on vascular reconstruction using P13K/Akt signaling [41].

3.4. Cytotoxicity assay

Total biflavonoids extract of *S. doederleinii* and its proliposomal formulation was assessed in MTT assay against HT-29 cell line revealing dose dependent cytotoxicity (IC_{50} = 38.76 and 24.33 µg/mL, respectively) [42]. Amongst diethyl ether, methanol, ethyl acetate, petroleum ether, and water fraction obtained from ethanol extract of *S. doederleinii* recorded sturdy cytotoxic action against cells of Hela cell line with IC_{50} value of 37.53±1.91 µg/ml whereas, weakest action was observed by water fraction against 7721 cell line with IC_{50} value of 346.94±10.15 µg/ml [10]. Against HepG-2, RD and LU cell lines, ethyl acetate extract showed strong lethality with 74.1±0.3, 69.6±0.2 and 82.7±0.4% of cell survival proved superior to ethanol extract revealing 94, 94.6 and 100% survival rate [43]. 2, 2", 3, 3"-tetrahydrorobustaflavone 7, 4', 7"-trimethyl ether and robustaflavone 7, 4', 7"-trimethyl ether were the biflavanone derived from *S. doederleinii* revealed strong cytotoxic activity against HCT116, NCI-H358, and K562 with IC_{50} values of 19.1, 23.5, 28.8µM for earlier compound and IC_{50} values of 15.6, 20.1, 22.5 µM for latter compound [16]. *S. doederleinii* lignan extracts revealed moderate cytotoxic potential towards L 929 murine cells on the contrary when individual components *viz*., (-)-lirioresinol B, (-)-lirioresinol A, (+)-wikstromol, and (+)-matairesinol showed strong action with IC_{50} value of 8.5, 9, 10, and 20 µg/ml respectively [20]. Novel biflavone, (2*S*)-2, 3-Dihydroametoflavone 5, 4'-dimethyl ether derived from *S. doederleinii* depicted strong activity against MCF-7 (IC_{50} =6.35µM) followed by A549 (IC_{50} =7.86µM) and SMMC-7721 cell line (IC_{50} = 10.18 µM) [21]. Brine shrimp lethality bioassay was used to determine cytotoxicity potential of aqueous and ethanolic extract of *S. doederleinii* and LC_{50} values found as 40141 and 97049 µg/ml respectively [9]. *S. doederleinii* ethyl acetate extract depicted strongest action against A549 cell line with IC_{50} value of 51.9±1.5 µg/ml while it failed to report any significant action against PC12 cell line having IC_{50} value >150 µg/ml [44]. Seven flavonoids extracted from *S. doederleinii* were evaluated against NCI-H460, A549 and K562 cell lines, of which only Seladoeflavone E, Seladoeflavone F and 3'-phenol-apigenin compound recorded cytotoxic effects against evaluated human cancer cell lines with 8.17-18.66 µM range of IC_{50} values [32]. Compare to doederflavone B, compound doederflavone A derived from *S. doederleinii* revealed strongest cytotoxic potential against A549, MCF-7, SMMC-7721, and LoVo cell lines with IC_{50}= 0.82±0.32, 3.35±0.40, 13.55±0.52, and 5.92±0.73 µmol/L respectively [34].

3.5. Anti-cancer activity

On the basis of inhibitory action against tumor and histopathological evidences it was quite clear that total biflavonoids extract of *S. doederleinii* and proliposomal formulation of same extract had recorded antitumor potential with least systemic toxicity, however proliposomal formulation of extract showed its significantly better efficacy compared to crude extract [42]. Total biflavonoids extracted from *S. doederleinii* recorded moderate activity against A-549 and 7721 cell lines with 120.51±8.09 and 131.74±6.31 g/mL respectively [36]. *S. doederleinii* ethyl acetate extract depicted strongest inhibitory action against HT29 a colorectal cancer cell line with IC_{50} values of 17.43±2.12. The extract induced cell morphological changes converting polygonal shapes in to round and enhances granular contents within cells. *S. doederleinii* extract found to arrest cell cycle of HT29 cells in G1 phase. The extract also showed to induce autophagy, and apoptosis in investigated colorectal cancer cell lines [45]. Ethyl acetate extract of *S. doederleinii* revealed inhibition of many CYP450 enzymes on dose dependent basis whereas inhibition of CYP2D6, CYP2C19, CYP3A was observed on time-dependent fashion [46]. Administration of *S. doederleinii*

aqueous extract orally at 250 mg/kg for 20 days showed tumor neutralizing activity on 20th day [47]. *S. doederleinii* polysaccharides recorded antitumor action against A549 cells (IC_{50}= 1528 µg/mL) and HCT-116 cells (IC_{50}=2341 µg/mL) [37]. Ethyl acetate extract fraction of *S. doederleinii* showed inhibitory action against HeLa (IC_{50} = 0.12mg/ml) and HepG2 (IC_{50} = 0.60 mg/mL) [28]. In MTT assay, *S. doederleinii* retards human NPC TW03 cells development through an direction related to cell cycle seize at S phase, retarding expression of Bcl-2 protein elevating Bax protein expression [48]. Three hydrophobic fractions *viz*., petroleum ether, dichloromethane and ethyl acetate fractions were assessed in MTT assay of which ethyl acetate fraction (31.2 µg/mL) revealed most significant anti-tumour action against Hep-2 cells under *in vivo* condition also it hampers relocation of cell. Same extract revealed a cell cycle seizure and triggered p53 gene expression [49]. Treatment of ethyl acetate extract of *S. doederleinii* to A549 cells found to trigger apoptosis; at higher concentration it also brings changes in membrane potential of mitochondria. The extract brought changes in membrane potential of mitochondrial membrane potential and triggered cell apoptosis through boosting expression of Bax and controlling Bcl-2 genes. Parallelly, extract also triggered caspase-9 and 3 and stopped cell cycle [50]. Essential oil of *S. doederleinii* obtained from habitat no. 6 and 5 revealed strongest action against A-549 and 7721 cell lines with IC_{50} values of 46.81±3.23 and 34.02±2.58 µg/mL respectively [39, 40]. Treatment of LLC and B16 cell lines with total biflavonoids extract recorded concentration dependent inhibitory action against them (IC_{50} = 36.29 and 95.65 µg/mL respectively) [51]. Rare biflavonoid identified as 'Delicaflavone' extracted from *S. doederleinii* brought suppression of human cervical cancer HeLa cells growth, extending to morphological variations, seize of G2/M phase of cell cycle, and brings apoptosis following dose- and time-dependent pattern [52]. Successful identification of two Lactate dehydrogenase inhibitors *viz*., amentoflavone and robustaflavone from *S. doederleinii* ethyl acetate extract was done through immobilized LDH on nanoparticles [52]. Out of ten evaluated *S. doederleinii* biflavonoids, 7-*O*-methyl-2, 3, 2", 3"-tetrahydro-3', 3"'-biapigenin and 3-dihydrorobustaflavone recorded substantial cytotoxic effect against A549 and MCF7 cell lines with IC_{50} = 14.41 and 14.55 µM, respectively [35].

