



Bibenzyls and bisbybenzyls of bryophytic origin as promising source of novel therapeutics: pharmacology, synthesis and structure-activity

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Abstract

Background The amphibian, non-vascular, gametophyte-dominant, bio-indicator class, bryophytes; with their wide ranges of habitat have attained importance due to their promising medicinal attributions and therapeutic role; mostly aided by presence of aromatic bibenzyl and bisbybenzyl class of compounds. Bibenzyls are steroidal ethane derivatives, resembling the structural moiety of bioactive dihydro-stilbenoids or iso-quinoline alkaloids. These stress triggered secondary metabolites are the by-products of the flavonoid biosynthetic pathway. Different classes of bryophytes (Bryophyta, Marchantiophyta and Anthocerotophyta) possess different subtypes of bibenzyls and dimeric bisbibenzyls. Among the liverwort, hornwort and mosses, former one is mostly enriched with bibenzyl type constituents as per the extensive study conducted for phytochemical deposit. Considering macrocyclic and acyclic group of bibenzyls and bisbybenzyls, generally marchantin type compounds are reported vividly for significant biological activity that includes neuro-nephro-cardio-protection besides anti-allergic, anti-microbial, anti-apoptotic and cytotoxic activities studied on *in-vitro* and *in-vivo* models or on cell lines.

Result The critical analysis of reported chemical and pharmaceutical attributions of bibenzyls and bis-bibenzyls yielded detailed report on this compound class along with their application, mode of action, natural source, techniques of synthesis, extraction procedure, isolation and characterization. Further, the structure activity relationship studies and bioactivity of bibenzyls derived from non-bryophytic origin were also summarized.

Conclusion This review encompasses prospective biological application of botanical reservoir of this primarily ignored, primeval land plant group where recent technical advances has paved the way for qualitative and quantitative isolation and estimation of novel compounds as well as marker components to study their impact on environment, as bio-control agents and as key leads in future drug designing.

Keywords bibenzyls · bisbybenzyls · marchantin · riccardin · anti-apoptotic · anticancer

Introduction

Bryophytes, the “amphibians of the plant kingdom”, are taxonomically placed between thallophytes and pteridophytes and subdivided into Bryophyta or mosses (~14,000 species),

Marchantiophyta or liverworts (~6000 species) and Anthocerotophyta or hornworts (~300 species) [1]. According to paleo-ontological dating, these are the oldest terrestrial plant group, originated 440–450 million years ago [2] These small-sized plants are photosynthetic, non-vascular, mostly un-lignified with heteromorphic alternation of generation and are highly susceptible to desiccation [3]. The difficulty in collection, identification and subsequent molecular analyses has rendered this plant group unexplored for decades in the field of pharmaco-nutraceutical studies [4]. Recent advances in quality control techniques and molecular data mining have widened the identification of phytochemical and pharmacological attributes of different species of bryophytes throughout the globe. Exposure to biotic and abiotic stresses often triggers production of biologically active, toxic,

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allelopathic secondary metabolites which shield them against microbes, insects, molluscs, mammals, heavy metals and ultraviolet radiation [5, 6]. Varieties of terpenoids include unstable dialdehydes and hemiacetals, flavonoids, many highly unsaturated fatty acids, alkanones and aromatic compounds such as bibenzyls [7–11] and bis-bibenzyls, acetogenins, phytoosterols and flavonoid glycosides were isolated or detected and subjected to hemisynthesis or total synthesis for further structural and functional elucidation [12]. This review comprises of the phyto-therapeutic bioactivities of one of the major phytochemicals harvested from bryophytes, the bibenzyls and bisbibenzyls [8, 13, 14]. Besides their characteristic odour and pungency, these compounds and their derivatives impart characteristic properties viz. allergic dermatitis, antimicrobial, anti-feedant, insecticidal, nematocidal, piscicidal, anti-radical, anti-thrombin, cytotoxic, neuro-nephro-cardioprotective properties and also possess inhibitory activities against 5-lipoxygenase, calmodulin, hyaluronidase, cyclooxygenase, DNA polymerase β , α -glucosidase, calcium and tubulin polymerization [15–24]. Some bryophytes also function as inhibitor of plant growth and mimicked structural moiety of sex pheromones [25, 26]. Liverworts are mostly enriched in lipophilic mono-, sesqui- and di-terpenoid content with typical bibenzyls and bis-bibenzyls which have also been isolated from different plant families. Bibenzyls are colourless solid ethane derivatives originated via flavonoid biosynthetic pathway. Different subtypes of bibenzyls and bisbibenzyls are present in different bryophyte species [27, 28] viz. cyclic (*Marchantia emarginata* Reinw., Blume & Nees); macrocyclic (*Asterella angusta* (Steph.) Pandé, K.P. Srivast. & Sultan Khan, *Blasia pusilla* L., *Dumortiera augustan* L.); chlorinated (*Riccardia marginata* (Colenso) Pearson); polychlorinated (*Riccardia polyclada* (Mitt.) Hässel); prenylated (*Radula perrottetii* Gottsche ex Steph.), cinnamoylated (*Polytrichum pallidisetum* Funck); geranylated (*Radula kojana* Steph.); hydroxybenzylated (*Radula complinata* (L) Dumort) [29–32] etc. Among all these classes and subclasses marchantin type of macrocyclic bis-bibenzyls have been reported to possess very promising bioactivities [33]. Till date almost more than 60 macrocyclic and acyclic bis-bibenzyls have been isolated and chemically synthesized to elucidate their structure, pharmacology, agricultural consortium and applications as nutraceuticals or cosmetics [34–36].

Methodology

Reliable and popular international scientific databases such as PubMed, Scopus, Science Direct, Research Gate, Google Scholar, etc. were searched using the search strings such as “bioactivity of bibenzyls”, “anti-cancer bryophytes”, “chemical composition of bryophytes”, “bibenzyl cytotoxicity”, “bibenzyl structures” and other

relevant keywords to retrieve a number of citations related to chemical and pharmaceutical attributions of bibenzyls and bis-bibenzyls. The retrieved citations were further cross-referenced and a total of 200 relevant references are reported here to depict the entire research related to many natural and synthetic bibenzyls and bisbibenzyls. Extensive research work on bryophytes from the group of scientists led by Professor Y. Asakawa (faculty of Tokushima Bunri University) is widely described in this review. Figure 1 stands for the pictorial presentation of the habits of some bryophytes taken in their wild environment. Images a, b and c were obtained from Wikimedia Commons under the GNU Free Documentation License (http://en.wikipedia.org/wiki/GNU_Free_Documentation_License), Image D was taken from similar source and licensed under the Creative Commons CC0 1.0 Universal Public Domain Dedication (<https://creativecommons.org/publicdomain/zero/1.0/deed.en>) and images numbered as g-h were included from our personal collection (photographed from Eastern Himalaya by the corresponding author). Further, the mode of action of bibenzyls and bis(bi)benzyls corresponding to their source bryophytes are extensively presented in Table 1 and bibenzyls derived from non-bryophytic origin, with corresponding bioactivity, are tabulated in Table 2. The molecular structures of these compounds are presented in Figure 2. Scientific names of the bryophytes were further validated from www.tropicos.com and chemical structures and molecular formula were retrieved from Pub Chem (<https://pubchem.ncbi.nlm.nih.gov/>)

Bioactivity of bibenzyls and bis(bi)benzyl

Bibenzyl and their dimeric form bis(bi)benzyls are the allelopathic protectant molecules reported to delay, bypass or prevent herbivory, pathogenesis, drought induced damage or untimely freezing under harsh unfavourable environmental stresses [3]. These bryophyte-specific macrocyclic compounds have demonstrated an array of bioactive properties such as anti-cancer, anti-microbial, anti-oxidant, LXR α activating, HIV preventive, enzyme (cyclooxygenase, lipoxygenase, tyrosinase, calmodulin) modulating and microtubule polymerizing activities [37–41]. Like other secondary metabolites isolated from higher group of plants, these compounds were also reported for some therapeutic application often accompanied with potent radical scavenging, anti-microbial and proapoptotic activities [14, 42, 43]. There are reports of many bibenzyls and derivatives which lack any pharmacological data till date. 3,3'-dimethoxy-4-hydroxybibenzyl isolated from *Plagiochila* species [44]. 3,5-dihydroxy-2-(3-methyl-2-butenyl) bibenzyl, 3,5-dihydroxy-6-carbomethoxy-

Fig. 1 Habits of few bioactive bryophytes; a. *Bazzania trilobata*, b. *Blasia pusilla* c. *Radula complanata* d. *Riccardia multifida*, e. *Marchantia paleacea*, f. *M. polymorpha*, g. *M. papillata*, h. *Dumortiera hirsuta*



2-(3-methyl-2-butenyl) bibenzyl [13], 3,3'-dimethoxy-4,5-methylenedioxy-4'-hydroxybibenzyl, 3,4,3',4'-dimethylene dioxybibenzyl, 3,3'-dimethoxy+methylene dioxybibenzyl and 3,3'-dihydroxy-4,5,4',5'-dimethylene dioxybibenzyl isolated from *Frullania* species, angustatin A from *Asterella angusta* [45], cavicularin isolated from *Cavicularia densa* Steph [46], isoplagiochins E, F, G, ptychantols A-C, isoperrotetin A [47] were reported with different medicinal properties. However, the following section depicts the medicinal efficacy of selected naturally derived and chemically synthesized bibenzyls and their derivatives, along with their sources and details of experimental methodologies.

Asterelin A, Asterelin B

Anti-fungal activity

These dibenzofuran bisbibenzyls were isolated from the liverwort *Asterella angusta* (Steph.) Pandé, K.P. Srivast. & Sultan Khan by bioactivity-guided fractionation and the extract was evaluated against the pathogenic fungi *Candida albicans* through bioautographic and broth microdilution assays; using fluconazole as standard drug. The minimum inhibitory concentration (MIC) value ranged from 16 to 512 µg/ml. The structures of the compounds were elucidated by 1D and 2D-nuclear magnetic resonance (NMR), mass spectroscopy (MS) and X-ray crystallographic diffraction (CD) analyses [48].

Table 1 Bioactivity of bibenzyls with their source(s), experimental organism and/or cell line(s)

bioactivity	name of the compound	source bryophyte	family of the bryophyte	experimental organism/cell line	experimental outcome	experimental details	mechanism of action	reference
cytotoxicity, pro-apoptotic, MDR reversal activity	brittonin A	<i>F. inouei</i>	Frullaniaceae	KB KB/VCR K562 K562/A02 KB KB/VCR K562	ID ₅₀ 42.1 ± 2.51 μM ID ₅₀ 33.7 ± 1.28 μM ID ₅₀ 49.6 ± 3.13 μM ID ₅₀ 30.9 ± 2.59 μM ID ₅₀ 24.4 ± 1.11 μM ID ₅₀ 26.3 ± 1.77 μM ID ₅₀ 42.8 ± 3.11 μM ID ₅₀ 21.0 ± 1.91 μM	determination of melting points, optical rotation, CD spectra, IR spectra, NMR spectra and HPLC	reversal of adriamycin resistance	[51]
cytotoxic activity	chrysothobibenzyl	<i>F. inouei</i>	Frullaniaceae	human cell lines (KB KB/VCR K562 and K562/A02)	ID ₅₀ 11.3 ± 1.43 μM, 12.8 ± 1.53 μM, 14.5 ± 1.94 μM and 12.0 ± 2.45 μM respectively	spectral analysis, NMR and HPLC study	MDR reversal	[51]
pro-apoptotic activity	dihydroptychantol A	chemically synthesized (natural source: <i>A. angusta</i>)	Aytoniaceae	human osteosarcoma U2OS cells	IC ₅₀ 29.6 μM (24hr), 24.7 μM (48 hr)	cytotoxicity assay using time-lapse microscopic studies, TEM, AO and DAPI staining, apoptosis and cell cycle distribution study by FACS, RT-PCR	autophagy induction, upregulation of cyclin B1 and nuclear p53, expression, downregulation of cytoplasmic p53, G ₂ /M cell cycle arrest	[52–54]
cytotoxic activity	lumularin	<i>D. hirsuta</i>	Marchantiaceae	human glioblastoma U87 cells	IC ₅₀ 21.2 μM (24hr), 23.7 μM (48 hr)	FT-IR spectroscopy, NMR, column chromatography	MDR reversal of chemoresistant cell line	[11]
anti-cancer activity	marchantin A	<i>M. polymorpha</i>	Marchantiaceae	Human MCF-7	IC ₅₀ 4.0 μg/ml	reversed-phase HPLC/UV, morphological study of apoptosis and cell cycle study using annexin V-FITC staining, densitometric analysis, RT-PCR, FACS and western blot screening	dose and time dependent apoptotic induction, upregulation of p21 and p27 gene, reduced cyclin B1 and D1 gene expression	[32]
cytotoxic activity	marchantin A	<i>M. polymorpha</i>	Marchantiaceae	rat myeloblastCC ₅₀ L6	IC ₅₀ 6.64 μM (standard: podophyllotoxin)	resazurin staining, spectrophotometric study, micro-titre plate assay	enzyme inhibition, anti-oxidant activity	[59]
anti-proliferation activity	marchantin C	<i>S. glaucescens</i>	Schistochilaceae	P388 leukemia cells	IC ₅₀ 8.5 μg/ml	bioactivity-guided isolation, cytotoxic assay	cytotoxicity	[66]
pro-apoptotic activity	marchantin M	<i>A. angusta</i>	Aytoniaceae	PC3	IC ₅₀ 5.45 μM/l	cytotoxicity assay via MTT and Western	cytotoxicity	[77]

Table 1 (continued)

bioactivity	name of the compound	source bryophyte	family of the bryophyte	experimental organism/cell line	experimental outcome	experimental details	mechanism of action	reference
cytotoxic activity	neomarchantin A, neomarchantin B	<i>S. glaucescens</i>	Schistochilaceae	P388	IC ₅₀ 18 and 7.6 µg/ml respectively	blotting, FACS, morphological investigation performed to study cell cycle regulation and apoptosis induction	caspase-3 activation, induction of PARP cleavage	[67]
pro-apoptotic activity	pakyonol	<i>P. intermedium</i>	Plagiochaceae	PC3	IC ₅₀ 7.98 µM/l	bioactivity-guided isolation, cytotoxic assay	apoptosis induction	[77]
cytotoxic activity, anti-tumor activity	pallidisetin A, pallidisetin B	<i>P. pallidisetum</i>	Polytrichaceae	human melanoma RPMI-7951 and human glioblastoma U-251	ED ₅₀ 1.0 µg/ml and 2.0 µg/ml respectively (for both cell line)	stereochemistry based study and cytotoxicity assay	growth arrest	[15]
pro-apoptotic activity	plagiochin E	<i>M. polymorpha</i>	Marchantiaceae	<i>C. albicans</i> strain (clinical isolate)	chromatin condensation, metacaspase activation, phosphatidylserine exposure increased many fold	TEM, PI, DAPI, FITC-annexin V and FITC-VAD-FMK staining based cytotoxicity decreasing	G ₂ /M cell cycle arrest, chromatin condensation, nuclear fragmentation, downregulated CDC28, CLB2, CLB4 expression, cytochrome c release, metacaspase activation	[83]
anti-cancer activity	riccardin C	<i>A. angusta</i>	Aytoniaceae	PC ₃	IC ₅₀ 34.9 ± 1.32 µM, 28.0 ± 1.86 µM, 40.1 ± 1.52 µM respectively	immunofluorescence microscopy, molecular modeling, MTT assay	cell cycle arrest, microtubule depolymerization	[16]
anti-cancer activity	riccardin C	<i>A. angusta</i>	Aytoniaceae	MCF-7, PC ₃ and KB	IC ₅₀ 3.22 µM/L	MTT, western blot, FACS and morphological screening was performed	inhibited cell proliferation	[77]
MDR reversal, anti-proliferative activity	riccardin D	<i>D. hirsuta</i>	Marchantiaceae	HUVEC	CGI 2.2% -28.5% after 72 hr. (applied concentration 2.5-30µM)	scratch assay, capillary tube formation assay, cell proliferation assay, western blot, RT-PCR, immunohistochemical staining, MTT assay performed	tumor angiogenesis prevented, VEGF level decreased, blood vessel formation inhibited	[89]
pro-apoptotic, topomerase-II inhibitory activity				HL-60, K562 and MDR K562/A02	IC ₅₀ 25.2 µM, 21.7 µM and 27.2 µM respectively (after 72 hr)	MTT, UV transilluminator based DNA fragmentation detection, Topo-I and Topo-II		[90]