3.6. Antiproliferative activity

Amongst five biflavonoids (Compound 1-5) isolated from hydro-ethanolic extract of *S. doederleinii*, compound-3 recorded strongest inhibitory action against A549 and H1299 cell line with IC_{50} = 2.3 and 4.0 µM respectively whereas compound identified as 'delicaflavone' revealed moderate activity against non-cancer MRC-5 cells with IC_{50} value of 36.8 µM. All compound recorded superior action compared to standard compound *Cis*-platin (DDP) [15]. Amongst five extracts of *S. doederleinii*, ethyl acetate extract revealed strong activity against A549, PC-9, k562, HL60 and CNE2 cell lines with IC_{50} values of 15.4±0.6, 38.9±6.3, 18.43±4.8, 43.9±4.2 and 36.1±4.5 respectively. Out of six biflavonoids isolated from *S. doederleinii*, compound 'amentoflavone' depicted strongest action against A549, PC-9, k562, HL60 and CNE2 cell lines with IC_{50} values of 36.3±5.3, 6.41±1.9, 5.25±0.87, 46.3±4.3 and 17.3±1.7 respectively [18]. Treatment of CNE-1 cells with ethanolic extract of *S. doederleinii* at 2.5 g/ml for 48 h recorded highest 52.5% of inhibition whereas similar concentration at same time period against C666-1 cells showed highest 43.6% of inhibitory action [53]. Hydroethanolic extract of *S. doederleinii* revealed dose and time dependent fashion antiproliferative action against HeLa cells. It was observed that treatment of cell with for 48 and 72 h showed stronger activity with IC_{50} values of 49.05±6.76 and 44.14±4.75 µg/mL respectively found much superior over a 12 and 24 h treatment period. The extract also recorded apoptosis trigger in HeLa cells by promoting Bax; switch on Caspases 9 and 3; facilitated autophagy and G0/G1 phase cell cycle restriction [54]. *S. doederleinii* ethanol extract inhibited nasopharyngeal carcinoma CNE cells based on time and concentration dependent manner. Extract also triggered caspase-3-dependent apoptosis in CNE cells. Interaction with extract also reduces Bcl-2 and enhancement of Bax [55]. Neolignan compounds such as seladoeneolignan A, amentoflavone and 7, 4'-di-*O*-methylrobustaflavone obtained from *S. doederleinii* revealed weak inhibitory action on Hep-2 and Eca-109 cells [23]. In case of HT-29 and HeLa cell lines, Ethyl acetate fraction of hydroethanolic extract of *S. doederleinii* exhibited strongest antiproliferative activity (IC_{50} = 55.6±1.3 and 69.2±1.3 µg/mL respectively), however, dichloromethane fraction recorded superior action against A459 (IC_{50} = 55.9±12.6 µg/mL) [24]. Amongst Hs27, HepG2, MCF-7 and MDA-MB 231 human cancer cell lines, HepG2 was the most susceptible cell line towards ethanolic extract of *S. doederleinii* at 48 hours post treatment with LC_{50} values of 306µg/ml while aqueous extract showed LC_{50} values of 329µg/ml towards same cell line at 72 hours post treatment [9]. Biflavonoid-rich extract of *S. doederleinii* showed antiproliferative and proapoptotic activity in Hep-2 and FaDu cell lines through curbing IKKβ and IkB-α kinase activity and latter negative expression of effector proteins associated with NF-kB/COX-2 signalling [30].

3.7. Alzheimer's disease

In Morris water maze test, Total extract obtained from *S. doederleinii* depicted a very outstanding enhancement on learning ability and memory function for Alzheimer's disease mice which chiefly confined in the improved distance and this functional progress is dose-dependent [56]. All eight triflavonoids isolated from *S. doederleinii* reported inhibitory action against β-secretase (BACE1) of which Selagintriflavonoid A recorded highest inhibitory activity with IC_{50} value of 0.75 µM while Selagintriflavonoid F depicted weakest activity with IC_{50} value of 46.99±0.72 µM [33].

3.8 Antimutagenic activity

S. doederleinii dried powder boiled for 2 hours and tested against *Salmonella typhimurium* TA98 in which mutation was induced using picrolonic acid. Extract revealed moderate antimutagenic activity with PI value of 47%; on the contrary, the same extract showed higher antimutagenic potential against benzo[a]pyrene induced mutations with PI value of 79.3% [57].

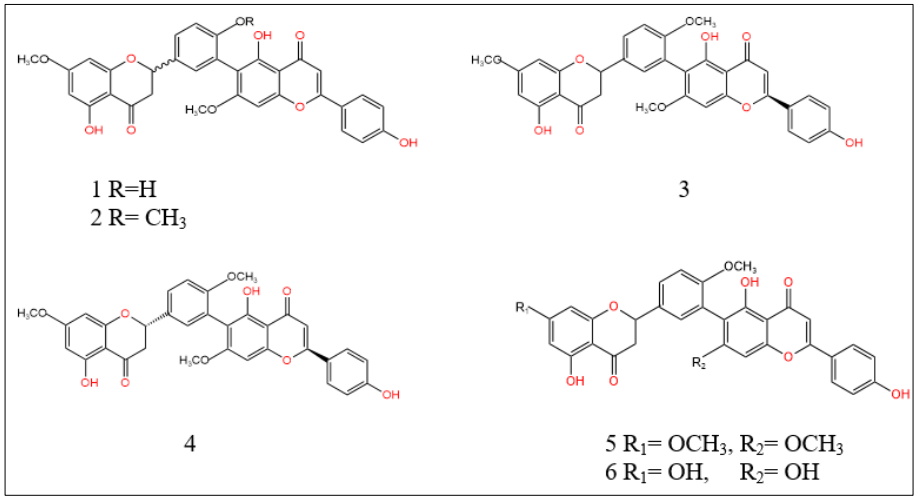


Fig 1: Novel biflavonoid 2, 3-dihydrorobustaflavone 7, 7"-dimethyl ether (1), 2, 3-dihydrorobustaflavone 7, 4', 7"-trimethyl ether (2), 2", 3"-dihydrorobustaflavone 7, 4', 7"-trimethyl ether (3), 2, 2", 3, 3"-tetrahydrorobustaflavone 7, 4', 7"-trimethyl ether (4), robustaflavone 7, 4', 7"-trimethyl ether (5), robustaflavone 4'-methyl ether (6) isolated from *S. doederleinii* Hieron [14, 16]

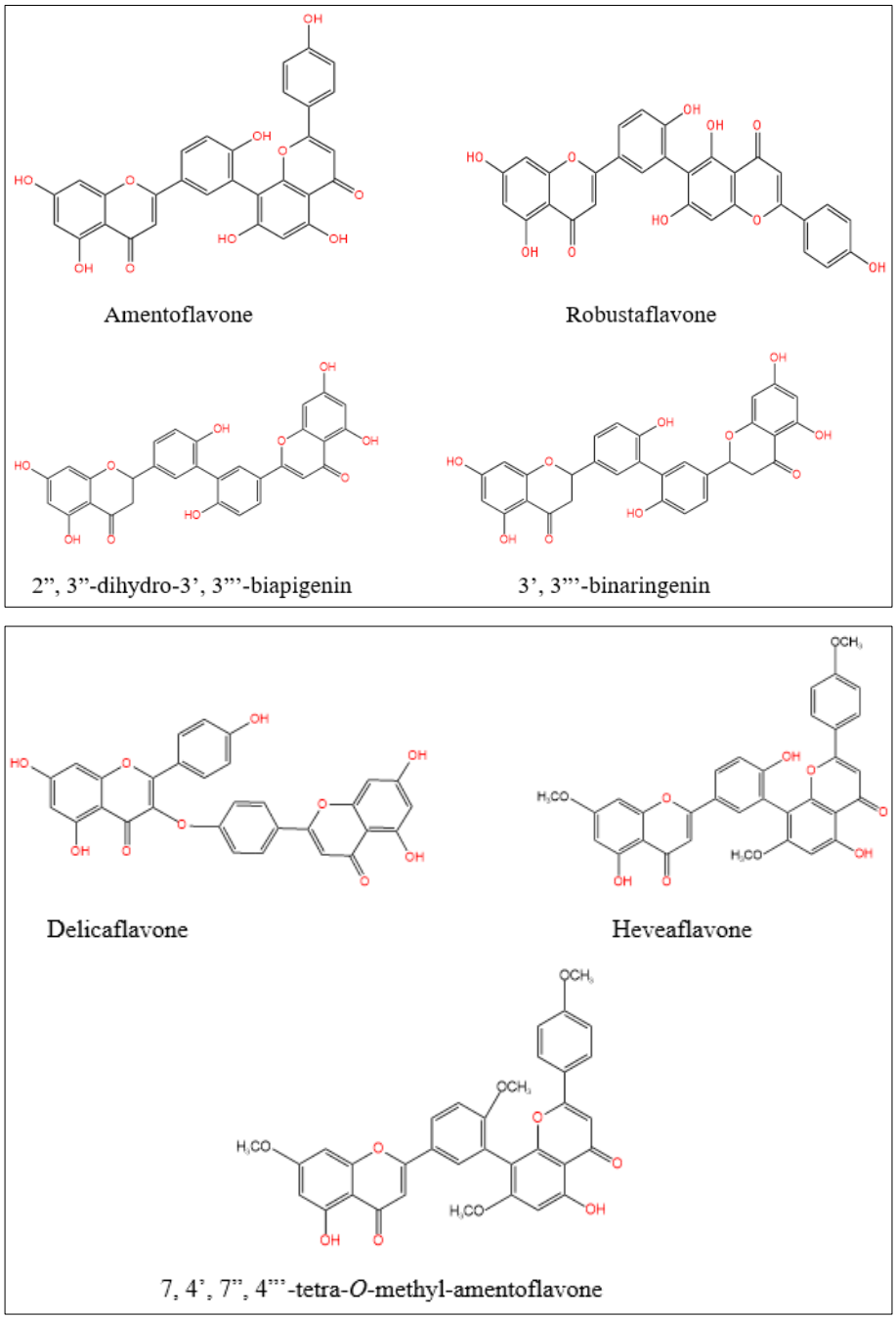


Fig 2: Seven biflavones extracted from *S. doederleinii* [17]