Table 1 (continued)

bioactivity	name of the compound	source bryophyte	family of the bryophyte	experimental organism/cell line	experimental outcome	experimental details	mechanism of action	reference
chemotherapeutic MDR reversal activity	2-Amino-thiazole derivative of DHA	chemically synthesized	NR	K562	11.56% inhibition	mediated supercoiled pBR322 DNA relaxation assay, FITC-Annexin V and PI staining, RT-PCR based expression analysis	reversal of vincristine and adriamycin toxicity	[41]
	2-Amino-thiazole derivative of dimethyl ether of DHA	chemically synthesized	NR	K562/A02 KB/VCR K562	10.11% inhibition 0.135 ± 0.009 ID ₅₀ µM 58.67 % inhibition	cytotoxicity assay, TEM, FACS, RT-PCR, AO and DAPI staining		
	2-Hydrazino-thiazole derivative of dimethyl ether of DHA	chemically synthesized	NR	K562/A02 KB/VCR K562	26.81 % inhibition 0.152 ± 0.003 ID ₅₀ µM 32.07 % inhibition			
cytotoxic activity	3,3',4,4'-tetramethoxybibenzyl	<i>F. inouei</i>	Frullaniaceae	KB/VCR KB	18.76 % inhibition 0.176 ± 0.016 ID ₅₀ µM ID ₅₀ 30.8 ± 1.74 µM	determination of optical rotation, melting points, CD, IR and NMR spectra, HPLC	reverted adriamycin cytotoxicity	[51]
cytotoxic activity	3,5-dihydroxybibenzyl	<i>Radula amoena</i> Herzog.	Radulaceae	K562 HepG-2 A549 SMMC-7721	ID ₅₀ >50 µM ID ₅₀ 39.2 ± 1.83 µM IC ₅₀ 19.1 µg/ml IC ₅₀ 16.55 µg/ml	cytotoxic assay, MTT	Inhibition of cell viability	[177]
chemotherapeutic activity	7-Hydroxyl-8-bromo derivative of dimethyl-ether of DHA	chemically synthesized	NR	K562 K562/A02 KB/VCR	38.55 % inhibition 11.86 % inhibition 0.177 ± 0.012 ID ₅₀ µM	cytotoxicity assay, cell cycle study, TEM based microscopic observation	reversal of drug resistance	[41]
cytotoxic activity	14-hydroxylumularin	<i>R. natans</i>	Ricciaceae	NCTC-Clone 929 fibroblast J 774 murine macrophage peritoneal macrophage (BALB/c mice)	cytotoxicity percentage ± SDare 7.91±2.89, 18.88±3.25, 1.40±0.9 respectively at 21.7µM	<i>in-vitro</i> cytotoxic assays in cellular lines and peritoneal macrophage	growth inhibition of cancer cell lines	[26]
glioma cell-induced angiogenesis inhibition	marchantin C	<i>S. glaucescens</i>	Schistochilaceae	human malignant glioma (T98G) and U87 glioma	57% inhibition of T98G induced tube formation, 2-fold sFlt-1 level uplift	tube formation assay, ELISA	microtubule depolymerization, cell invasion blocked, inhibition of cellular migration	[68, 70]
prevention of intestinal polyposis	riccardin D	<i>D. hirsuta</i>	Marchantiaceae	male <i>APC^{Min/+}</i> mice	polyp number reduction 79.3% in colon, downregulation of β-catenin and cyclin D1 expression	immunohistochemical staining, western blotting, (RT-PCR, ELISA)	anti-angiogenesis	[92]
inhibition of tubulin polymerization	isoplagiochin A, isoplagiochin B	<i>P. emarginata</i>	Plagiochilaceae.	Tubulin <i>in-vitro</i>	IC ₅₀ 50 and 25 µM respectively	MC conformational search, NMR, spectrophotometric study	cytotoxicity	[42]
	radulanin K	<i>R. javanica</i>	Radulaceae	guinea pig macrophage	IC ₅₀ 6µg/ml	radical scavenging assay		[57]

Table 1 (continued)

bioactivity	name of the compound	source bryophyte	family of the bryophyte	experimental organism/cell line	experimental outcome	experimental details	mechanism of action	reference
anti-radical, anti-oxidant							Inhibited superoxide anion radical release	
	paleatin B	<i>M. paleacea</i>	Marchantiaceae	<i>in-vitro</i> assay	IC ₅₀ 11.7 μM/l	arachidonic acid peroxidation assay	enzymatic inhibition	[64]
	marchantin A	<i>M. polymorpha</i>	Marchantiaceae	NO inhibition	EC ₅₀ 20 μg/ml	DPPH radical scavenging	prevented release of superoxide radical	[58, 132]
	marchantin H	<i>P. intermedium</i>	Plagiochaceae	rat brain	IC ₅₀ 0.51±0.03 μM	<i>in-vitro</i> anti-peroxidant activity assay	prevented lipid peroxidation, reduced cytochrome c release	[178]
nitric oxide inhibitory activity	2-geranyl-3,5-dihydroxybenzyl	<i>R. appressa</i>	Radulaceae	lipopolysaccharide stimulated RAW 264	IC ₅₀ 4.5 μM	cell culture assay		[28, 125]
anti-bacterial activity	lumularin	<i>D. hirsuta</i>	Marchantiaceae	<i>P. aeruginosa</i>	MIC 64 mg/ml.	anti-bacterial assay		[11]
	2,4,6-trichloro-3-hydroxybenzyl, 2,4-dichloro-3-hydroxybenzyl, 2-chloro-3-hydroxybenzyl	<i>R. marginata</i>	Aneuraceae	<i>B. subtilis</i>	ZOI 2mm	disk diffusion assay		[18]
anti-influenza	marchantin E	<i>F. muscaticola</i>	Frullaniaceae	H3N2, H1N1 influenza A and B viruses	strongest growth inhibition at 50 μM	PA endonuclease inhibition assay, anti-influenza A virus assay, docking simulation	viral growth inhibition	[76]
5-lipoxygenase and cyclooxygenase inhibition	paleatin B	<i>M. paleacea</i>	Marchantiaceae	<i>in-vitro</i> assay	IC ₅₀ 0.78 and 45.2 μM/l respectively	reversed-phase-HPLC based analysis, positive control	exerted lipophilicity, enzymatic inhibition, radical scavenging	[64]
leishmanicidal	14-hydroxylumularin	<i>R. natans</i>	Ricciaceae	<i>Leishmanidomonovani</i> , (PP75) <i>L. braziliensis</i> (M2903) <i>L. amazonensis</i> (PH8)	100% percentual lysis (control Resveratrol)	nordihydroguaiaretic acid and indomethacin respectively <i>in vitro</i> culture based assays	growth inhibition	[26]
anti-feedant	2,6,3'-trichloro-3-hydroxy-4'-methoxybenzyl, 2,4,6,3'-tetrachloro-3,4'-dihydroxybenzyl	<i>R. polyclada</i> ,	Ricciaceae	<i>Spodopteralittoralis</i> larva	moderate activity	disk-choice bioassay	growth inhibition	[25]
anti-fungal	Asterelin A, Asterelin B,	<i>A. angusta</i>	Aytoniaceae	<i>Candida albicans</i>	MIC 128 and 512 μg/ml respectively (standard: Fluconazole)	bioautographic assay, microdilution method	growth inhibition	[48]
	bazzanin B,	<i>B. trilobata</i>	Lepidoziaceae	<i>Cladosporiumcucumerinum</i> , <i>Botrytis cinerea</i> , <i>Pyriculariaoryzae</i> , <i>Septoriatritici</i>	IC ₅₀ 17.5, 18.9, 3.9, 23.5 μg/ml respectively	microliter plate test, bioautography assay, anti-fungal glass house test	growth inhibition of spore suspension, disease	[19]

Table 1 (continued)

bioactivity	name of the compound	source bryophyte	family of the bryophyte	experimental organism/cell line	experimental outcome	experimental details	mechanism of action	reference
	bazzanin S			<i>Cladosporiumcucumerinum</i> , <i>Botrytis cinerea</i> , <i>Pyriculariaoryzae</i> , <i>Septoriaatrifici</i> , <i>Phlyophthorainfestans</i>	IC ₅₀ 30.8, 50.6, 2.6, 4.5 and 29.2 µg/ml respectively (standard: folicur, rovril, amistar)		development reduced	
	isoplagiochin D	<i>B. trilobata</i>	Lepidoziaceae	<i>Cladosporiumcucumerinum</i> , <i>Botrytis cinerea</i> , <i>Pyriculariaoryzae</i> , <i>Septoriaatrifici</i>	IC ₅₀ 13.0, 7.6, 4.0, 15.9 µg/ml respectively	bioautography assay, microtiter plate test, anti-fungal glass house test	growth inhibition, disease development reduced	[19]
	riccardin D	<i>D. hirsuta</i>	Marchantiaceae	<i>C. albicans</i>	MID 0.4 µg. (standard: miconazole) 256 µg/ml	bioautography assay	inhibition of fungal growth	[20]
	marchantin H	<i>P. intermedium</i>	Plagiochaceae	<i>C. albicans</i> CA 02 (fluconazole-sensitive) and <i>C. albicans</i> CA 10 (fluconazole-resistant)		microdilution method	drug resistance reversed	[55]
	11-O-demethyl marchantin I	<i>A. augusta</i>	Aytoniaceae	<i>C. albicans</i> ATCC10231	MIQ 0.4 µg. MIC 64 µg/ml	microdilution method, bioautographic assay	growth inhibition	[48]
	marchantin A	<i>M. emarginata</i> subsp. <i>Tosana</i>	Marchantiaceae	<i>C. albicans</i>	MID 2.5 µg	bioactivity-guided fractionation, anti-fungal assay (standard miconazole)	growth inhibition	[58]
	2,6-dichloro-3-hydroxy- 4-methoxybibenzyl.	<i>F. muscicola</i>	Frullantiaceae	<i>Artemiasalina</i>	L.C ₅₀ 0.44 ppm (average)	brine shrimp lethality bioassay	growth inhibition	[26]
	4-hydroxy-3'-methoxybibenzyl	<i>P. stephensoniana</i>	Plagiochaceae	<i>C. albicans</i>	MFC 62.5 µg/ml	disk assay	growth inhibition	[97]
	13,13'-O-isopropylidene riccardin D	<i>M. polymorpha</i>	Marchantiaceae	<i>C. albicans</i>	MID 0.25 µg/ml (standard miconazole)	disk assay	growth inhibition	[20]
anti-dermatophyte fluconazole reversal activity	4-hydroxy-3'-methoxybibenzyl plagiochin E	<i>P. stephensoniana</i> synthetic compound	Plagiochaceae NR	<i>T. mentagrophytes</i> <i>C. albicans</i> (isolate SDEY-24R and SDEY-09R and resistant strains QL-14- and QL-28)	MIC 125 µg/ml FIC 0.3125 to 0.375; MIC 16, 16, 16, 32 µg/ml respectively (without fluconazole)	disk assay drug pump efflux using Rhodamine 123 efflux, Overexpression study of MDR gene CDR1	growth inhibition drug refractory activity	[97] [21]
anti-biofilm formation	riccardin D	<i>D. hirsuta</i>	Marchantiaceae	<i>C. albicans</i>	MIC ₉₀ 16 µg/ml;	anti-fungal Susceptibility Test, RT-PCR, FM	downregulation of HR genes (EFG1, HWPI, ALS3), growth inhibition	[31]
anti-trypansomal activity	plagiochin A	<i>P. sciophila</i> <i>R. perrottetii</i>	Plagiochilaceae Radulaceae	<i>T. brucei</i> brucei (strain GUTat 3-1) <i>T. brucei</i> brucei	downregulation of HR genes (ALS1, ALS3, CDC35, ECE1, HWPI, EFG1)	RT-PCR, SEM, CLSM, fluconazole, XTT reduction assay	<i>in-vivo</i> hyphal growth inhibition, HR gene downregulation, Ras-cAMP-Efg pathway blocked, prevented biofilm maturation	[91]
					IC ₅₀ 0.93 µg/ml (standard: Eflornithine, Suramin)	<i>in-vitro</i> assay	cytotoxicity	[61]
						<i>in-vitro</i> assay		[61]

Table 1 (continued)

bioactivity	name of the compound	source bryophyte	family of the bryophyte	experimental organism/cell line	experimental outcome	experimental details	mechanism of action	reference
anti-protozoal activity	2(R)-2-isopropenyl-6,7-dihydroxy-4-(2-phenylethyl)dihydro-benzofuran marchantin A	<i>M. polymorpha</i>	Marchantiaceae	<i>Plasmodium falciparum</i> strains, NF54 <i>Trypanosoma bruceirhodesiense</i> <i>T. cruzi</i> <i>Leishmaniatodonovani</i> <i>Trichostrongylus colubriformis</i>	IC ₅₀ 0.44 µg/ml (standard: Eflornithine, Suramin) IC ₅₀ 3.41 µM IC ₅₀ 2.09 µM IC ₅₀ 14.90 µM IC ₅₀ 1.59 µM IC ₅₀ 0.13 mg/ml	<i>in vitro</i> <i>P. falciparum</i> assays, Anti-protozoal activity assays, PfFAS-II enzyme inhibition assays, larval motility inhibition assay	growth inhibition, enzymatic regulation	[59]
nematocidal activity	3-Methoxy-4-hydroxybibenzyl	<i>P. stephensoniana</i>	Plagiochilaceae				viability reduced	[1]

Bazzanin B, Bazzanin S

Anti-fungal activity

The bio-autography on thin layer chromatographic (TLC) assay-guided fractionation was employed to isolate bisbibenzyls bazzanin B (6',8'-dichloroisoplagiochin C) and bazzanin S (6'-chloroisoplagiochin D) from dichloromethane and methanol extracts and also from ethyl acetate-soluble fraction of alcoholic extract of the air-dried liverwort *Bazzania trilobata* (L.) Gray. These extract showed significant colony inhibiting activity against five phyto-pathogenic fungi detected by microtiter plate assay [49]. The structures of isolated bibenzyls were confirmed by extensive NMR spectral analysis [19]. Bazzanin S has formed a larger zone of inhibition (ZOI) compared to its per-methylated derivative when acted against *Cladosporium cucumerinum*, a fungal plant pathogen. The activity was tentatively attributed to the presence of a free OH- group which may be responsible for contributing this inhibitory activity. It has shown inhibitory activity against *Pyricularia oryzae* with half maximal inhibitory concentration (IC₅₀) values of 3.9, 4.0 and 2.6 µg/ml whereas IC₅₀ values for *Septoria tritici* were observed as 23.5, 15.9 and 4.5 µg/ml. Activity of bazzanin S and bazzanin B against *C. cucumerinum* and *Botrytis cinerea* were comparable with standard drugs like tebuconazole, iprodione and azoxystrobin. However, all isomers of bazzazins A-S are reported from *B. trilobata* [47]

Brittonin A, Brittonin B

Anti-proliferative activity

These methoxylated bibenzyls, isolated from the liverwort *Frullania inouei* S. Hatt., showed profound cytotoxicity and significant anti-proliferative activity with 50% infectious dose (ID₅₀) values ranging from 11.3 to 49.6 µM when tested on human tumor cell lines *viz.* KB, KB/VCR, K562 or K562/A02. These compounds were also reported from *Frullania brittoniae* subsp. *truncatifolia* A. Evans [50]. These compounds have exhibited multi-drug resistance (MDR) with reversal fold values ranging from 3.19 to 10.91 (5 µM) for vincristine-resistant KB/VCR cell lines and 4.40 to 8.26 (5 µM) for adriamycin-resistant K562/A02 cell lines, respectively. Structure elucidation was accomplished through NMR assay, time-dependent density functional theory (TDDFT)-CD calculations and single-crystal X-ray diffraction measurements [51]. Molecular structures of these phytochemicals were