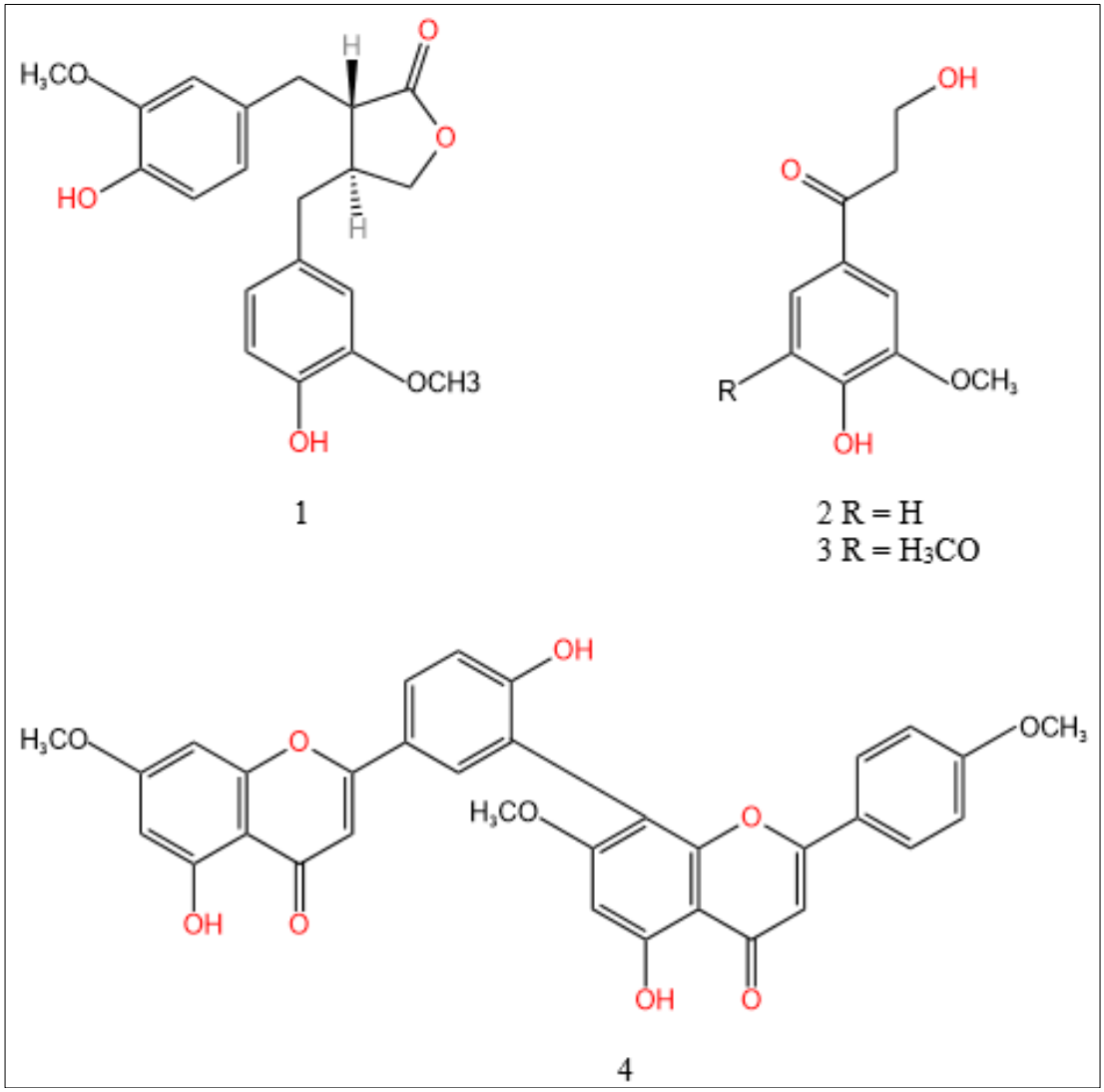
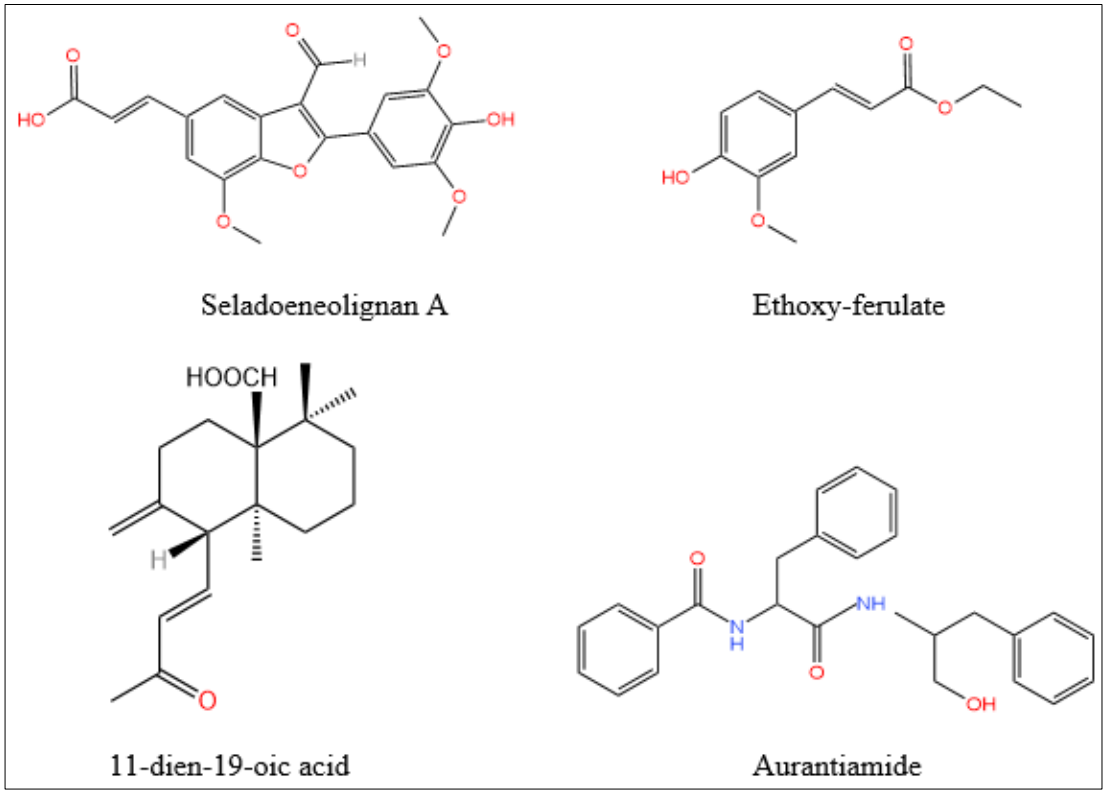


Fig 3: Phenolic compounds (+)-matairesinol (1), hydroxy-1 -(3-methoxy-4-hydroxyphenyl)-propan-1 -one (2), 3-hydroxy-1 -(3, 5-dimethoxy-4-hydroxyphenyl)-propan-1-one (3), heveaflavone (4) isolated from *S. doederleinii* [20]



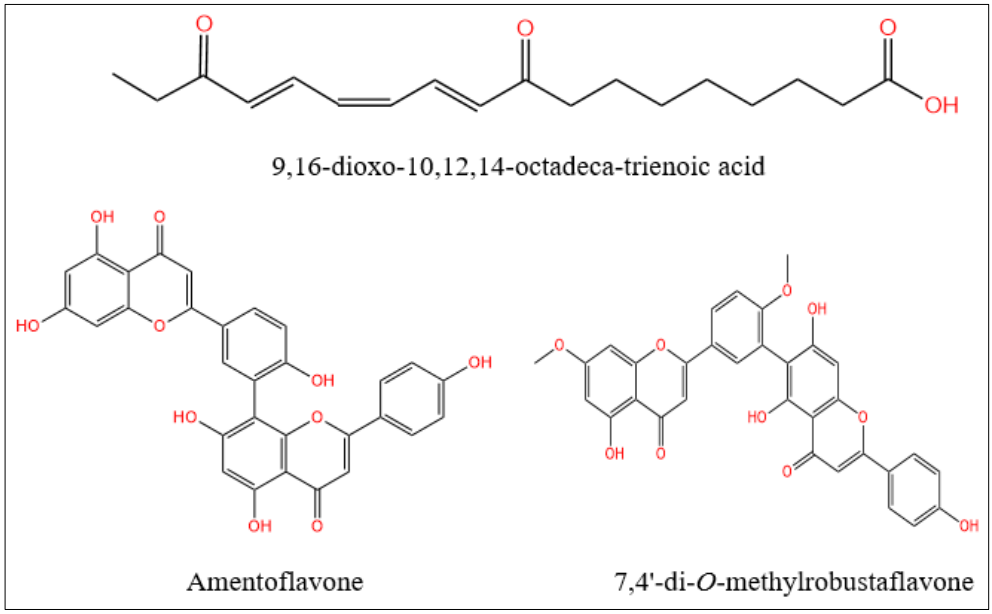


Fig 4: Chemical structures of compounds isolated from petroleum ether and ethyl acetate fractions of 80% ethanol extract of *S. doederleinii* [23]