Table 2 bibenzyl and derivatives isolated from non-bryophytic origin

name of the compound	source organism	plant family	Category	plant part used	biological activity	animal model/cell line/assay type	isolation and identification performed by using	reference
bambusifolol, 3-hydroxy-5-methoxy bibenzyl	<i>Eria bambusifolia</i> Hook.f	Orchidaceae	angiosperm	whole plant	cytotoxic	HL-60, SMMC-7721, A-549, MCF-7 and SW-480	spectroscopic analysis	[111]
bulbotetusine	<i>Bulbophyllum reusiusculum</i> Rehb. f	Orchidaceae	angiosperm	tuber	cytotoxic	human tumor cell lines	sephadex LH-20 column chromatography, NMR	[179]
Chrysotoxine	<i>Dendrobium pulchellum</i> L.	Orchidaceae	angiosperm	stem	cytotoxic neuroprotective	H460, H23 cell lines SH-SY5Y cells	HPLC, NMR	[180]
dendrosignatol	<i>Dendrobium signatum</i> Lindl.	Orchidaceae	angiosperm	whole plant	cytotoxic	MDA-231, HepG2 and HT-29	Spectroscopic analysis and MS	[161] [181]
dendrowillol A	<i>Dendrobium williamsonii</i> L.	Orchidaceae	Angiosperm	whole plant	Cytotoxic	HL-60	spectroscopic analysis	[182]
gavilein	<i>Gavilea lutea</i> (Comm. ex Pers.) M.D. Correa	Orchidaceae	angiosperm	stem	anti-fungal, leishmanicidal	<i>Candida albicans</i> , <i>Leishmania donovani</i>	1D and 2D NMR, UV, IR and HRESIMS.	[183]
gigantol	<i>Dendrobium draconis</i> Rehb. f.	Orchidaceae	angiosperm	whole plant	anti-metastasis	H460 cells	HPLC and NMR spectroscopy	[184]
moscatilin (4,40 -dihydroxyl-3,30 , 5- trimethoxybibenzyl)	<i>Dendrobium nobile</i> Lindl.	Orchidaceae	angiosperm	stem	anti-mutagenic	umu gene (<i>Salmonella typhimurium</i> TAI535/pSK1002)	silica gel CC, EI-MS, 1H and 13C NMR	[185]
nobilin D, nobilin E	<i>Dendrobium loddigesii</i> Rolfe	Orchidaceae	angiosperm	stem	anti-cancer	HUVECs	Silica gel CC, IR-spectroscopy, MS, NMR	[186, 187]
perrottetin H	<i>Dendrobium nobile</i> Lindl.	Orchidaceae	angiosperm	stem	anti-oxidant	DPPH assay	spectroscopic analysis	[134]
gigantol, batatastin III, 4 ϕ -hydroxy-3,3 ϕ ,5-trimethoxybibenzyl, 3,3 ϕ ,4 ϕ ,5-tetramethoxybibenzyl, 3,4 ϕ -dihydroxy-5-methoxybibenzyl, 3 ϕ -O-methylbatatastin III, 3,3 ϕ ,5-trihydroxybibenzyl, and 3,4 ϕ ,5-trihydroxybibenzyl,	<i>Hymenophyllum barbatum</i> (Bosch) Baker	Hymenophyllaceae	pteridophyte	whole plant	NM	NM	HPLC	[124]
stilbestemin B 3'- β -D-glucopyranoside, stilbestemin H 3'- β -D-glucopyranoside, and stilbestemin I 2'- β -D-glucopyranoside	<i>Stemona tuberosa</i> Lour	Stemonaceae	angiosperm	root	neuroprotective	SH-SY5Y cell	HPLC	[189]
2-[4-hydroxy-3-(4- hydroxyphenyl) benzyl]-4-(4- hydroxyphenyl) phenol (20C)	<i>Gastrodia elata</i> Blume	Orchidaceae	angiosperm	NM	neuroprotective	MPTP/p mouse model	NM (reagent purchased)	[190]
4,5,4'-trihydroxy-3,3'-dimethoxybibenzyl	<i>Dendrobium ellipsophyllum</i> Tang and Wang	Orchidaceae	angiosperm	whole plant	anti-proliferation	H292 cell line	VLC, MPLC, NMR, UPLC-MS	[191, 192]

Table 2 (continued)

name of the compound	source organism	plant family	Category	plant part used	biological activity	animal model/cell line/assay type	isolation and identification performed by using	reference
shuangshencaosu	<i>Dendrobium secundatum</i>	Orchidaceae	angiosperm	Stem	anti-oxidant	DPPH assay	VLC, spectral analysis	[193]
2,2-dimethyl-5-methoxy-7-[2-(3"-hydroxyphenyl)ethyl]chromene	<i>Hermidium bulleyi</i> (Rolfe) Tang & F. T. Wang	Orchidaceae	angiosperm	tuber	not evaluated	NM	CC	[194]
5-(2,3-dimethoxyphenethyl)-6-methylbenzo[d][1,3]dioxole, dibenz[b, f]floxepine,	<i>Bulbophyllum kwangtungense</i> Schlecht.	Orchidaceae	angiosperm	stem	cytotoxic	HeLa cell line	2D-NMR	[195]
10,11-dihydro-2,7-dimethoxy-3,4-methylene-dioxy dibenz[b, f]floxepine								

AO: Acridine orange, CGI: cell growth inhibition, CLSM: Confocal laser scanning microscopy, DAPI: 4', 6-diamidino-2-phenylindole, FIC: fractional inhibited concentration, FITC: fluorescein isothiocyanate, FM: Fluorescence Microscopy, HR gene: Hyphae Related gene, MC: Monte Carlo, MFC: minimum fungicidal concentration, MPLC: medium pressure liquid chromatography, NR: not required, PI: propidium iodide, SEM: Scanning electron microscopy, SD: standard deviation, VLC: vacuum-liquid chromatography

determined with the help of NMR, TDDFT CD and single-crystal X-ray diffraction analysis.

Chrysotobibenzyl

Anti-proliferative activity

This methoxylated bibenzyl isolated from *Frullania inouei* S., exhibited anti-tumorigenic and MDR reversal properties against different human cell lines by significantly inhibiting tumor proliferation [51].

Dihydroptychantol A (DHA)

Multidrug resistance reversal activity

This macrocyclic bisbibenzyl and its derivatives, isolated from *A. angusta*, with thiazole rings were chemically synthesized to evaluate their efficacy as MDR reversal agents in cancer therapeutics. Cytotoxicity and MDR reversal activities were evaluated against adriamycin-resistant K562/A02 cells, vincristine-resistant KB/VCR cells and in their parental cells by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay [48]. The most sensitive cell line was K562 and the KB/VCR cell line was found to be the most resistant while cell viability showed sharp decline in both cell lines after treatment with the chemically synthesized DHA derivatives [19, 49]. Further, DHA and its derivatives demonstrated remarkable MDR reversal and adriamycin cytotoxicity towards human myelogenous leukemia cell line (K562/A02) as detected by MTT assays with reversal fold value of 8.18 (20 μ M). The *p*-glycoprotein (*P*-gp)-mediated MDR was achieved by dose-dependent reduction of its expression in pre-treated K562/A02 cells detected by flow-cytometry, reverse transcription polymerase chain reaction (RT-PCR) and increased adriamycin and rhodamine123 accumulation was noted when K562/A02 cells were exposed to various concentration of DHA [51, 52]. The mechanism of MDR reversal showed by this anti-fungal compound is correlated with functional inhibition and expression blockade of *P*-gp that ultimately prevented drug efflux [48, 53]. The synthetic counterpart of this novel compound has caused autophagy and apoptosis against human osteosarcoma U2OS cell line accompanied with the formation of double membrane-bound autophagic vacuoles, G₂/M-phase cell cycle arrest, increase in the level of autophagy marker LC3-II and increased nuclear expression of p53. It has also decreased the expression of cyclin B and cytoplasmic p53 to stimulate autophagy [53, 54].

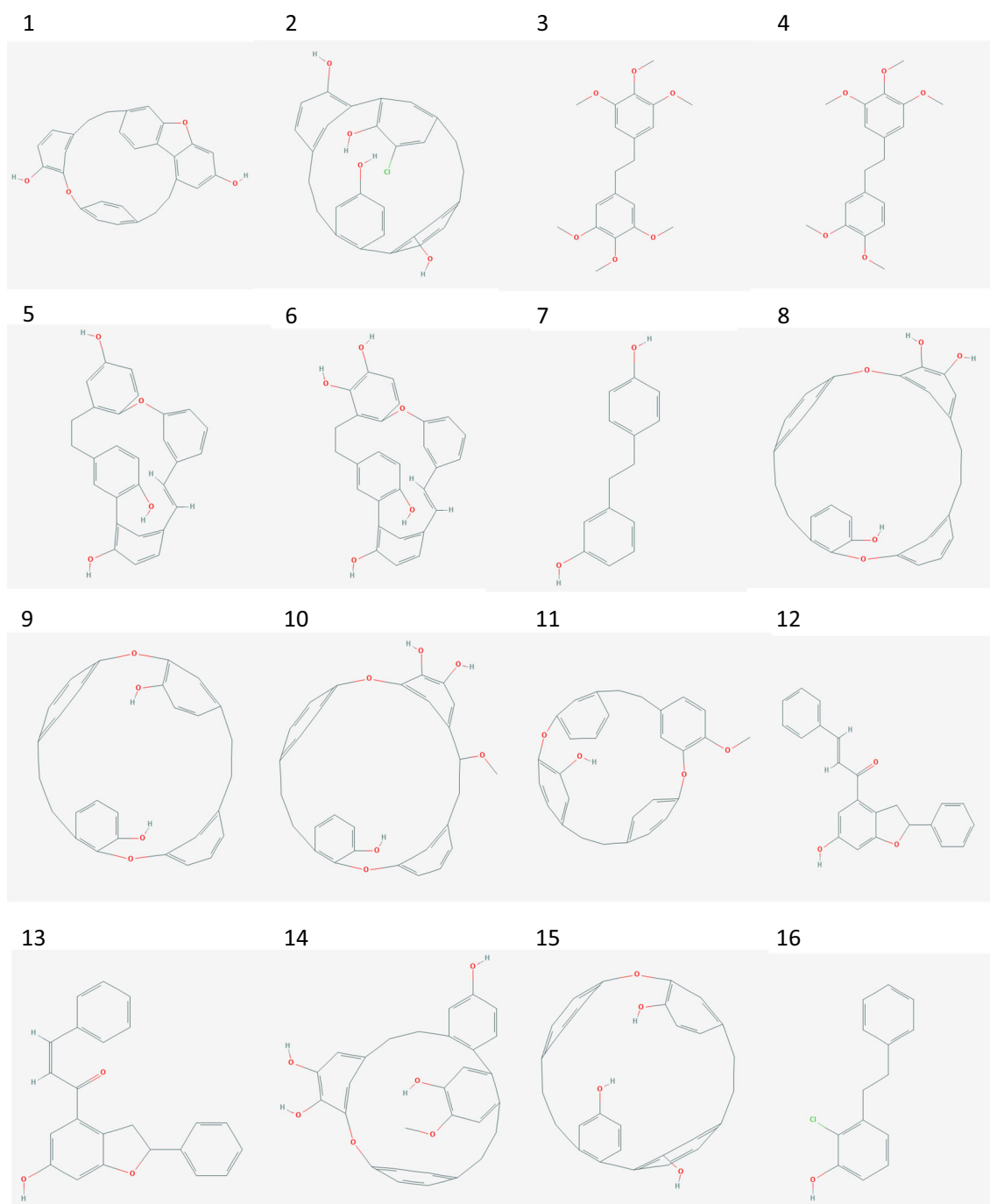


Fig. 2 Structures of bioactive bibenzyls: 1.Asterelin A (C₂₈H₂₂O₄) 2.Bazzanin S (C₂₈H₂₃ClO₄) 3.Brittonin A (C₂₀H₂₆O₆) 4.Chrysotobibenzyl (C₁₉H₂₄O₅) 5.Isoplagiochin A (C₂₈H₂₂O₄) 6.Isoplagiochin B (C₂₈H₂₂O₅) 7.Lunularin (C₁₄H₁₄O₂) 8.Marchantin A (C₂₈H₂₄O₅) 9.Marchantin C (C₂₈H₂₄O₄) 10.Marchantin E

(C₂₉H₂₆O₆) 11.Pakyonol (C₂₉H₂₆O₄) 12.Pallidisetin A 13.Pallidisetin B (C₂₃H₁₈O₃) 14.Plagiochin A (C₂₉H₂₆O₆) 15.Riccardin C (C₂₈H₂₄O₄) 16.2-chloro-3-hydroxybibenzyl (C₁₄H₁₃ClO)

Isoplagiochin A, Isoplagiochin B

Anti-tubulin polymerization activity

Isoplagiochin A and B, the macrocyclic bis(bi)benzyls were isolated from the liverwort *Plagiochila fruticosa* J.

Proc. Linn. Soc. Their structures were established using two dimensional (2D)-NMR spectra, X-ray crystallography and chemical degradation assay [55]. It is also reported from *P. diversifolia* Lindenb & Gottsche and *P. permista* var *intergerrima* Herzog [47]. It has shown remarkable inhibitory effect on tubulin polymerization

with respective IC_{50} value of 50 and 25 $\mu\text{g/ml}$ [42]. Isoplagiochins C and F were also isolated from *Plagiochila* sp. [44].

Isoplagiochin D

Anti-fungal activity

Isoplagiochin D was isolated from dichloromethane and methanolic extracts of the liverwort *B. trilobata* by bioautography [49] on TLC and showed significant anti-fungal activity against five human pathogenic fungi in the 96-well microtiter plate assay. Solvent (50 μl) was kept in negative control well and for positive control 50 μl solutions of the standard drugs viz. folicur, rovril and amistar were used. It has shown highest IC_{50} value of 15.9 $\mu\text{g/ml}$, against *S. tritici*, among all of the five fungi [19]. It is also reported from *Lepidozia incurvata* Lindenb and *Herbertus sakurarii* (Warnst) S. Hatt [47].

Isoriccardin C

Anti-fungal activity

This novel bisbibenzyl was isolated from *Ptagiochasma intermedlum* L. and spectral data analysis was used to reveal its structural configuration. It has shown significant anti-fungal activity against the fluconazole-sensitive and resistant strains of *C. albicans* [56]. It is also reported from *Lepidozia incurvata*, *Herbertus sakurarii*, and *P. fruticosa* [47].

Lunularin

Cytotoxic activity

Lunularin has been isolated from *Dumortiera hirsuta* (Sw.) Nees. This bibenzyl compound showed moderate cytotoxic activity against human HepG2 cell line (IC_{50} value=7.4 $\mu\text{g/ml}$) besides exhibiting significant anti-microbial activity against *Pseudomonas aeruginosa* with MIC value of 64 $\mu\text{g/ml}$ [11].

14-hydroxylunularin

Anti-protozoal activity

This hydroxyl-bibenzyl, has been isolated from *Ricciocarpos natans* Corda, August Karl Joseph. *In silico*, *in vitro* and *in vivo* anti-protozoal activities of this

natural phytochemical were assayed against culture and intracellular forms of *Leishmania* sp. and *Trypanosoma. Cruzi* using resveratrol, pentamidine and benznidazole as standard compounds. The respective IC_{50} values against test organisms were 0.5, 1.1, 1.1 and 17.3 μM . In *Leishmania* infected mice, oral and subcutaneous administration of the compound at a dose of 10 mg/kg of body weight for 15 days significantly decrease the lesion weight and the parasite load which clearly demonstrated its leishmanicidal potential [26].