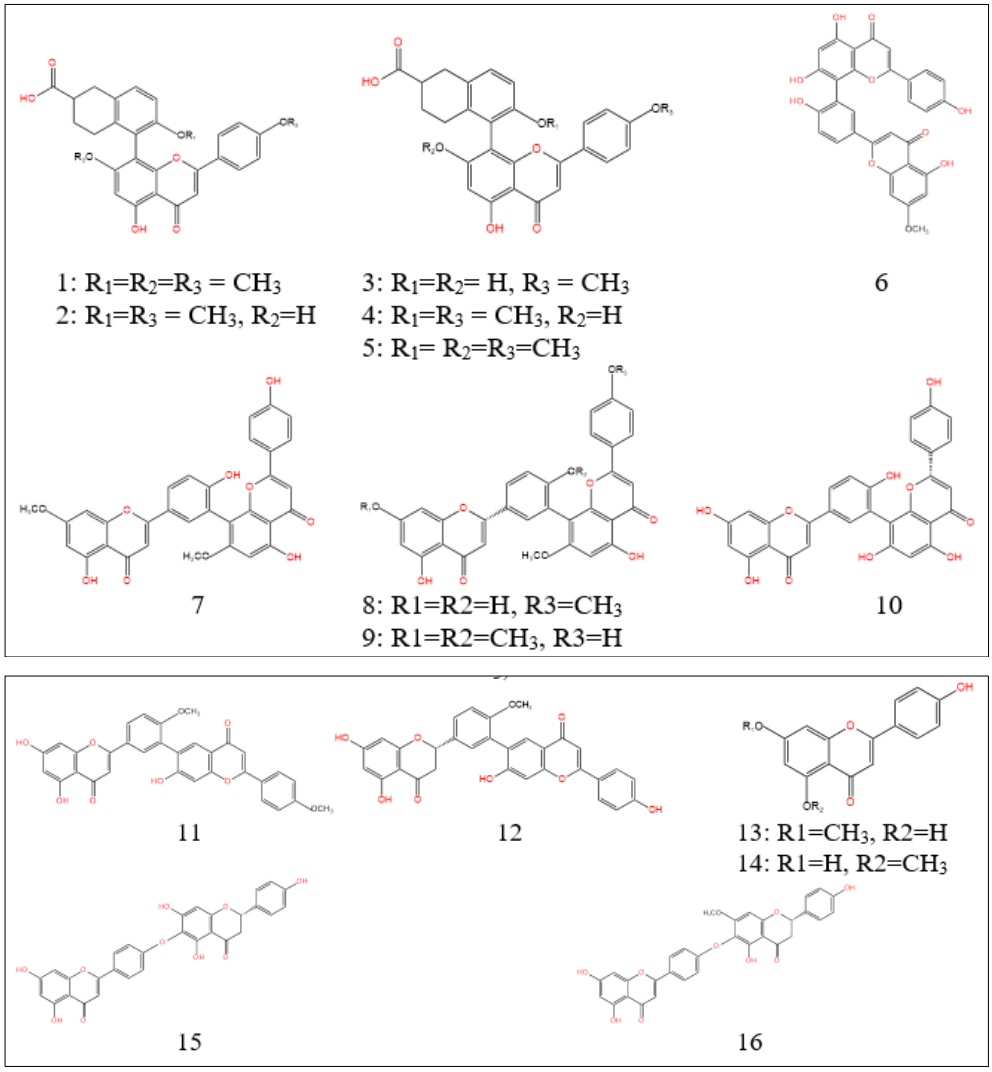


Fig 5: Flavonoids, 3-(5-hydroxy-7-methoxy-2-(4-methoxyphenyl)-4-oxo-4H-chromen-8-yl)-4-methoxybenzoic acid (1); 3-(5, 7-dihydroxy-2-(4-methoxy-phenyl)-4-oxo-4H-chromen-8-yl)-4-methoxy-benzoic acid (2); 8-(5-acetyl-2-hydroxyphenyl)-5, 7-dihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one (3); 8-(5-acetyl-2-methoxyphenyl)-5, 7-dihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one (4); 8-(5-acetyl-2-methoxyphenyl)-5hydroxy-7-methoxy-2-(4- methoxyphenyl)-4H-chromen-4-one (5); Sequoiaflavone (6), 7, 7″-dimethyletheramentoflavone(7); 2, 3-dihydro-4‴-methyl ether amentoflavone (8); 2, 3-dihydro-7, 4′-dimethyletheramentoflavone (9); 2″, 3″-Dihydroamentoflavone (10); 4′, 4‴-dimethyletherrobustaflavone (11); 2, 3-dihydro-4′-methyletherrobustaflavone (12); 5, 4′-dihydroxy-7-methoxyflavone (13); theve-tiaflavone (14); 2″, 3″-dihydrohinokiflavone (15); and 7″-methylethertetrahy-drohinokiflavone (16) isolated from *S. doederleinii* [24]

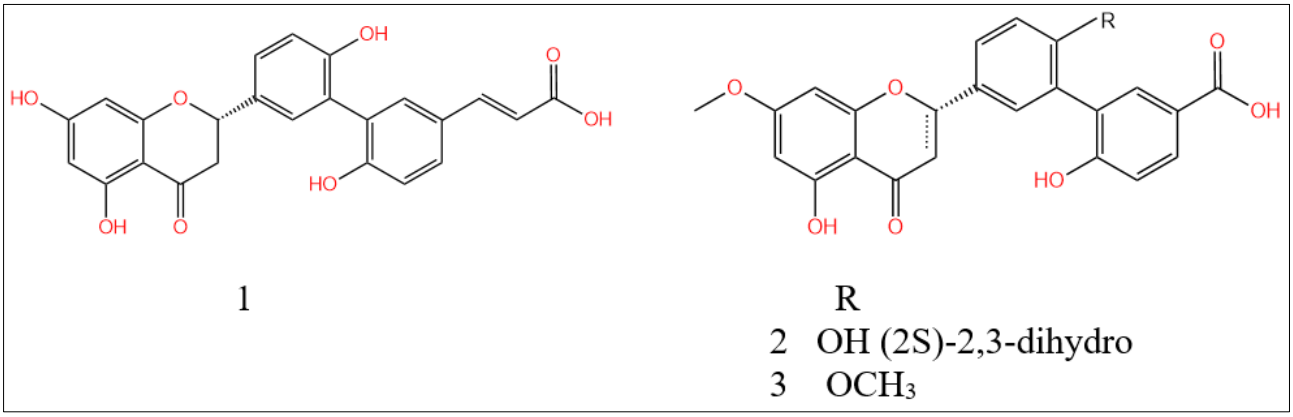


Fig 6: Flavonoids Seladoeflavones G (1), Seladoeflavones H and I (2, 3) isolated from *S. doederleinii* [25]