Marchantin A

5-lipoxygenase inhibitory activity

Chromatographic quantification of the methanol extract of Japanese *Marchantia polymorpha* L. over silica gel and Sephadex LH-20 has successfully detected the presence of cyclic bis-bibenzyls, marchantin A (30 g) and its analogues marchantins B, C, D, E, G and J [8]. Highly pure marchantin A (80–120 g) has also been extracted from 6.67 kg of dried *M. paleacea* var. *dipteral*. It has shown 89% 5-lipoxygenase inhibitory activity against LTB_3 or 5S,12R-dihydroxy-6,8,10,14-eicosatetraenoic acid at 10^{-5} M and at the same concentration, for 5-HETE or 5-hydroxy-6,8,11,14-eicosatetraenoic acid inhibition was found to be almost 99% [57].

Anti-proliferative, Cytotoxic and anti-oxidant activity

Compounds isolated from *M. polymorpha* and *M. tosona* Steph. have shown cytotoxicity against the KB cell line [58, 59]. Bioactivity-guided separation of the compound from the extract of *M. emarginata* subsp. *Tosana* (Steph.) Bischl., was evaluated for its anticancer activity. The structural identification was performed by spectral analysis. The anti-proliferative activity of this compound has been reported against human MCF-7 breast cancer cells with an IC_{50} value of 4 $\mu\text{g/ml}$ along with anti-radical activity with half-maximal response (EC_{50}) 20 $\mu\text{g/ml}$. The alteration in expression of different cell cycle regulators such as p21, p27, cyclin B1, and cyclin D1 along with increased level of apoptotic markers viz. cleaved caspase-8, caspase-3, caspase-9, and poly (ADP ribose) polymerase (PARP) showed the underlying mechanism of cytotoxicity. Presence of phenolic hydroxy groups at C-1' and C-6' positions were assumed to be responsible for inducing cytotoxic and antioxidant activities [32]. Marchantin A exhibited anti-proliferative activity against rat myeloblast cell line (CC₅₀ L6) with IC_{50} 6.64 μM , when compared with control drug podophyllotoxin. Further, it decreased cell viability of breast cancer cell line, A256 (IC_{50}

5.5 μM) and showed positively regulated synergism in the presence of the Aurora-A kinase inhibitor (MLN8237) [60]. It has been further reported against MCF7, KB and A256 the respective IC_{50} values were 11.5, 3.7 and 5.5 μM ; and for its analogues Marchantin B and E, IC_{50} values were found to be 3.2 and 7.6 μM respectively [1].

Anti-trypanosomal activity

Marchantin A has shown remarkable *in-vitro* anti-trypanosomal activity (IC_{50} 0.27 $\mu\text{g/ml}$) against *Trypanosoma brucei* strain GUTat 3.1 and potent cytotoxicity against human KB cell line [61] and human MRC-5 cells (IC_{50} 3.60 $\mu\text{g/ml}$) with moderate selectivity when compared with therapeutic standard drugs eflornithine and suramin [62].

Anti-microbial activity

Significant anti-microbial activity for marchantin A was reported [57], against different bacteria such as *Acinetobacter calcoaceticus* (MIC 6.25 $\mu\text{g/ml}$), *Bacillus cereus* (MIC 12.5 $\mu\text{g/ml}$), *Cryptococcus neoformans* (MIC 12.5 $\mu\text{g/ml}$), *B. megaterium* (MIC 25 $\mu\text{g/ml}$), *Salmonella typhimurium* (MIC 100 $\mu\text{g/ml}$) as well as against fungi like *Aspergillus fumigates*, *A. niger*, *Penicillium chrysogenum*, *Sporothrix schenckii*, *Trichophyton rubrum* (MIC 100 $\mu\text{g/ml}$ for all fungal species) [8, 58, 59].

Anti-protozoal activity

Marchantin A, extracted from diethyl ether extract of *M. polymorpha* has shown *in-vitro* anti-protozoal activity against *Plasmodium falciparum*, *Leishmaniadonovani*, *Trypanosoma brucei* rhodesiense and *T. cruzi*. To ensure role of marchantin A against prophylaxis of malaria, enzyme inhibition assay for PfFAS-II pathway was performed further and moderate activity of marchantin A (IC_{50} 18.18 μM) was noted [60].

Other pharmacological activities

Marchantin A has been reported for its wide range of therapeutic application apart from the above-mentioned ones; which include significant calmodulin inhibitory activity (ID_{50} 1.85 $\mu\text{g/ml}$) [57], cyclooxygenase inhibitory activity (IC_{50} 46.4 μM) [59], DNA polymerase β inhibition, *in-vivo* muscle relaxing capacity and cardiotoxic activity (0.1 mg compound increased coronary blood flow at rate of 2.5 ml/min) [63–65]. The presence of marchantin A was also reported in oil bodies of *M. polymorpha* [66].

Marchantin A trimethyl ether

Muscle relaxation activity

This compound is a derivative of marchantin A, possessing similar macrocyclic skeleton structure. Pharmacological study has revealed its significant skeletal muscle relaxation activity which was found to be about 3.5 times greater than that of standard drug d-tubocurarine. Moreover, it caused dose dependent reduction of contraction in frog rectus abdominus [64].

Marchantin C

Cytotoxic activity

Marchantin C was isolated by bioactivity-directed isolation from *Schistochila glaucescens* (Hook) A. It was extracted and screened for cytotoxicity against P388 leukaemia cells [67]. It has also been identified from *D.hisuta* extract via spectral analysis [11]. Further the dose-dependent pro-apoptotic effect of this macrocyclic bis(bi)benzyl has been observed in human glioma A 172 cells through RT-PCR and western blot assay. Morphological studies and DNA laddering assay confirmed the inhibitory effects of marchantin C on cellular growth, viability and colony forming capacity of treated A 172 cells accompanied with nuclear fragmentation, appearance of apoptotic bodies and DNA laddering fragments which could be the outcome of regulation of Bax-Bcl-2 proteins resulted in *in vivo* and *in vitro* anti-tumor activity mediated by cell cycle arrest in A172 and reduction in microtubule quantity in Hela cells [29, 43]. Human cervical carcinoma xenografts exhibited increased expression level of apoptosis with inducers like cyclin B1, Bax and caspase-3 [43, 68]. Matrix metalloproteinase 2, the main factor associated with migration of cancer cells was found to be reduced in marchantin C (8–16 μM) treated T98G and U87 glioma cells [69]. Marchantin C and its synthetic dimethyl ether derivative, 7,8-dehydromarchantin C was found to alter reversal of vincristine-resistance in KB/VCR cells [70]. By using conditional media for endothelial cell tube formation assay, role of marchantin C has been observed on angiogenic inhibition of T98G glioma cells by up-regulating sFlt-1 [71]. Significant microtubule depolarizing capacity was also observed in KB, MCF-7 and PC3 cell lines [16]. First report on the α -glucosidase inhibitory activity of macrocyclic bisbenzyls was obtained from this compound (52.2% at 1 mM) [28].

Marchantin C isomer (Isomarchantin C)

Enzyme inhibitory activity

Isomarchantin C, isolated from *M. polymorpha* and *M. palmata* Reinw.Nees & Blume showed strongest inhibitory effect against cathepsins L (95%) and cathepsin B (93%), (both were related to osteoporosis and allergy) at 10^{-5} M concentration. These enzymes are related with osteoporosis and allergy [59, 71].

Marchantin E

Enzyme inhibitory activity

This antifungal bibenzyl, extracted from the liverwort *Frullania muscicola* Steph is an important enzyme activity modulating agent [73]. The spectral diffraction analysis by infra-red (IR), ultra-violet (UV), 1-dimensional (1D)-NMR, 2D-NMR, and optical rotatory dispersion (ORD) spectroscopy have confirmed the structure of the compound [56, 74], and the compound was found to prevent calmodulin activity (ID_{50} 2 $\mu\text{g/ml}$) [58]. Significant cyclo-oxygenase (IC_{50} 58.0 μM) and 5-lipoxygenase inhibitory activity was also reported [64, 75], respectively. Presence of 3,4-dihydroxyphenethyl group in structural moiety played an important role on inhibition of PA endonuclease *in-vitro* which may be termed as “fitting and chelating model”. The compound was also found to be capable of inhibiting the growth of H3N2 as well as H1N1 influenza A and B viruses [76].

Marchantin H

Anti-oxidant activity

This macrocyclic bis(bi)benzyl can function as an effective chaperone protecting antioxidant [3] against peroxidative damage. It was reported to inhibit non-enzymatic iron-induced lipid peroxidation in rat brain homogenates ($IC_{50} = 0.51 \pm 0.03 \mu\text{M}$) and suppressed NADPH-dependent microsomal lipid peroxidation ($IC_{50} = 0.32 \pm 0.01 \mu\text{M}$) when compared with the standard drug desferrioxamine. Due to its anti-radical activity concentration-dependent reduction in oxygen consumption during peroxy radical-induced human erythrocyte ghost oxidation has been observed [56]. This versatile biomolecule also inhibits copper-induced human low-density lipoprotein oxidation as well as alleviates superoxide anions generated by the xanthine/xanthine oxidase system.

Anti-microbial activity

The anti-microbial efficacy of this potent antioxidant compound has been examined *in-vitro* against the fluconazole drug resistant strains of the pathogenic fungi *C.albicans*. It was found that for both tested strains (CA 02 and CA 10) the MIC value of marchantin H was 256 $\mu\text{g/ml}$ [55].

Marchantin M

Cytotoxic activity

Marchantin M, a cyclic bisbibenzyl, isolated from *A.angusta* extract was found to be cytotoxic against chemo-resistant prostate cancer PC3 cells. Inhibition of cell proliferation was detected by MTT assay as well as dose dependent elicitation of apoptosis (IC_{50} value=5.45 $\mu\text{M/l}$) along with up-regulation of Bax expression. PARP cleavage and caspase-3 activity were confirmed by western blotting, flow cytometry and morphological observations [77]

11-O-demethyl Marchantin I

Anti-microbial activity

This dibenzofuran bisbibenzyl was extracted from *A. angusta* and spectral analysis through X-ray crystallography has confirmed the structural moiety. The application of microdilution assay and TLC bioautographic assay were used to elucidate its antifungal attributes [48].

NeomarchantinA, Neomarchantin B

Cytotoxic activity

These phytochemicals were isolated by the bioactivity-directed isolation from the extracts of *S. glaucescens* along with marchantin C and a mixture of sesquiterpene/bis-bibenzyl dimers which have shown significant cytotoxicity against P388 cell line with IC_{50} value of 8–18 $\mu\text{g/ml}$ [66].

Anti-fungal activity

Neomarchantin A, a potent anti-fungal compound against the pathogenic strain of *C. albicans*, was isolated from the hydroalcoholic extract of air-dried thallus of *M. polymorpha*. Application of TLC bioautography assay has shown minimum inhibitory dose value of this compound was 0.25 μg

when compared with standard control miconazole ¹H- and ¹³C-NMR data were compared for the structural elucidation [20]. It was also reported for its *in-vitro* anti-fungal activities [55].

Pakyonol

Cytotoxic and anti-proliferative activity

Pakyonol, a macrocyclic bisbibenzyl, obtained from *Plagiochasma intermedium* (Horik.) Inoue has inhibited androgen-insensitive PC₃ cell proliferation and decreased cell viability by 9.8%, 23.2%, 42.1%, 56.8% respectively at concentration of 5, 10, 20, and 50 μM/l in a dose-dependent and time-dependent manner [77]. It has also showed growth inhibitory activity against *C. albicans*. It was also found to be effective in alleviating P-gp mediated MDR in adriamycin-induced tumor cell line K562/A02 mediated by 4.78-fold decrease in IC₅₀ value in the presence of 3 μg/ml pakyonol under 48 h treatment. The regulatory drug transport activity of this natural compound has been determined by intracellular accumulation and retention of the rhodamine-123 in resistant cancer cells [55].

Paleatin B

Cytotoxic and enzyme inhibitory activities

This acyclic bis-bibenzyl isolated from the thalloid liverwort *M. paleacea* var. *diptera* (Nees & Mont.) S. Hatt. showed cytotoxicity against KB and P-388 cell line. It also demonstrated DNA polymerase β and cyclooxygenase inhibitory activities with IC₅₀ value of 45.2 μM [64].

Pallidisetin A, Pallidisetin B

Cytotoxic activity

These cinnamoyl bibenzyls were isolated via bioassay-guided fractionation of an ethanolic extract of *Polytrichastrum pallidisetum* (family: Polytrichaceae) and spectral analyses and chemical correlation were employed to elucidate their structures. It showed cytotoxic efficacy against different human tumor cell lines, viz. RPMI-7951 melanoma and U-251 *Glioblastoma multiforme* has been reported many years back [15].

Perrottetin A–D

Anti-microbial and enzyme inhibitory activity

Prenyl bibenzyls, perrottetin A–D isolated from the liverwort *R. perrottetii* showed anti-microbial activity against *Streptococcus aureus*. Their structures have been determined by spectral methods and chemical transformation analyses [7]. Perrottetins were reported to have 5-lipoxygenase and cyclooxygenase inhibitory activities [56, 64, 78].

Perrottetin E

Cytotoxic activity

This prenyl bibenzyl, extracted from *R. perrottetii*, exhibited pronounced cytotoxicity (ID₅₀ 12.5 μg/ml) against the human KB cells [58]. Ether analogues of this bis(bi)benzyl, (perrottetin F and perrottetin G), were also isolated from same source [79, 80].

Anti-thrombin activity

Perrottetin E isolated from *Jungermannia comata* Nees was tested for anti-thrombin activity (IC₅₀ 18 μM) which was correlated with blood coagulation and cardioprotection [81].

Perrottetin F

PA endonuclease inhibitory activity

Perrottetin F isolated from *Plagiochila sciophila*, Nees ex Lindenb, showed significant DNA polymerase β inhibitory activity as well as *in vitro* PA endonuclease inhibitory activity due to the presence of 3,4-dihydroxyphenethyl group in its structural moiety, indicating its potential as new therapeutic agent in influenza A inhibition [1].

Anti-viral activity

This compound was also reported to decrease the viral infectivity titer and the inhibition of growth the influenza B/Malaysia/2506/2004 virus at a dose of 50 μM [76].

Plagiochin A

PA endonuclease inhibitory activity

Plagiochin A, a medicinally potent marchantin-related phytochemical, extracted from *M. polymorpha* was found to inhibit

influenza PA endonuclease activity *in vitro* and also exhibited significant activity against virus infectivity titer [76].

Anti-trypanosomal activity

This compound has also been isolated from *P. sciophila* and exhibited significant *in-vitro* anti-trypanosomal activity against *T. brucei* with IC_{50} values ranging from 0.69–0.93 $\mu\text{g/ml}$. Its moderate cytotoxicity against human MRC-5 cell was determined by selectivity index [cytotoxicity (IC_{50} for the MRC-5 cells)/anti-trypanosomal activity (IC_{50} for the GUT at 3.1 strain)] [61].

Neurotrophic Activity

The compound was reported for up-regulation of choline acetyl transferase activity at 10^{-6} M in a neuronal rat brain cell culture [82].

Plagiochin E

MDR reversal activity

This bisbibenzyl compound, isolated from *Marchantia polymorpha*, exhibited profound MDR reversal activity [28]. However, pro-apoptotic metacaspase dependent pathway was also found to be induced by plagiochin E in *C. albicans* [83]. Plagiochin E down-regulated the expressions of CLB2, CDC28 and CLB4 that ultimately caused G2/M cell cycle arrest. Moreover, enhanced cytochrome c release, nuclear fragmentation and metacaspase activation by the compound also promoted yeast apoptosis [83]. Microscopic study revealed antifungal mechanism of this macrocyclic bisbibenzyl is closely associated with cell wall degradation, enzymatic inhibition of chitin synthetase, *in-vitro* and *in-vivo*, as well as up-regulation of gene *CHS2* and *CHS3*, and down-regulation of *CHS1* [2]. The anti-fungal efficacy of plagiochin E against *C. albicans* could be derived from enhancement of mitochondrial F0F1-ATPase, as well as mitochondrial membrane potential, the activity of mitochondrial dehydrogenases was blocked that resulted into depletion of ATP production and ultimately ROS accumulation [83].

Pusilatins A–D

DNA polymerase inhibitory activity

These bisbibenzyl dimers, extracted from *B. pusilla*, were reported for different bioactivities [58, 85]. Pusilatin B and C have shown weak HIV-ameliorative activity, moderately inhibited the activity of DNA polymerase β (IC_{50} 13 and

5.16 μM respectively); Pusilatin B and C have also exhibited cytotoxicity in KB cells (ED_{50} 13.1 and 13 $\mu\text{g/ml}$ respectively) [85].

Radulanin A, Radulanin L, Radulanin K

Anti-oxidant activity

Greenish oil ether extract of *Radula appressa* Mitt., houses these prenyl bibenzyls that showed moderate anti-oxidant efficacy by inhibiting nitric oxide production in lipopolysaccharide stimulated RAW 264.7 cell line with respective IC_{50} value of 20 μM and 15.3 μM [28]. Radulanin L, a novel dihydrooxepin obtained from *R. complanata* was structurally elucidated by comparing ^1H and ^{13}C NMR spectral data with previously discovered radulanin A and radulanin H [7, 13]. Radulanin K from *R. javanica* inhibited the superoxide anion radical release from guinea pig macrophage with IC_{50} value 6 $\mu\text{g/ml}$ and also possessed significant cyclooxygenase inhibitory activity (IC_{50} 39.7 μM) [64].

Radulanolide

Anti-microbial activity

This novel prenyl bibenzyl, produced by *R. complanata* was screened for antimicrobial activity against *S. aureus* [13, 80].

Riccardin A, Riccardin B

5-lipoxygenase inhibitory activity

These cytotoxic cyclic bisbibenzyls were obtained from *Riccardia multifida* (L.) S. Gray and their structure determination was done by X-ray diffraction analysis and 400-MHz ^1H NMR analysis. These were the first bis-bibenzyls to inhibit KB cells at a concentration of 10 and 12 $\mu\text{g/ml}$, respectively besides demonstrating potent 5-lipoxygenase inhibitory activity [8, 35, 58].

Riccardin C

Cytotoxic activity

This cyclic bisbibenzyl with cyclooxygenase inhibitory activity was obtained from the Chinese liverwort *P. intermedlum*. It was also reported from *Reboulia hemisphaerica* (L.) Raddi [7]. Riccardin C is a dimethoxy derivative of riccardin A [7]. It enhanced cholesterol efflux from THP-1 cells and can

increased plasma HDL level without elevating triglyceride level in mice [44, 86, 87], as it worked as the liver X-receptor (LXR) α agonist and (LXR) β antagonist [58]. AIt was found to be cytotoxic to human prostate cancer PC3 cells via inducing apoptosis with an IC₅₀ values of 3.22 μ M/l and was also able to modulate the expression levels of apoptosis-related proteins (Bcl-2, Bax and PARP). For 10 μ M/l riccardin C, total percentage of apoptotic cells were found to be 6.21 accompanied with 0.1%, 3.4%, 84.1%, 88.3% repression of cell viability at different concentrations of this bisbibenzyl under 24, 48, and 72 h treatment [77].

Anti-fungal activity

A. angusta (family: Aytoniaceae) is another source of riccardin C. It has shown potent *in vitro* anti-fungal properties along with synergistic fungal resistance modifying capacity when applied on three resistant strains of *C. albicans* in combination with fluconazole [55, 64].

Riccardin D

Anti-proliferative and chemo-preventive activities

The macrocyclic bis(bi)benzyl, detected in the liverwort, *Monoclea forsteri* Hook [12] has demonstrated anti-proliferative activity on human glioma A172 cells and induced apoptosis at a dose of 16 μ M and caused reversal of P-gp-mediated MDR [88]. It was also isolated from the liverwort *D. hirsuta* and significantly affected the biofilm formation in *C. albicans* through downregulating the mRNA expression levels of hyphae specific genes and inhibited hyphal growth which were determined by the XTT (2,3-bis(2-methoxy-4-nitro-5-sulfo-phenyl)-2H-tetrazolium-5-carboxanilide) reduction assay and live/dead cell staining [31]. This compound altered the activity of DNA topoisomerase II and thus functioned as natural therapeutic agent against cancer. Weekly incubation of human umbilical vascular endothelial cells (HUVEC) with riccardin D has effectively reduced cell proliferation marked by MTT assay. It has also decreased the motility and migration of treated cells, blocked capillary tube formation and reduced the level of some angiogenic factors such as VEGF (vascular endothelial growth factor), phospho-VEGF receptor 2, EGF receptor and MMP-2 (matrix metalloproteinase). Such angiogenic reduction was also observed in H460 (human lung cancer carcinoma) cell line via CD34 immuno-histochemical staining and xenograft analysis [89]. It has exhibited remarkable DNA topoisomerase-II dependent anti-proliferative effect on human leukemia cell lines *viz.* HL-60, K562 and MDR K562/A02 cells dependent [67, 90]. The brominated and amino-methylated derivatives of riccardin D have shown significant

anti-proliferative activity against KB, MCF-7 and PC3 cell lines and caused microtubule depolymerization. Such activity of this macrocyclic bisbibenzyl indicates applicability of the compound as potent chemotherapeutic agent [91]. The treatment of *APC^{Min/+}* mice with riccardin D for 7 weeks has significantly inhibited intestinal adenoma formation, and reduced polyp number by 41.7%, 31.1%, 44.4% and 79.3% respectively, in proximal, middle and distal portions of small intestine and colon as detected via immune-histochemical staining. To elucidate chemopreventive mechanism of riccardin D, western blotting, RT-PCR and enzyme-linked immunosorbent assay in intestinal polyps were performed and anti-proliferative and anti-angiogenic activity of this compound have been revealed. It has also downregulated the *Wnt* signaling pathway and altered the levels of inflammatory mediators present in polyps [92].

Biofilm inhibitory activity

Underlying mechanism behind therapeutic application of riccardin-D against *C. albicans* biofilms formation was evaluated through XTT reduction assay, quantitative real-time RT-PCR, scanning electron microscopy and laser confocal scanning. Riccardin-D had altered the Ras-cAMP-Efg pathway by downregulation of hypha-specific genes such as *ALS1*, *ALS3*, *ECE1*, *EFG1*, *HWPI* and *CDC35* which resulted in retardation of hyphal growth, defective biofilm maturation and dose-dependent antifungal activity when used alone or with fluconazole [91].

Riccardin F

Reversal of adriamycin induced drug resistance

Riccardin F, a macrocyclic bisbibenzyl isolated from *P. intermedium* exhibited anti-fungal activity against fluconazole resistant and sensitive strains of *C. albicans* accompanied with alteration of P-gp mediated drug resistance in adriamycin treated cancer cell line K562/A02 following a 48 h treatment. By monitoring fluorescence intensity of rhodamine-123, drug transportation capability of P-gp was determined. Retention of this fluorescence substrate for P-gp has indicated that MDR reversal and recovery of adriamycin accumulation by riccardin F is correlated with inhibition of P-gp activity [55, 93].

2-geranyl-3,5-dihydroxybi-benzyl

Anti-oxidant and enzyme inhibitory activity

The compound was extracted from *R. Kojana* and has shown significant lipoxigenase and calmodulin inhibitory

activities [80]. Further, this compound extracted from *R. appressa* showed strong nitric oxide inhibitory activity *in-vitro* in cultured cell line of lipopolysaccharide stimulated RAW 264 with IC₅₀ value 4.5 μM, stronger than that of standard drug L-N⁶-1-iminoethyl)lysine (18.6 μM). The structure determination was performed by 2D-NMR and CD spectral analyses [28].

2,4,6-trichloro-3-hydroxybi-benzyl, 2,4-dichloro-3-hydroxybibenzyl, 2-chloro-3-hydroxybibenzyl

Anti-microbial activity

These chlorinated bibenzyl, isolated from the liverwort *R. marginata* (family: Aneuraceae) showed significant antimicrobial activity against gram positive bacteria *Bacillus subtilis*, pathogenic fungus *C. albicans*, dermatophytic fungus *Trichophyton mentagrophytes* and the plant pathogenic fungus *Cladosporium resinae*, at 30 μg per disk concentration. 2,4-dichloro-3-hydroxybibenzyl was proved to be the most potent against *T. mentagrophytes* and *C. resinae* with zone of inhibition of 12 and 2 mm respectively [94].

2,6-dichloro-3-hydroxy-4'-methoxybibenzyl, 2,6,3'-trichloro-3-hydroxy-4'-methoxybibenzyl, 2,4,6,3'-tetrachloro-3-hydroxybibenzyl 2,4,6,3'-tetrachloro-3,4-dimethoxybibenzyl

Anti-fungal and anti-feedant activities

These bioactive polychlorinated bibenzyls were the arsenal of some *Riccardia* sp. against pathogens and herbivores. TLC-bioautographic study with a *Cladosporium herbarum* culture, showed fungicidal activities greater than standard ketoconazole with inhibition zones ranging from 1.2 cm to 2.9 cm, manifested by these compounds except 2,4,6,3'-tetrachloro-3-hydroxybibenzyl. 2,6,3'-trichloro-3-hydroxy-4'-methoxybibenzyl and 2,4,6,3'-tetrachloro-3-hydroxybibenzyl were also tested for anti-feedant activity against *Spodoptera littoralis* larvae and showed moderate result at FR₅₀ = 0.63 and 0.43 respectively. These chlorinated bibenzyls were also assayed for brine shrimp lethality activity at 50% lethal concentration (LC₅₀) 0.42–2.35 ppm, with two standard drugs ketoconazole and asuntol with LC₅₀ value 14.9 ppm and 10.8 ppm respectively [25].

2(R)-2-isopropenyl-6,7-dihydroxy-4-(2-phenylethyl) dihydrobenzofuran

Anti-trypanosomal activity

This prenyl bibenzyl, isolated from *R. perrottetii* demonstrated significant anti-trypanosomal activity against *T. brucei*, with an IC₅₀ value of 0.44 μg/ml [13] which are 3.6- and 5.2-fold higher than the standard drugs suramin and eflornithine, respectively. It has also demonstrated slight cytotoxicity against human diploid embryonic cell line MRC-5 with an IC₅₀ value 7.46 μg/ml [61].

3-hydroxy-4'-methoxybibenzyl

Anti-fungal activity

The compound, isolated from the liverwort *F. muscicola* (family: Frullaniaceae), showed anti-fungal activity through bioassay directed analysis. Structure confirmation was accomplished via spectral data analysis of IR, UV, NMR as well as ORD [74].

3-methoxy-4'-hydroxybibenzyl

Nematocidal activity

3-methoxy-4'-hydroxybibenzyl isolated from the New Zealand liverwort, *Plagiochila stephensoniana* Mitt, showed *in vitro* nematode larval motility with an IC₅₀ value of 0.13 mg/ml against the third-stage larvae of the sheep parasite, *Trichostrongylus colubriformis* [95].

3,3',4,4'-tetramethoxybibenzyl

Anti-proliferative activity

This bibenzyl obtained from *F. inouei* was found to be highly methoxylated and cytotoxic to different human tumor cell lines. It has shown significant anti-proliferative efficacy accompanied with potent reversal of MDR [51]

3, 4'-dimethoxybibenzyl

This antimicrobial prenylbibenzyl was obtained from *R. complanata*, it is chemically very close to *R. buccinifera* L. [7].

3,5-dihydroxy-2-(3-methyl-2-butenyl) dihydroxybibenzyls

Vasopressin antagonist activity

The bibenzyl was isolated from *R. complnata* and its ¹H and ¹³C NMR spectral data were utilized for structure determination. This prenyl bibenzyl, obtained from *R. perrottetii* showed vasopressin antagonist activity at ID₅₀ 27 µg/ml [8]. It was also obtained from *R. kojana* and screened for 5-lipoxygenase and calmodulin inhibitory activities [13].

Anti-oxidant activity

This compound was also extracted via bioactivity-guided fractionation from the ether extract of *Plagiochila ovalifolia* Mitt. and showed DPPH- (2,2-diphenyl-1-picrylhydrazyl) radical scavenging anti-oxidative activity [96].

3,5-dihydroxy-4-(2, 3-epoxy-3-methylbutyl) bibenzyl

Anti-microbial activity

This prenyl bibenzyl, isolated from *R. complanata*, which showed some anti-microbial activity [7].

4-hydroxy-3'-methoxybibenzyl

Anti-microbial activity

This bibenzyl was isolated from three species of New Zealand liverwort genus *P. stephensoniana* Mitt. (10.5 mg/g dry weight); *P. deltoidea* Lindenb. (0.54 mg/g DW) and *P. banksiana* Gottsche. (0.05 mg/gm dry weight) [44]. The alcoholic extract of *P. stephensoniana* exhibited significant anti-bacterial activity against gram-positive bacteria *Bacillus subtilis* with ZOI 3–5mm plus 12–300µg extract/disk when compared with chloramphenicol (30 µg/disk). The minimum fungicidal activities against the yeast *C. albicans* and dermatophyte *Trichophyton mentagrophytes* were found to be 125µg/ml and 62.5µg/ml, respectively, in dilution assay comparable with anti-fungal drug nystatin [97].

Cytotoxic activity

It showed cytotoxicity against the cell line of monkey kidney cells (BSC), at 60 µg/well but no significant inhibition was observed against the growth of P-388 leukemia cell line (IC₅₀ >25.0 pg/ml) when compared with mitomycin-C [97].

4,4'-dihydroxybibenzyl

Anti-fertility inhibiting activity

The chemically synthesized isomers of 4,4'-dihydroxybibenzyls has shown different anti-oestrogenic and fertility inhibiting efficacy in mice model. Among different isomeric configurations, erythro- α -ethyl- α -methyl 4,4'-dihydroxybibenzyls is a potent pro-oestrogen. It has shown highest anti-oestrogenic and anti-fertility activities activities intra-vaginally when applied in a dose lesser than 1µg/day [98].

13'-O-isopropylidenericcardin D

Anti-fungal activity

This compound was isolated as an artefact during separation of the ethanolic extract of *M. polymorpha* though not detected by HPLC/MS method. It has shown effective growth inhibiting property against *C. albicans* detected by TLC bioautography with minimum inhibitory dose (MID) value 0.4µg [20].

Bibenzyl cannabinoids: therapeutically most studied derivatives of bibenzyls

The novel bibenzyl cannabinoid (BC), perrottetinene acid, have been isolated from ether extract of *Radula marginata* Gottsche, Lindenb. & Nees; species specific variability of (–)-cis-perrottetinene content is also reported. The structure, (established by 2D-NMR), possessed similarity with Δ 1-tetrahydrocannabinol, which is also a BC compound extracted from *R. perrottetii* [99]. Perrottetinene was also reported from *Radula laxiramea* Steph [100, 101], and *R. appressa* [28]. In nature, the occurrence of BC is very rare but due to the wide distribution of such compounds in *Radula* species, they are considered as chemosystematic markers of Radulaceae [14]. Δ 8-tetrahydrocannabinol and Δ 9-tetrahydrocannabinol (isolated from *Cannabis sativa* L.), both structurally quite similar to the Δ 1-tetrahydrocannabinol (isolated from *R. perrottetii*) are already reported for psychopharmacological activities [102]. No pharmacological study on Δ 1-tetrahydrocannabinol has yet been reported but *R. perrottetii* has been commercially exploited for cosmetics grade cannabinoids [103]. Perrottetinene is another BC reported from *R. perrottetii* and its structure has been established by spectral analysis [10]. *Radula* species is also enriched in different variants of prenylated bibenzyl which are *ortho*-derivative or abnormal cannabinoids [99]. Synthesis of bibenzyl/*o*-cannabicyclol hybrid along with some bibenzyl/monoterpene hybrids and

prenyl bibenzyl derivatives have also been reported [104]. This represents bibenzyl iso-tetrahydro cannabinoids from *Radula* species [12, 75]. Total synthesis of (–)-cis-perrottetinene and its *in vitro* pharmacological activity on experimental BALB/c mice model have also been documented [105]. They demonstrated the ability of both cis-perrottetinene and Δ^9 -trans-tetrahydrocannabinol are to trigger hypothermic response by affecting expression of cannabinoid receptors (human cannabinoid receptor type 1, CB1R). Moreover, these compounds affect activity of endocannabinoid-degrading enzymes [105]. Cannabinoid type drugs are presently recommended for many neurodegenerative disorder, anti-neoplastic chemotherapy, post-traumatic stress (PTS), epilepsy, multiple sclerosis etc. and therefore these compounds have immense commercial prospects in medical industry. These compounds are known to ameliorate the progression of atherosclerosis, myocardial and cerebral ischaemia [106]. Identification and validation of genes [cannabigerolic acid (CBGA), stilbene acid (SA) geranyl diphosphate (GPP)] associated with cannabinoid biosynthesis have already been achieved [103]. Moreover, transcriptome analysis based approach revealed the presence of six transcription factor (TF)-family unique in *R. marginata*. Considering all these facts, it maybe concluded that *Radula* could function as an alternative cannabinoid resource [107] and manipulation of cannabinoid synthesis pathway via genetic engineering could widen our knowledge in this aspect [108].