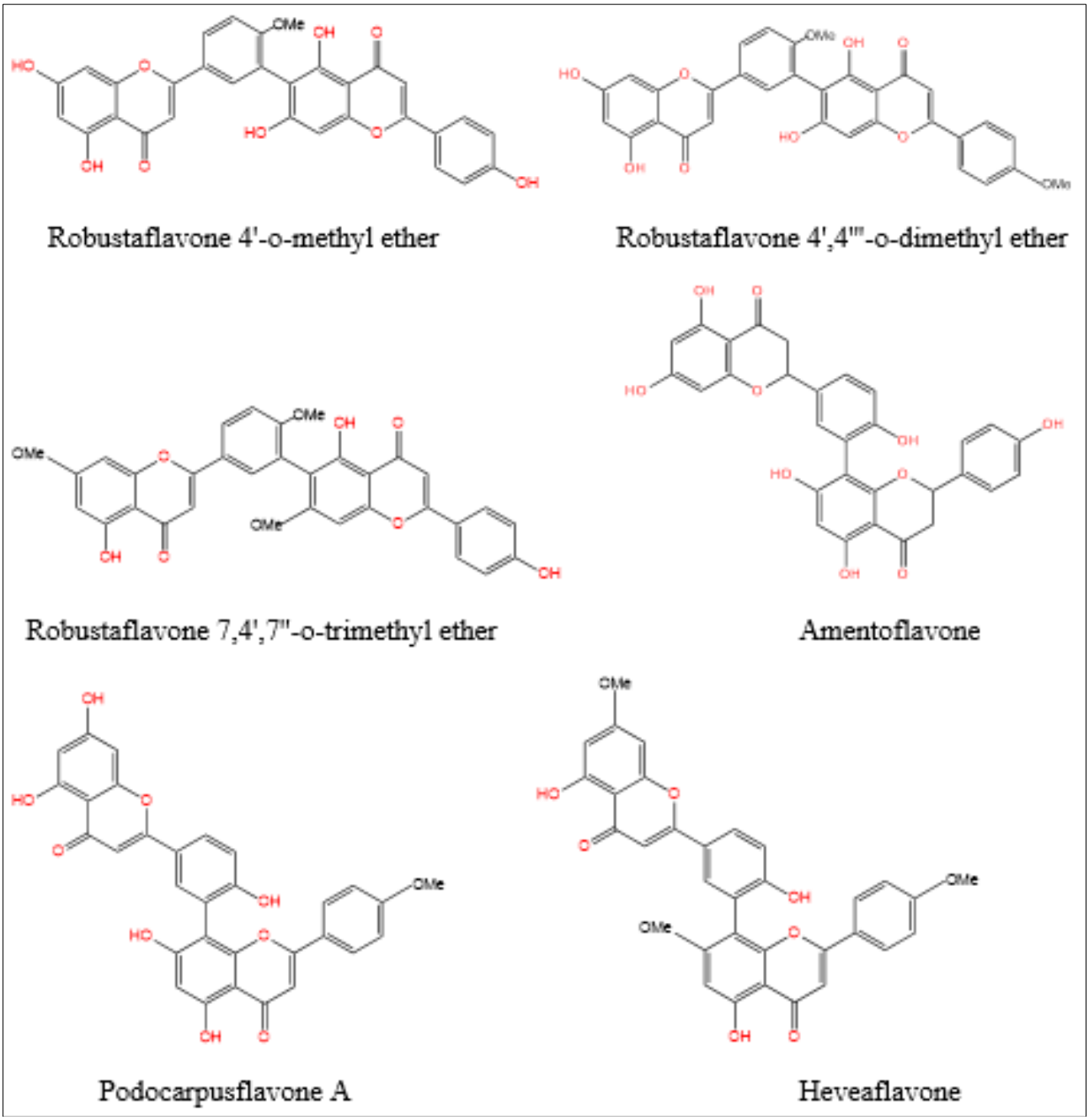


Fig 7: Chemical structures of the flavonoids retrieved from ethyl acetate extract of *S. doederleinii* [31]

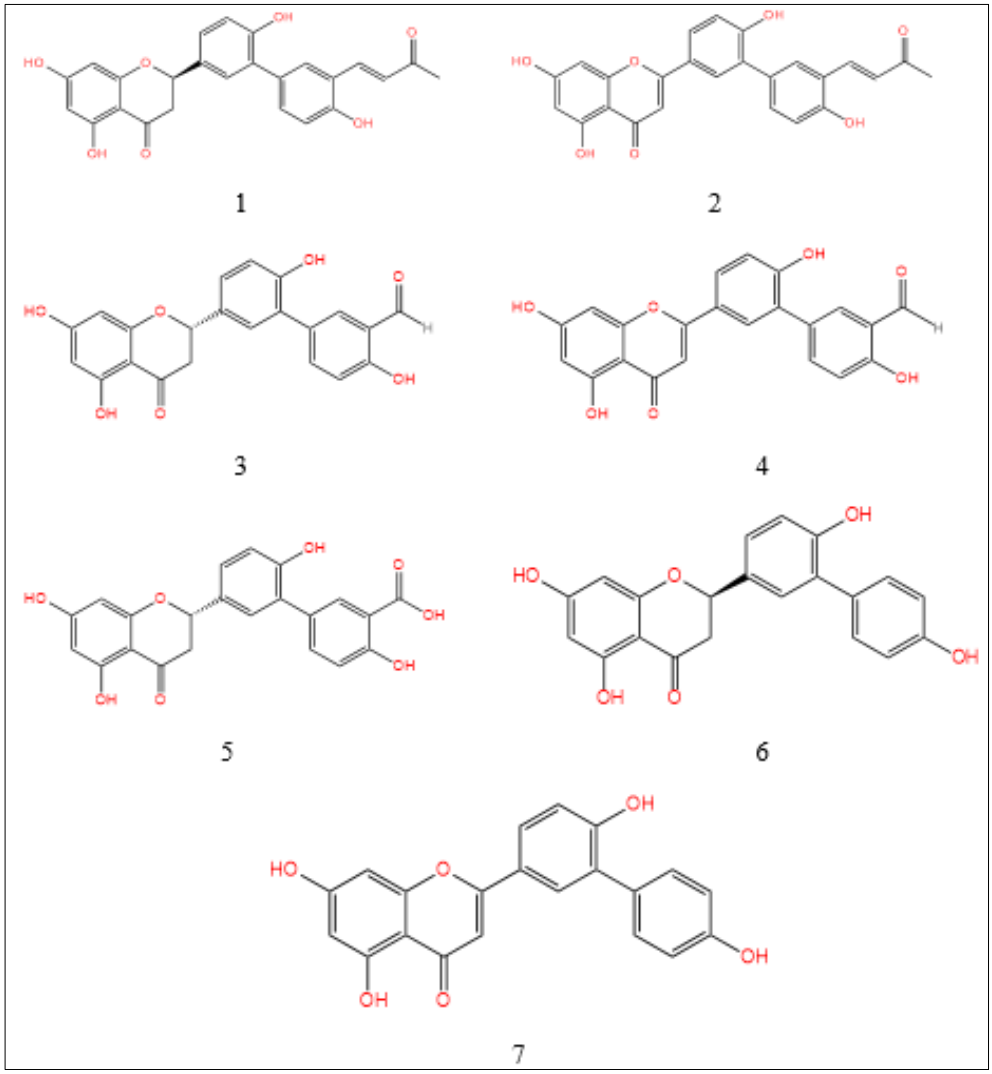
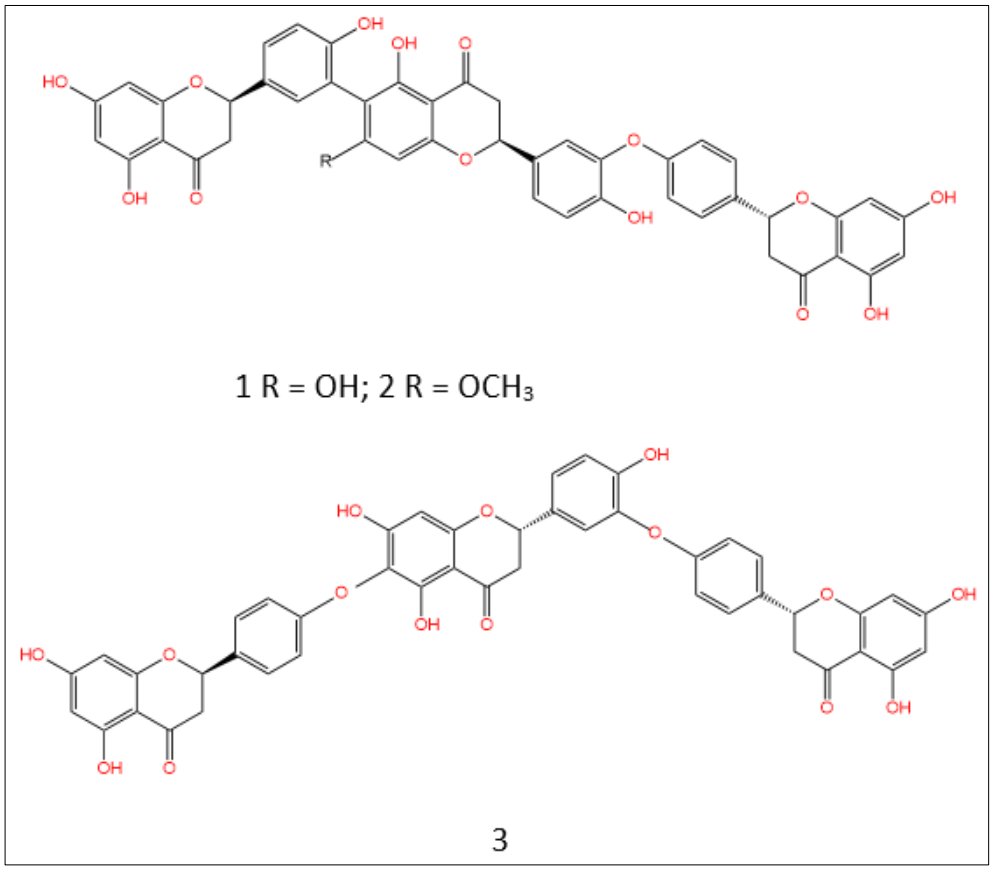