Therapeutic application of bibenzyls and its derivatives, extracted from non-bryophytic sources

Dendrobium is not only an important genus of the plant family Orchidaceae but it is also extensively reported in traditional Chinese remedies against a list of ailments due to the presence of variable types of secondary metabolites [109]. Therapeutic properties of the plant is contributed by polysaccharides, coumarins, sesquiterpenes, stilbenoids, phenanthrenes, alkaloids and fluorenones. Bibenzyls and bisbibenzyls are also reported from different species of the genus for their significant therapeutic activities [110, 111] (Table-2). Several researchers elucidated the free radical scavenging activity of different phytochemicals and possible contribution of anti-oxidative property to boost other bioactivities; bibenzyls derived from *Dendrobium* are of no difference [112]. For example, enzymatic antioxidant efficacy is reported for dendrocandins C-E, gigantol and batatasin II isolated from *D. candidum* [113], and *D. chrysanthum* respectively [114, 115]. Bibenzyl compounds obtained from ethanolic extract of *D. denneanum* showed dose-dependent free radical scavenging activity determined by ORAC (oxygen radical absorbance capacity) assay, DPPH, pyrogallol autoxidation method and Fenton reaction

[116]. An anti-androgenic bibenzyl, bifluranol has been reported to possess curative properties against benign prostatic hyperplasia [117]. Moreover, moscatilin derived from *D. nobile* Lindley ameliorated the ischemia/hypoxia of retinal cells [118]. Table 2 summarizes the bioactive properties of different bibenzyl and bis-bibenzyl derivatives isolated from different sources apart from the bryophytes. Moreover, in these plants, many other compounds with bibenzyl skeleton have already been reported. Analysis of structural moiety and determination of chemical class has been worked out using spectroscopic or chromatographic techniques but for all these compounds clinical and/or preclinical trials are not yet performed. In the next paragraph, we have compiled information on bibenzyl components isolated mostly from Orchidaceae family.

Bibenzyls such as moenylin, moscatilin and isoamoenylin from *D. amoenum* Wall. ex Lindl. [119], cumulatol (3,3'-dihydroxy-4,4',5,5'-tetramethoxy bibenzyl) and tristin (3,4',5-trihydroxy-3'-methoxy bibenzyl) from *D. cumulatum* Lindl. And *Bulbophyllum triste* Rchb. f. have been reported [120]. Batatasin-III was isolated from *Cirrhopetalum andersonii* Hook. f. whereas crepidatin, a novel bibenzyl derivative was identified and extracted from *D. crepidatum* Griff. [121]. Aloifol-I, batatasin-III, bulbophyllin, bulbophyllidin, 3,3', 5 trimethoxy bibenzyl and 3,3' dimethoxy-4,5 methylene dioxybibenzyl from the members of the orchid family have also been documented [158]. Phytochemical screening, spectroscopic analysis and NMR have revealed the presence of natural oxepines with bibenzyl moiety [5-(2,3-dimethoxyphenethyl)-6-methylbenzo[d][1,3]dioxole, and the other dibenzo [b, f]oxepine, 10,11-dihydro-2,7-dimethoxy-3,4-methylene-dioxy dibenzo[b, f]oxepine], in alcoholic leaf and stem extract of *Bulbophyllum kwangtungense* Schlecht. [123]. This chemical class has played a critical role in chemotaxonomy and evolution of bryophytes as number of bibenzyls are reported from pteridophytes and algae too, supporting the progressive theory of evolution. Interestingly, the presence of structurally similar monomeric bibenzyls *viz.* lunularin, lunularic acid and prenyl bibenzyl both in some ferns (*Notholaena dealbata*, *N. limitanea*, *Sceptribidium ternatum*) and Hepaticae is also reported [124]. Cyclic bisbibenzyl derivatives and 2,2-dimethylallyl- and geranyl bibenzyls from Hepaticae have also been recorded [7, 35, 125, 126]. Lunularic acid and its derivatives such as 3-4' dihydroxy stilbene were identified in *Hydrangea macrophylla* Thumb. Ser. root extracts along with cirrhopedalidin and cirrhopedalinin [127, 128]. These compounds were also detected in Chlorophyta, Phaeophyta and Rhodophyta [127, 129, 130]. Canniprene, an iso-prenylated bibenzyl originated uniquely from *Cannabis sativa* L., was found to be able to inhibit inflammatory eicosanoids production via modulation of the 5-lipoxygenase pathway. Moreover, it was found to decrease the synthesis of prostaglandin through the cyclooxygenase/microsomal prostaglandin E₂ synthase

pathway. Other spiranoid bibenzyls harvested from *C. sativa* are cannabispiranol and cannabispirenone which showed no significant result in these bioassays [131].

In neuroprotection, scientists featured the bibenzyl compound, 20C, isolated from orchid *Gastrodia elata* Blume. It is also reported for oxidative stress-ameliorating efficacy against tunicamycin induced damage in endoplasmic reticulum and rotenone-triggered apoptosis [132, 133]. The rotenone-induced neurotoxicity and Parkinson's disease (PD) development involves reduction of nuclear factor erythroid 2-related factor (Nrf2)-mediated antioxidant enzyme activity as well as DJ-1 level. The 20C pre-treatment reverted rotenone-induced oxidative damage in PC12 and SH-SY5Y cell lines, triggered overexpression of hemeoxygenase-1 (HO-1), activated phosphoinositide-3-kinase (PI3K)/Akt signaling pathway and blocked ShRNA-mediated DJ-1 knockdown of. All these indicates novel therapeutic mechanism of 20C against tissue damage and progression of PD [134].

Ethnobotany

In the present era bubbling with widened popularity of “clinical herbalism”, one can easily observe the worldwide extensive research on medicinal plants and subsequent studies that links ethnomedicinal properties with clinical as well as pre-clinical findings. However, similar extensive research outcome is quite absent in the field of ethnobotany and allied investigation on medicinal properties of bryophyte. The concept of “ethnobotany” emerged as a subject during late 1950s; till date it is an almost virgin area of research with fewer reports and documentation. The prime barriers in similar research are smaller size of bryophytes, restricted distribution, morphological identification as well as chemical characterization. Furthermore, most of the reports were only cited from China (Traditional Chinese Medicine) and North America. Bryophytes *viz.* *Polytrichum*, *Sphagnum* and *Marchantia* genus are mostly reported for traditional uses [135]. Later, different species of *Conocephalum*, *Frullania*, *Marchantia*, *Riccardia* and *Riccia* along with *Reboulia hemispherica* and *Dumortiera hirsuta* from selective areas of the eastern Himalayas were reported for their ethnomedicinal use [136]. The same paper also mentioned the presence of different bibenzyls and bis(bi)benzyl derivatives from *D. hirsuta*, *R. hemispherica*, *M. polymorpha* and *F. muscicola*. Though, as per the present available data, correlating the presence of bibenzyl or bibenzyl derivative with ethnomedicinal usage is not possible. However, traditionally used bryophytes from Eastern Himalayan region is enriched with a number of bibenzyls and sesquiterpenoids which may have possibly contributed towards the biomedical efficacy of these species [136]. Ethnomedicinal uses, chemical constituents and pharmacological activity of 52 bryophytes belonging

to 20 families of the liverwort and 13 families of the mosses were also reported [137]. Though this paper elaborately described all these aspects but it was not clearly mentioned how biochemical compounds, isolated from all these bryophytes, contributing in reported bioactive properties of the same. However, the authors understand through clinical and pre-clinical investigation by screening of bryophytes available in vast geographical region, could answer such ambiguity in future.

Bibenzyls: structure activity relationship (SAR) studies

The multifaceted roles played by very important class of secondary metabolites of bryophytic origin, bibenzyls and bisbibenzyls are quite fascinating. This section details the streamlined information retrieved from various *in-silico*, *in-vitro*, and *in-vivo* studies that elucidate the critical mechanism of action and correlation between structural configuration and bioactivity, of these phyto-constituents [28]. The conformational flexibility rendered by variable presence of C-ring has greatly promoted various bioactivity and one of the book chapter [47] written on bryophytes clearly presented the positional aspects.

In this section, the contribution of functional groups, ligands, active molecules, chemical bonds and structural moiety on the myriads of bioactivities has been discussed. The bio- and chemical diversity of bibenzyls and their origin wise differences in functional aspects are largely contributed by structure–function interrelationship. Macrocyclic bis(bi)benzyls are studied mostly for bio-activities and presence of free phenolic hydroxyl group on the benzene rings that plays important inhibitory role against fungal agents whereas the presence of methylation in the OH groups decreases such efficacies [19, 20, 48]. Further the results obtained from different antimicrobial assays indicated that the antifungal efficacy of macrocyclic bis(bi)benzyls depends on the bis(bi)benzyl type nucleus and additional benzene nucleus. The presence of an additional aromatic *O*-methyl group was found to reduce the *in vitro* antifungal activity. Macrocyclic bis(bi)benzyls exerted direct antifungal action by forming pores in cell membranes, leading to fungal cell lysis [55, 138]. The structure-activity relationship studies supported by *in silico* non-stochastic quadratic fingerprinting determined that the leishmanicidal and anti-protozoal activities of 14-Hydroxylunularin are actually the outcome of sp³ hybridization and presence of free hydroxyl group on the aromatic rings [26]. Position of methoxy and hydroxyl group on bibenzyl aromatic ring and their position-effect as per the SAR have been critically demonstrated in some popular liverwort bibenzyls. As we have discussed earlier, the presence of methoxy group at C-1', C-6' and C-13 positions of marchantin A (IC₅₀ value=0.27µg/ml) gives rise to marchantin A trimethyl

ether, which is functionally almost 12-fold less active (IC_{50} value=3.24 μ g/ml). Furthermore, another derivative of marchantin A, marchantin C, lacking the hydroxyl group at the C-6' position was found to be responsible for its 10-fold less activity [63]. However, marchantin E showed similar activity (IC_{50} value=0.69 μ g/ml) as shown by marchantin A due to the presence of methoxy groups at the C-7' position. If we consider both antimicrobial and anti-trypanosomal activities, hydroxyl groups at the C-1', C-6' and C-13 positions were found to be crucial for bioactivity of marchantin A. Moreover, another interesting fact is that the tautomer of marchantin C, isomarchantin C possesses ether linkage at C13–C10' position with hydroxyl groups present at C-10 and C-11', but it has failed to demonstrate any anti-trypanosomal activity. Similar pattern of SAR has been followed in case of ptychantol A with weak bioactivity (IC_{50} value=5.42 μ g/ml). The C-13' position is highly important for anti-trypanosomal activity and compounds having hydroxyl group at this key position are generally weaker in terms of activity [28, 29, 43]. However, C-14 and C-10' biphenyl bond of plagiochin A, C-14 and C-12' biphenyl bonds of riccardin A, and C as well as the presence of no bond at either B or D rings in case of perrottetin F demonstrated moderate activity and indicated that presence of ether linkage or biphenyl bond at the B or D rings present in bis(bi)benzyls are not useful in enhancing the bioactivity of any marchantin group of compound. Another compound 2(R)-2-isopropenyl-6,7-dihydroxy-4-(2-phenylethyl) dihydrobenzofuran with isopropenyl-furan moiety has shown strong inhibitory activity (IC_{50} value=0.44 μ g/ml) against species of *Trypanosoma* but 2-geranyl-3,5-dihydroxy bibenzyl showed weak anti-trypanosomal activity when compared to radulanin A, radulanin H and this isopropenyl-furan bibenzyl. Later it was demonstrated that the particular difference in bioactivity was due to the presence of carboxyl group at the C-7 position of 2-geranyl-3,5-dihydroxy bibenzyl while the three others were lacking it. So both C-13' and C-7 position were found to be important for anti-trypanosomal activity. Marchantin A, marchantin E, plagiochin A and 2(R)-2-isopropenyl 6,7-dihydroxy-4-(2-phenylethyl) dihydrobenzofuran all have shown potent inhibition against *Trypanosoma* when compared to the standard drugs eflornithine and suramin (IC_{50} value 2.27 and 1.58 μ g/ml respectively) [61].

Antioxidation or free radical scavenging activity is considered as the basic underlying mechanism of many therapeutics. Asakawa (1994) reported the superoxide anion radical scavenging role of radulanin K extracted from *Radula javanica* on guinea pig macrophage [57]. If we consider the chemical structure of most extensively studied bibenzyl marchantin A, it is clearly evident that the presence of hydroxyl groups at C1' and C6' positions are significantly contributing in free radical scavenging and cytotoxic activities of the compound. The DPPH assay and structural conformational study further

demonstrated that due to the absence of hydroxyl group at the C-6 position in marchantin C, it exhibited less antioxidant activity [32]. Another important observation is that the introduction of hydroxyl group at C-7' position or C-7, C-8 unsaturation could dampen the nitric oxide inhibition activity and possibly due to that structural difference in the trimethyl ether derivatives of marchantin A and B, they are less potent than the parent molecule [28]. The inhibitory activity, radical scavenging property and therapeutic efficacy of any plant derived botanical could be detected easily *in-vitro* by different enzymatic assays (lipoxygenase, peroxidation, cyclooxygenase etc.). SAR study has revealed the substitution pattern of different bibenzyl compounds are responsible for primary inhibition. In case of 5-lipoxygenase, the inhibitor molecule requires at least two functional groups to react with enzyme's active site as well as to show lipophilicity. According to the structural information on marchantin A, the catechol moiety in ring C and the phenolic hydroxy group in ring A, are mainly responsible for enzyme inhibition. Similar pattern has been observed in marchantin B and radulanin H but in marchantin D, presence of hydroxyethyl bridges reduces the efficacy. Moreover, two catechol moieties and absence of cyclic bis(bi)benzyl ring has critically enhanced similar bioactivity in paleatin B and perrottetin D. Acyclic structure has helped the first compound to get fit within the active site of the enzyme and stabilized its lipophilic chain too [64]. These peculiar patterns of lipophilicity are very useful to describe antioxidant activity, semiquinone radical formation and cytotoxicity exhibited by bibenzyls. In addition, perrottetin D acts as a phenolic antioxidant and forms a pyrogallol-type radical even at room temperature [64]. In pharmacological activity related section we have mentioned nitric oxide inhibition activity of bibenzyl and bis(bi)benzyls, isolated from *R. appressa*. Their efficacy has been tested on lipopolysaccharide induced RAW 264.7 cell line and strikingly all the tested compounds were almost as potent as L-N6 -1-iminoethyl)lysine, the control. The important observation was both prenylated bis(bi)benzyls and bibenzyl-cannabinoids (radulannin A, radulannin L, 2-geranyl-3,5-dihydroxybibenzyl, 2(S)-2-methyl-2-(4-methyl-3-pentenyl)-7-hydroxy-5-(2-phenylethyl), *O*-cannabichromene, 6-hydroxy-4-(2-phenylethyl) benzofuran and *o*-cannabicyclol) have shown strong antioxidant activity [28, 125].

Bibenzyls are reported for many other activities too. The thaloid liverwort, *Blasia pusilla* derived cyclic bis-bibenzyl dimers are responsible for plant growth inhibition whereas plagiochine A derived from *Plagiochila sciophila* showed neuritic sprouting and enhanced choline acetyl transferase activity [57]. Marchantin A and its trimethyl ether exhibited ameliorating effect against nicotine induced muscle contraction in mice model which was comparable with the standard drug d-tubocurarine. According to the researchers, due to the absence of nitrogen atoms, structural similarity with the active muscle relaxing drugs, presence of an *o*-hydroxyl group in

marchantin A and an *o*-methoxy group in marchantin A trimethyl ether exhibited muscle relaxation activity [57, 63, 139]. Presence of phenolic hydroxyl group with benzene ring has been detected in another important compound, isoplagiochin A. Apart from this there is ether linkage and biphenyl bond present in isoplagiochin A, B and in all plagiocin-type bisbibenzyls isolated from *Plagiochila sciophila* Nees ex Lindenb. [28, 36, 125]. Significant cardioprotection and other biological role rendered by bibenzyl riccardin C and its *O*-methyl derivatives (riccardins A, riccardin F etc.) were noted due to the presence of phenolic hydroxyl groups as well as C-1, C-2' and C-14, C-11' diaryl ether bonds, in their structure [35, 40]. Halogenated natural products are common among marine organisms [54]. Similarly, in bibenzyl and bisbibenzyl compounds, the presence of halogen molecule is quite regular in occurrence. In bazzanin A (6'-chloro isoplagiochin C) desorption chemical ionisation (DCI)-MS has determined the presence of chlorine atom in the benzene ring along with the phenolic hydroxyl groups and two benzylic methylene. Similar structural conformation was noted in bazzanin B (6',8'-dichloro isoplagiochin C), bazzanin C (6',8',12-trichloro isoplagiochin C), bazzanin D (6',8',10'-trichloro isoplagiochin C), bazzanin E (6',8',10',12-tetrachloro isoplagiochin C), bazzanin F (6',8',10,14'-tetrachloro isoplagiochin C), bazzanin G (2,6',8',10,10'-pentachloro isoplagiochin C), bazzanin H (6',8', 10,10', 14'-pentachloro isoplagiochin C) and bazzanin I (2,6',8',10', 12,14'-hexachloro isoplagiochin C) detected by high resolution MS, proton-proton and proton-carbon shift correlated 2D experiments, NMR analysis. Bazzanin J or 6', 12-dichloroisoplagiochin D is the chlorinated derivative of isoplagiochin D, which was reported from *Plagiochila fruticosa* Mitt. [49]. The “fitting and chelating model” mediated structural contribution potentiated *in-vitro* PA endonuclease inhibitory activity of riccardin D, marchantins A and plagiocin A where the presence of 3,4-dihydroxyphenethyl group in structural moiety played the key role against H3N2, H1N1 influenza A and B viruses during the evaluation of more than 33 different types of phytochemicals [76]. Structural conformational study conducted through systematic unbounded multiple minimum search and NMR indicated the mobility of macrocyclic rings of riccardin A and marchantin A. It is assumed that the mobility of the former one is more restricted due to the introduction of the biphenyl linkage to the macrocyclic ring. This structural feature also evidenced for the reduced affinity of riccardin A towards calcium ions when calcium inhibitory activity was compared between these two macrocyclic bibenzyls at ID₅₀ value 1.85 and 2.0 µg/ml [126]. Wide range of bioactivities like antibacterial activity against gram-negative and positive bacteria, growth inhibition against *Mycobacterium tuberculosis*, *M. avium* and *M. nocardia*, and enzymatic inhibition of 5-lipoxygenase and calmodulin activity could be interpreted by mode of action based on calcium-ion binding. The inhibitory role played by

marchantin C, isoplagiochins A and B against tubulin polymerization was tentatively attributed on the restricted biaryl ring system which is favourable for tubulin binding. These bibenzyls with two aromatic rings connected by a two-carbon bridge with a double bond also function as potent antitumor agent [29, 42, 43, 88]. The structural and therapeutic similarity of marchantin A and isoquinoline alkaloid, cepharathine is mostly due to a common receptor binding phenomenon [86, 87]. Macrocyclic marchantins A and E are also able to activate the nuclear-receptor farnesoid X-receptor (FXR) required to control critical gene expression in bile acid and cholesterol homeostasis up to a level comparable with the chenodeoxycholic acid [39]. Not only the presence of phenolic groups but also its active binding to the aromatic ring system is necessary for functional state of bibenzyls. DHA, an antifungal agent extracted from *Asterella angusta*, enhanced adriamycin cytotoxicity in drug resistant K562/A02 cells but in DHA derivatives, where phenolic groups were methylated, reversal fold of compounds were weaker [52]. Phytochemical investigation of the ethyl acetate extract of the leaves and the stems of *Bulbophyllum kwangtungense* Schlecht., has revealed the presence of two novel stilbenoids, as confirmed by repeat column chromatography as well as 2D-NMR spectroscopic analyses. These compounds were characterized as 5-(2,3-dimethoxyphenethyl)-6-methylbenzo[d][1,3] dioxole, and 10,11-dihydro-2,7-dimethoxy-3,4-methylene-dioxy dibenzo[b,f] oxepine. The most striking part of this discovery is the identification of a natural bibenzyl compound with methyl group in the benzene ring, which is a very rare phenomenon. These compounds are also known as natural oxepines. Though reports on the isolation of such phytochemicals from natural sources are very rare, but till date most of them were reported for their potential anti-tumor activities. However, anti-tumor activities of the new compounds were also determined *in vitro* against *Hela* cells and the second compound showed significant cell growth inhibition with IC₅₀ value of 47.2 µg/ml [83, 123]. Researchers have found the differences between NMR shift data of sesquiterpene and bisbibenzyl are due to the ‘shielding’ or ‘deshielding’ mechanism on aromatic rings of the bis(bi)benzyls by some protons of the sesquiterpene moieties which provide great challenge in force field parameterization as well as in extensive conformational analysis and molecular modelling of bibenzyls [66, 86, 126]. In addition, primary selection of natural products as potent future drug is done via molecular docking and ligand matching. In this process, by using *in-silico* tools and knowledge of stereochemistry the compounds are critically analysed to calculate their probability of being an active drug. The example of marchantin C is important in this context as the chemical structure of this macrocyclic bis(bi)benzyl is structurally similar to combretastatin A-4 (CA-4). CA-4 is a popular dihydrated dimer which is already reported as a vascular

tumor targeting agent due to its potent microtubule polymerization inhibitory role [140, 141]. Inhibition of microtubule polymerization, cell cycle arrest at G2/M phase and halt in mitosis progression have been mediated by marchantin C in A172 and *HeLa* cells possibly due to the presence of bibenzyl skeleton and methoxy group [43]. The elucidation of tubulin binding mechanism of bis(bi)benzyls at the molecular level has revealed that the tubulin has three ligand binding sites namely colchicine, *Vinca* alkaloid, and taxane [142, 143]. The taxane binding site is for depolymerization of microtubules but if any antimetabolic compound gets attached to *Vinca* alkaloid or colchicine binding site they do inhibit the polymerization of microtubules. CA-4 binds to the colchicine binding site [144–146]. Therefore, it can be assumed that bis(bi)benzyls which are structurally similar to CA-4, might also get attached to the colchicine binding site to block microtubule polymerization. Further study has also indicated the role of hydroxyl group in strong hydrogen bond mediated interaction between tubulin and bibenzyl compound and introduction of any halogen atom, as observed in riccardin D, alters the electron distribution and potentiates stronger hydrogen bond formation [16]. Backbone conformation is another important feature of any potent antimetabolic agent. It was reported that the presence of two aromatic rings and their attachment through the double bond contribute in ideal backbone conformation which can be observed in case of marchantin class of bibenzyls [42]. Apart from studying the modes of action of anti-cancer activity of bibenzyls, the inhibitory role of marchantin E against influenza PA endonuclease activity was also analysed by researchers. In this case *in silico* docking simulation process is used to decipher the role of dihydroxy phenethyl group. The experimental data clearly demonstrated that the dihydroxy moiety present in dihydroxy phenethyl group of marchantin E actually chelates the Mn^{2+} ions present in active site of PA endonuclease and as a result marchantin E gets well anchored to the active site of the enzyme via some hydrophobic interaction [140, 141, 147, 148]. Moreover, conserved amino acid domain of Arg84, Asp108, Glu23, Glu80, Glu119 His41, and Lys134, in influenza virus A and B actually aid in PA endonuclease inhibition as showed by marchantin E [76]. Riccardin C which have shown anti-MRSA activity have shown presence of phenolic hydroxyl group and the 2-phenoxyphenol moiety is essential for such activity but confirmation of particular molecular target is yet to be done [149].

Critical appraisal of medicinal property and underlying mode of action of important bibenzyls

The series of papers and book chapters published by Asakawa and group for over a decade, largely emphasized the

application of bryophytes and its phyto-chemical constituents to act as pharmaco-therapeutic natural product [1, 4, 7, 12, 14, 36, 47, 139]. The presently available data on chemical diversity of bryophytes indicated the presence of numerous bioactive terpenoids, sterols, essential oil, fatty acids, alkanones and other aromatic compounds such as bibenzyls and bis(bi)benzyls. However, in the present review work, we have tried to streamline the biomedical application of bibenzyls and its derivatives. In natural products based research, the first stage of screening bioactivity of any compound (isolated and characterized already) is *in-vitro* and/or *in-vivo* experiments, which may further be supported by different enzymatic assays. It is quite evident that lots of *in-vitro* studies have indicated cytotoxic efficacy of bibenzyls and bis(bi)benzyls [1, 19, 32, 41, 51, 53, 66]. However, less number of compounds, were screened under the second phase which includes protein-interaction, similarity based sequencing, moiety based molecular docking etc. For very few compounds SAR based information is available i.e. marchantins A, B, E [28, 61, 125], riccardin A [126], 14-Hydroxylunularin [26] and data available on third and fourth stage of trials is quite limited. Interestingly, almost 35 years back, in 1985, synthetic non-steroidal, poly-fluorinated bibenzyl drug, bifluranol (trade name prostarex) went through human trial for its anti-androgenic properties against benign prostatic hyperplasia. After completion of 12 weeks study period in double blind trial, 35 patients suffering with bladder outflow obstruction, exhibited improvement in urinary flow and frequency ($p < 0.05$) when compared to diethylstilbestrol [117]. The compound was previously reported for anti-fertility activity in mice and rat models [150].

Bryophytes, especially the liverworts and mosses, have been reported for their allelopathic and anti-microbial properties. In many cases, presence of selective chemicals insisted strong odor which helped bryophytes to serve as repellent. The table 1 clearly illustrated many of the bibenzyls and bisbibenzyls are reported for anti-microbial activity. In case of antifungal most of the experiments were performed against *C. albicans*. However, a large variety of bacteria were studied to ensure anti-bacterial efficacy of this natural product. Currently, emergence of strain VISA (vancomycin-intermediate-resistant *Staphylococcus aureus*) and MRSA (methicillin-resistant *Staphylococcus aureus*) have shown MDR feature under clinical investigation and incurred threat to community-acquired infections (CAI) [149]. The bisbibenzyls isolated from bryophytes, exhibited anti-MRSA bactericidal activity towards these pathological strains. It is further noted, that leakage of cell membrane and/or formation of mesosome in *S. aureus* N315 are responsible for such antibacterial activity of riccardin type phenolic components when compared with vancomycin [151]. The study of cellular efflux of ethidium bromide (fluorescent DNA-binder) or enhanced intracellular gradient of Na^+ and reduction of concentration of

K+ could indicate clearly how this anti-MRSA activity is manifested in this gram positive bacteria [152]. Plagiochin class of compounds with different C-ring linkages provided variable data on molecular dynamics based calculations and clearly indicated conformational flexibility determines the extent of bacteriocidal efficacy [152]. Riccardin C exerted anti-MRSA activity against strain OM584 and OM481 with MIC value of 3.2 µg/ml when compared with standard ZYVOX or linezolid [149].

However, if we dig deeper, presence of similar compounds is indicative of its efficient cytotoxicity. The mechanism of such anti-proliferative activity is variable but DNA polymerase inhibitory activity is important one among them. It is noteworthy, that the popular anti-cancer alkaloid of *Catharanthus roseus*, vincristine, which is marketed as “vindesine”, function as DNA polymerase inhibitor [153]. Such *Vinca* alkaloids are microtubule destabilizers and critical target in oncotherapy but their drug resistance, systemic toxicity, complex and expensive synthesis, poor rate of bioavailability limited cost-effective application [16]. In anti-HIV-1 activity exhibited by marchantins A, B, D, paleatin B and perrottetin F; IC₅₀ value ranged from 5.3 µg/ml to 23.7 µg/ml [137, 154]. These compounds showed activity against TIBO-resistance HIV-1 reverse transcriptase [85]. The enzymatic inhibition strategy is often at par with different biological activities. Scientists have reported calmodulin and 5-lipoxygenase inhibition in marchantins D, E, perrottetins A, D and riccardin A (ID₅₀ 2.0–95.0 µg/ml) [7, 8, 56], Cyclooxygenase inhibitory activity was also demonstrated by perrottetin D, radulanin H, paleatin B, marchantins A, B, E with respective IC₅₀ values as 26.2, 39.7, 45.2, 46.4, 55.9 and 58.0 µM [64]. It is important to note, among naturally originated drugs acetylsalicylic acid (semi-synthetic form of salicylic acid) act as cyclooxygenase inhibitor [153]. The tyrosinase inhibition is another important aspect. The bibenzyl xyloside compounds isolated from *Chlorophytum arundinaceum* Baker (Liliaceae) and some chemically synthesized compounds derived via Wittig reaction from 2,4-dihydroxybenzaldehyde, also reported such activity (IC₅₀ 1.6 µM) when compared with kojic acid [155, 156]. These indicates future direction of similar investigation could yield positive result when performed with bibenzyls from bryophytic origin. In the year, 2009, the pandemic, caused by H1N1 and H5N1 influenza virus compelled scientist all over the world to search for novel anti-influenza lead from nature. During such screening, Iwai et al., 2011, first time reported liverwort based bibenzyl compounds, plagiochin A and marchantins A, B, E could inhibit activity of influenza A endonuclease which can be of significant importance [76].

Apart from SAR studies various mode of action revealed anti-cancer properties exhibited by bibenzyls and their derivatives. For DHA, its induction of autophagy and apoptosis was observed in human U2OS cells. The formation of autophagic vacuole, elevated level of LC3-II autophagy protein marker, p53 phosphorylation, up-regulation of p21Waf1/

Cip1 (p53 target gene) are all the parts of this autophagic induction. Moreover, reduction of cyclin B1 expression caused cell cycle arrest at G2/M-phase which is another part of apoptotic mechanism exerted by DHA, but complete elucidation of p53 signaling pathway regulation and modulation of nuclear and cytoplasmic functions of p53 is still incomplete [53]. For marchantin A induced apoptosis of MCF-7 cell line, the mechanism is regulated by caspase-dependent pathway. The decreased expression of cyclin proteins (cyclin B1, cyclin D1, p21, P27) halted the progression of cell cycle through G0/G1 phase (<5 lg/ml dosage) or at G2/M phase where 7.5–10.0 µg/ml marchantin A had been applied. The structural and functional similarities of marchantins A and C as well as the presence of aromatic ring at C-10 and C-6 potentiated them as ideal chemotherapeutic agents [32]. In recent times, hormone resistant prostate tumors emerged as critical challenge to the oncologists. It could be noted, in therapy of prostate cancer, application of bis(bi)benzyl at low concentration (<10 µM/L) suppressed androgen receptor signaling in LNCaP cells which is essential for cell viability [77]. Over-expression of topoisomerase II plays critical role in proliferation of endothelial cancer cells [157–159]. Riccardin D mediated anti-angiogenesis also involves suppression of many angiogenesis-promoting factors EGF, VEGF mitogen, VEGF receptor and MMPs [160] as studied in HUVEC cell line [90]. The upregulation of VEGF expression triggers oncogenic mutations, vascular endothelial cell proliferation, enhances vascular permeability which ultimately resulted in tumorigenesis. However, the inhibition of DNA topoisomerase II, has been found in riccardin D pretreated HL60, K562 and MDR resistant K562/A02 cell line. Interestingly, anti-mitotic agent podophyllotoxin which is marketed as semisynthetic drug etoposide also works on principle of DNA topoisomerase II inhibition [153]. Oxidative stress is closely assisted with Parkinson's disease related neurodegeneration. Some bibenzyls isolated from the Orchidaceae family exerted reversal of neurotoxicity. However, the bibenzyl compound, chrysotoxine, prevented 6-hydroxydopamine (6-OHDA) induced cytotoxicity in SH-SY5Y human neuroblastoma cell line, inhibited NF-kB translocation, blocked iNOS upregulation and reduced intracellular nitric oxide (NO) level significantly. These modulations suggested probable efficacy of chrysotoxine as psycho-active drug [161]. Plagiochin E mediated cytotoxicity that relies on metacaspase signaling pathway included G2/M cell cycle arrest, chromatin condensation, cytochrome c release, nuclear fragmentation, and phosphatidylserine exposure. Release of cytochrome c, CDC28, CLB2, CLB4 over-expression and ROS accumulation caused metacaspase activation and triggered apoptosis in *C. albicans* [83].