Fig 8: Novel flavonoids, seladoeflavones A-F (1-6) and 3'-phenol apigenin (7) isolated from *S. doederleinii* [32]



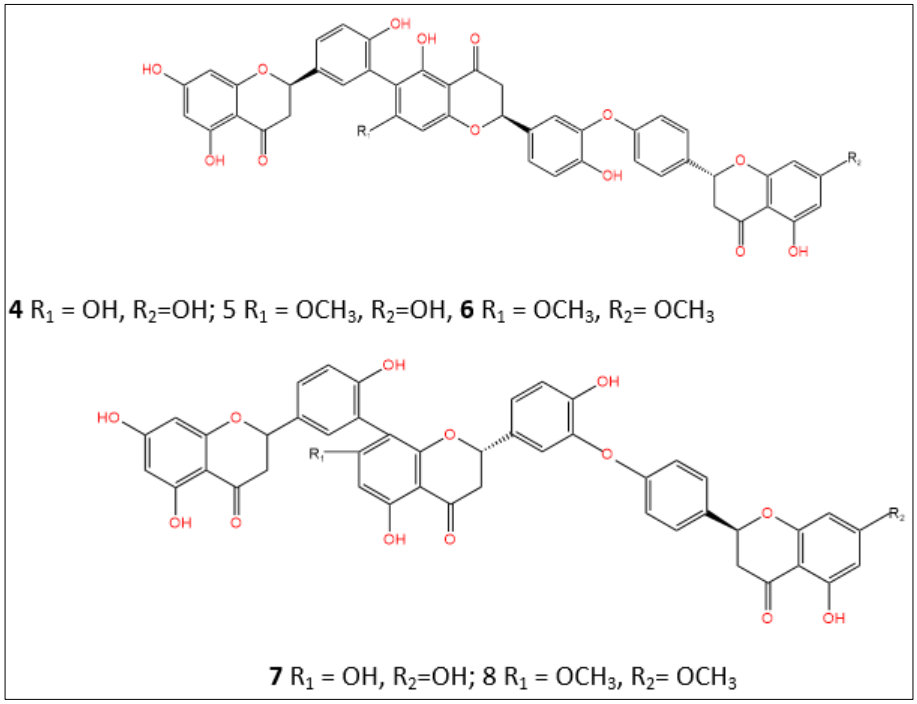


Fig 9: Selagintriflavonoids A-H isolated from *S. doederleinii* [33]

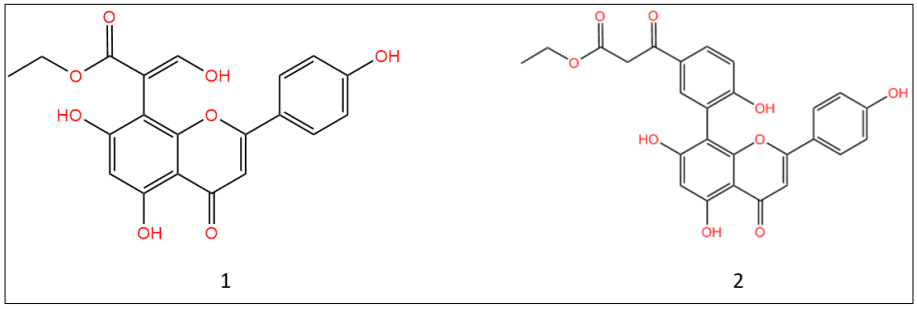


Fig 10: Doederflavones A and B (1 and 2) derived from *S. doederleinii* [34]

Conclusion

S. doederleinii is rich source of secondary metabolites. It also found as richest source of flavonoids. Derived phytomolecules revealed diverse pharmacological activities. These molecules need to be evaluated for their therapeutic properties *in vitro* and *in vivo*. Phytocompounds like triflavonoids isolated from *S. doederleinii* needs to be evaluated further against Alzheimer's disease. Plant parts depicted strong medicinal capacity and have significant action against various diseases, making it as a resourceful plant with potent therapeutic potential. Pharmacological potential of *S. doederleinii* needs to be explored in various dimensions against some critical diseases. Present review will assist the new generation of researchers to design and adopt new research ideas on *S. doederleinii*.

Conflict of Interest

No conflict of interest to be declared.

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