The features which are generally involved with cancer chemotherapy are reduced drug accumulation, low uptake and high efflux, broad distribution, reversal of drug resistance,

DNA repair, and prevention of tissue damage, cell-cycle regulation, apoptotic induction and maintenance of signaling pathways [162]. There are many research reports which indicated tumors are achieving resistance against broad spectrum of chemotherapeutic drugs. Therefore, MDR reversal is another critical property of chemotherapeutic drug designing. Most significantly introduction of MDR is triggered by overexpression of ATP binding cassette (ABC) transporter proteins. However, among these, transmembrane glycoprotein (P-gp), one ATP-dependent drug transporter, which carries drug molecule out of the cell and thus lowers intracellular accumulation and increases drug efflux, is considered as potential candidate for reversal of multidrug resistance [52]. DHA and many of its derivatives and other bibenzyl compounds also showed similar multidrug resistance reversal in chemo-resistant cancer cells [41, 51]. If we look into other activities, riccardin D synergistically acted against *in vitro* growth of *C. albicans*, and reverted fluconazole resistance. It is assumed that riccardin D interfered with the fluconazole-targeted ergosterol biosynthesis pathway [41, 53]. On the other hand, riccardin C acted as a cardioprotective agent as it was found to increase plasma HDL level in mice without altering concentration of triglyceride. It promoted cholesterol efflux (THP-1 cell line) and could be counted as promising anti-obesity natural product [58]. In search of relation between chemical diversity of natural products and their functionality it was found that cyclotheonamide A targeted thrombin protein [153] and similar screening was done on perrotetin E which was an important cardioprotective agent [81].

The class bibenzyl cannabinoids are already reported for their psycho-therapeutic and other bioactivities and in the section “Bibenzyl cannabinoid: therapeutically most studied derivatives of bibenzyls”, we have discussed the importance of *Radula* genus in this aspect. However, cannabinoid moiety based synthetic drugs which acts on cannabinoid receptors type 1 (CB1) and 2 (CB2) are potential lead for modern drug discovery and Δ^9 -tetrahydrocannabinol is one such important candidate. The authors have mentioned structural similarity of Δ^9 -tetrahydrocannabinol (from *C. sativa*) with Δ^1 -tetrahydrocannabinol (from *Radula* sp.). So, the principle of mechanism may be applied to both types of compound or other types of phytocannabinoids. Moreover, the endocannabinoid system associated with endocannabinoid metabolizing enzymes could modulate lots of physiological responses and various *in vivo*, *in vitro*, *in silico* screening of therapeutic application have further supported that claim. The study for natural cannabinoid ligands has been performed in angiosperms but in bryophytes similar studies are extremely few [163].

Bioprospecting of unexplored natural sources is critical in modern research as it ensures not only identification of target protein but also accelerates detection and standardization of new drugs. The appraisal of bibenzyl oriented synthetic chemistry has clearly pointed out the presence of chiral isomers free

of stereogenic carbons and conformational variability due to positional difference of C-ring, is highly crucial for biological activity. Highly-classified synthesis model analysis manifested role of Wittig and other related reactions in cost-effective (yield-wise) synthesis of broad spectrum bibenzyl and bis(bi)benzyl compounds [164]. Professor Y. Asakawa mentioned identification of 103 bibenzyls from liverwort which are synthesized by dimerization of lunularic acid in his number of papers [1, 165, 166]. However, revelation of functional prospects or critical analysis of underlying mechanism of action of any bioactivity is highly required to categorize the natural products on the basis of their application. Structural characterization or chemical screening is closely correlated with that phase. It is noted by Tulp and Bohlin, that large number of structure-wise different chemical compounds, may or may not be isolated from distantly related organism could fall into the same functional category [153]. Further, genome wide sequencing or molecular modeling or screening of protein-protein interaction could reveal how their structural characters are enhancing or reducing some activities. This categorization and identification of natural products based on functional versus chemical diversity helps scientists to understand which natural product are suitable for drug mimicking based screening and why. In this article we discussed medicinal activities of bibenzyl type of compounds in light of their mode of action. The mechanism based similarity of some standardized drugs, already available in market, are also mentioned. These findings will aid in understanding the potential of bibenzyl in future pharmaco-therapeutic research.

Research insights on bryophyte derived bibenzyls; past present and future

Investigation of natural products is an integral part of modern research and obviously for ancient land plants like bryophytes such systemic investigation is highly essential to establish the chemo-taxonomical database and to interpret their physiology and cellular metabolism. For millions of years, the phytochemicals, including aromatic complex molecules like bibenzyls and bisbibenzyls, are playing the role of ‘survival key’ to enable them to sustain under broad habitat zone (i.e. polar, arctic, and boreal). The occurrence of bibenzyls in algae, bryophyte, pteridophyte, and orchids has intrigued interest among researchers to establish chemical inter-relationships on point of evolutionary pattern of phytochemical linkage [1, 36, 128, 139, 167]. Natural product oriented bioprospecting has also indicated convergent evolution of bryophytes [105, 124]. Researchers have found surprising functional similarity of MADS box transcription factor (type II) or MIKC class gene in evolutionary distant groups. In seed plants they are contributing in flower development whereas in non-seed plants they are regulating sporophytic and gametophytic

alteration of generation [168]. In future, such insights into evolutionary pattern could illuminate any phytochemistry oriented study of any plant lineage. So, to understand the complex metabolic pathway leading to bibenzyl production, both in non-seed plants and flowering plants; or to determine which stage of development is triggering the secondary metabolite accumulation; the genome specific molecular interpretation is highly recommended. Scientific interpretation of their taxonomical lineage, ecological adaptations, anatomical development or chromosomal evolution from fossil study of this primeval land plant has been challenging for a long time. Even nowadays, bryophyte oriented research, in terms of pharmacological, biochemical or molecular analysis, is significantly low around the globe. Considering its role as pollution indicator, toxin-accumulator or “nutrient redistributor” [169] the plant lineage demands more attention from modern research.

Over the last two decades, advent of modern qualitative high-end tools like; high performance TLC, high performance liquid chromatography (HPLC), Fourier transform infrared (FTIR) spectroscopy, gas chromatography (GC)-MS, NMR, matrix-assisted laser desorption/ionization, liquid chromatography with diode array detection (LC-DAD), X-ray crystallography etc. has contributed broadly in phytochemical research. Along with qualitative and quantitative analytical research, the application of bio-informatics, molecular docking and functional moiety based similarity-studies have contributed greatly in identification of functional leads in drug discovery. In recent times, eco-metabolomics emerged as a novel subject where interaction of ecological and biochemical features are studied as well as correlated. Recently, computational workflow based data interpretation model was applied to understand seasonal variability of secondary metabolite content in bryophytes [170]. In future such research output may pave ways for illustration of plant metabolomics and their mode of action. Eminent bryologist Asakawa and his collaborators are doing fantastic research on bryophytes and pharmaco-active properties of bibenzyl and bis(bi)benzyl type of compounds. In one of his book chapter [4], the total procedure of collection, extraction, distillation procedure, TLC, HPLC, GC-MS, use of solvents, purification steps were clearly mentioned. Nowadays, qualitative variation of active phytochemicals due to altitude, season of growth and tissue type of mother plant could be detected quantitatively using these cutting-edge techniques. In this context, one could consider the prospects of maintaining bryophytic *in-vitro* culture to ascertain production of novel and medicinally expendable botanical products [171]. Biotransformation could also be of similar significance [172], where fungi *Aspergillus niger* (TBUYN-2) and *Neurospora crassa* converted marchantin A into 10-hydroxymarchantin A, 3'-hydroperoxymarchantin A and 5'-hydroperoxymarchantin A. The axenic culture is another reported method which can be useful in extraction of medicinally valuable bibenzyls and bisbibenzyls under

laboratory condition. This method has been employed on *M. polymorpha* for extraction of marchantin A [173]. Emergence of such novel strategies and revelation of genomic data of non-seed plants holds the future strategic key for next level investigation of bibenzyl and bis(bi)benzyl molecules isolated from large number of bryophytes.

Discussion

Bryophytes are reported from almost all parts of the world yet a little is known about their chemistry and to be exact, among all classes of bryophytes only the mosses and liverworts were examined critically. However, there are several examples, related to terpenoids, phenolics, biflavones, stilbenoids-bibenzyls etc. which demonstrate the unique phytochemical richness of bryophytes. Presently, natural products, their synthetic and semi-synthetic analogs are playing vital role in drug discovery [163]. The present article provides multi-directional views deeply assisted with bibenzyl oriented research, their structure-function wise diversity and future application of the screening endeavor. In this review, we have provided insight on classical topics like ethnobryology; summarized pharmacological properties of large number of bibenzyl and their derivatives; included ongoing research status on bibenzyl cannabinoids as well as bibenzyls extracted from Orchidaceae family; discussed various aspects of SAR, mode of action and research insights; critically analyzed potential of bibenzyl type of molecule as therapeutic lead component and tried to assess the overall impact of bibenzyl and bisbibenzyls extracted from bryophytes. However, we have noted some ambiguity also. Marko et al., 2017, reported ethnomedicinal property, chemical constituents and pharmacological activity of 52 bryophytes belonging to 20 families of liverwort and 13 families of mosses [137]. Though this paper elaborately described all these aspects but it was not clearly mentioned how biochemical compounds, isolated from all these bryophytes, contributing in reported bioactive property of the same. A number of bibenzyl and bis(bi)benzyl types of compounds have been isolated, characterized and pharmacologically tested till date but there are large numbers of compounds present which are not evaluated for their probable medicinal application. In this review, the authors have clearly mentioned different bibenzyls and their derivatives and presented available data on bioactivity-based investigation. The authors have also observed, for some bioactivity the reported articles are describing variable outcome. The liverwort sensitivity (as determined by patch test) and the relation of these bryophytes with allergic contact dermatitis. The six species of *Frullania* were described but this paper not mentioned any protective role of bibenzyl against acute dermatitis [174]. However the role of sesquiterpene lactones, especially frullanolide as sensitizer in this context was noted. On the other hand, the similar activity of 4-hydroxy-3'-methoxybibenzyl act against dermatophytic fungi *Trichophyton mentagrophytes*

was already reported [97]. Similarly *M. polymorpha* was reported for allergic contact dermatitis but the identification of allergens is still not completed [58]. In some cases, many bioactivities were represented as unpublished data [58] which has filled such claims with some ambiguities. According to previous report, a large number of bryophytes *Plagiochilafruticosa*, *P. ovalifolia*, *Bazzania pompeana*, *Porella caespitans*, *Marsupella emarginata*, *Radula perrottetii* etc, were examined as cytotoxic against P-388 in crude ether extract form but such claim was not validated in later days by further investigations. But on other hand, Prof. Asakawa's claim on chemopreventive compound isomarchantin C [1, 34, 58] as potent inhibitor of cathepsin L (95% inhibition at 10^{-5} M) and cathepsin B (93% inhibition at 10^{-5} M) activity were proved [1]. Interestingly, in his two major reviews, Prof. Asakawa described different aspects of phytochemical activity isolated from bryophytes in a very similar manner [1, 58]. However, we have tried to focus mainly on bibenzyl type of compounds. In natural product based research proper identification and authentication of study material are highly important. However, in some older paper [175, 176] we have noticed taxonomic validation part is absent.

The traditional reports or preclinical and clinical studies have also supported myriads of medico-therapeutic properties of bryophytes such as anti-pyretic, anti-arthritic, anti-tuberculosis, anti-hematemesis, anti-dermatomycosis, anti-pneumonia, anti-hepatic and wound-burn-fracture healing properties. Mostly the marchantin-type bibenzyls were investigated; but it could be observed, that the other types of bibenzyls and bis(bi)benzyls are also pharmacologically important. However, critical evaluation of cited references revealed bibenzyl compounds are mostly studied on both *in-vitro* cell lines and *in-vivo* experimental organisms, for cytotoxic or anti-proliferative properties, along with various structure-function studies. Apart from *in-vitro* or *in-vivo* cytotoxic assays, growth inhibition studies (anti-bacterial, anti-fungal, anti-viral, anti-trypanosomal, anti-feedant, nematocidal) of bibenzyl and its derivatives, were also conducted by many researchers. However, lack of proper standardization protocol, unavailability of pharmacological data of structurally characterized compounds, difficulty of identification, collection and maintenance of bryophytes played delimiting role in bryophyte-originated bibenzyl related research. Similar phenomenon could be observed for bibenzyl cannabinoids isolated primarily from different species of genus *Radula*. Notably, *Radula* preparations are also popular as “legal-high” due to high cannabinoid content [105]. The cannabinoids, (extracted from *C. sativa* and other angiosperms), extensively studied for psycho-active efficacy but the natural compound perrottetinene acid and its decarboxylated form perrottetinene, (harvested from bryophyte), have not been studied well and thus their pharmacological applications are not validated scientifically [103].

Conclusion

The approaches towards phytochemical data-mining are integral part of future drug development program including detection, isolation, characterization, structure conformation, therapeutic evaluation, quality control, determination of bioactive mechanism and *in-silico* drug designing from these novel active chemical group of bibenzyls from bryophytes. Assessment of this potent chemical group is the essential part of widening the sector of complementary and alternative medicines and natural product derived nutraceuticals and dietary supplements. Under *in-vitro* or *in-vivo* studies, the tested chemical is applied on micromolecular level but in most of the cases, the inter-molecular interaction, pharmacokinetics or stoichiometric calculation, toxicity and lethality determination are not fully defined. Before recommending bibenzyl compounds as potent chemotherapeutic agent or exploiting its multi-array of SAR in drug designing, all these knowledge-gap must be filled. What could be the possible application of bibenzyl cannabinoid isolated from bryophytes? how it can stimulate endocannabinoid system? what role its special structural moiety is playing? what possible role bibenzyls could play as cytotoxic agent? what is the probable chances of marchantin-group of bibenzyl to emerge as potential therapeutic lead? all these answers must be answered and validated. Exploitation of MDR reversal, cellular toxicity, growth inhibition or every other possible bioactive window must ensure cost-effectiveness as bryophytes are morphologically insignificant and hard to identify. The labor-intensive, complex extraction and characterization of natural products are often not met with expected outcome under *in-silico* screening. Moreover, lacunae of mode of action often delays higher stages of experimental approaches for any natural product. However, the descriptive review has covered bryophyte originated bibenzyl research in some unexplored areas. Similar research, would therefore, elaborate knowledge about bryophytes as novel source of therapeutically active natural products and the role of bibenzyl and bis(-bi)benzyl compounds as potential lead molecule of pharmaceutical importance would be understood in a better way.

Author's contribution SN prepared the manuscript, tables and figure 2. AD contributed in language correction, critical editing, prepared figure 1 and contributed photograph of bryophytes (figure 1, G and H) from his personal photography collection.

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Compliance with ethical standards

Ethical declaration No specific declaration is provided as this article is a review.

None of the authors have financial relationship with a commercial entity that has an interest in the content of this study.

Conflict of Interest The authors declare that they have no conflict of interest.

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