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Bio-evaluation studies of phytoconstituents- A review of the patents granted and filed by CSIR

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Botanicals have become a very important part of our life and are increasingly used as a primary source of actives in pharmaceuticals, cosmetics, nutraceuticals and personal care products. Extensive studies have been conducted on botanicals to understand their chemical profile and most of them have a history of safe use. Technical advances to isolate the bioactives, determine their molecular structure as well as their mechanism of action has generated considerable data and are available in the form of scientific publications as well as filing of patents. In this review, we aim to present the information pertaining to therapeutic applications of bioactives from different medicinal plants as disclosed in filed and granted patents to one of the largest publicly funded organizations in India namely Council of Scientific and Industrial Research (CSIR). The review also presents an assignee focused analysis and provides insights into the level of patent filing activity in the area of bioactives and the therapeutic applications by CSIR, India. Such information can provide a valuable tool for exploiting a firm's portfolio of patent holdings to assist decision-makers to identify the most valuable patents; product area or business opportunities among its own patent holdings.

Keywords: Bio evaluation, Bioactives, *In-vitro*, *In-vivo*, Patents, Phytoconstituents

IPC code; Int. cl. (2021.01)- A61K 36/00

Introduction

Since ancient times medicinal plants or herbs have been the primary source of medicines for people of every culture throughout the world. According to World Health Organization (WHO) about 65-80% of the world's population living in developing countries depends essentially on plants for primary healthcare[1]. On the other hand amongst developed countries there is a renewed interest in herb-based medicines as alternatives to synthetic drugs, nutraceuticals, and dietary supplements. This interest is evident from the fact that the total global herbal drug market is estimated to be US$62 billion and by the year 2050 is expected to grow to US$5 trillion[2]. Out of over 35000 herbs traded globally, at least 9,000 are known to have medicinal properties and 2,000-3,000 of them are widely-traded high-value products in commercial use[3].

Herbal formulation research practice is now preceded by an in-depth investigation into the mechanism of actions of the plants or its bioactive constituents using different research study designs. A large number of clinical trials are conducted worldwide in order to establish and generate data relating to clinical evidence of herbal based products.

Additionally, considering the interest in the structure and activity data of bioactive constituents from medicinal plant sources, a large number of organic chemists from various laboratories and universities have explored natural product chemistry. Thousands of chemicals were isolated and characterized from medicinal plants and evaluated for their biological properties using various study models. This information is published not only in the form of scientific literature but is also protected as patents focusing on new processes for the isolation of bioactives, new biological activity and formulations thereof. This is evident from the fact that around one lakh patent documents pertaining to polyherbal and phytopharmaceutical formulations or processes of extracting bioactives from natural resources have been filed in the last five years. Many of these process and composition of matter patents appear to be extensions of different traditional systems of medicine. Hence exploring the level of patent activity in this area would provide insights regarding the

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degree of interest by firms and inventors in securing intellectual property rights and can be used as a valuable tool for exploiting a firm's portfolio of patent holdings mainly to assist in taking decisions pertaining to product development or creating business opportunities.

Most of the review articles published till date focus on the patent and scientific literature pertaining to a single bioactive or a medicinal plant and its applications[4-6]. However, none of the published literature provide insights on the bio-evaluation studies for the bioactive constituents filed by CSIR, India. Such an analysis will be helpful to gain an understanding of the relative positions of the firmactive in perusing research on natural bioactives and its therapeutic applications.

Methodology

Data mining

An assignee focused patent search strategy was formulated using the assignee name i.e. Council of Scientific and Industrial Research CSIR and the assignee code (COUI-C) as assigned by Derwent Innovation Index-Clarivate™. The search was further refined using a combination of keywords pertaining to medicinal plants and the patent classification codes relevant to medicinal preparations containing bioactive compounds or bioactive enriched fractions from traditional herbal medicines. This resulted in to around unique 201 patent documents which were screened to shortlist 53 patents disclosing the bio evaluation studies of the plant/herbal bioactives mainly for therapeutic applications.

Inclusion and exclusion criteria

The search also retrieved patents which focused on synthetic routes of preparing the bioactives and their derivatives, methods of isolating the bioactive, methods of preparing the herbal formulations etc. From this data set, the documents which focused on evaluating the biological properties of the bioactives, bioactive enriched fractions or formulations comprising of one to two bioactives were only considered for this review. The patent documents claiming the process of isolation of the bioactives, synthetic methods, polyherbal formulations were excluded from the review.

Data analysis

Patents filed and issued to the assignee CSIR, India were analyzed to understand its research interest pertaining to the pharmacological evaluation of bioactives from natural sources and their therapeutic applications. To facilitate the analysis, each of the 53 patents were grouped based on the therapeutic application. Using this categorization, a technology matrix was created which included the details of the botanical source for the bioactive, chemical classification of the bioactive, type of study namely: *in vitro*, *in vivo* or clinical, type of study assay, route of administration, effective dosage etc. Indicator variables like the patent filing trend over the years by the assignee was examined to achieve a general understanding of the extent to which the research organization is active in this area.

Bio evaluation investigations

The patents were initially classified based on the type of bio-evaluation investigation as disclosed in the patent document for the bioactive, bioactive enriched fractions or derivatives thereof. The bio-evaluation investigations as disclosed in the patent documents included: i) *in-vitro* studies, ii) *in-vivo* studies, and iii) *in-vivo* and *in-vitro* studies.

In-vitro studies

Grouped under this category were patent documents wherein the bioactives were mainly evaluated using cell lines. The cell lines used by the inventors for biomedical research mainly included colon cancer cell lines, breast cancer cell lines, ovarian cancer cell lines, liver cancer, leukemia and fibrosarcoma cell lines. On the other hand, anti-diabetic research was carried out mainly using 3T3L1 adipocytes. The anti-bacterial efficacy of the bioactives was evaluated using strains of *Escherichia coli* and *Staphylococcus epidermidis*.

In-vivo studies

Grouped under this category are the patent documents wherein the studies were carried out in animal models. The analysis reveals that most of the studies were performed in animal models induced with certain conditions. For example, mice infected intraperitoneally with parasite (multi-resistant strain of *P. yoelii* nigeriensis) and streptozotocin-induced diabetic rats were considered as the *in-vivo* study models for evaluation of anti-malarial, anti-hyperglycemic and hypolipidemic activity of the bioactives.

In-vitro and in-vivo studies

Grouped under this category were patent documents which disclosed the bio evaluation

investigations using both *in-vitro* cell lines as well as animal models. The actives which were investigated using both the study designs included antiulcer, anti-inflammatory, antifungal, and veridical activities. The bio evaluation studies focusing on bioactives or their derivatives mainly included 45 unique medicinal plants. The top 15 medicinal plants as evaluated by CSIR as the assignee and the type of bioevaluation investigations are depicted in Fig. 1. The most explored plants were *Artemisia annua* and *Stereospermum personatum* which have been investigated for its pharmaceutical applications using both *in-vitro* and *in-vivo* study models.

Year-wise filing activity

The patent filing activity by CSIR that disclose medicinal plants and its bio-evaluation studies is depicted in Fig. 2. Priority year was considered for studying the trend. The earliest filing was in 1978 and maximum patenting activity was seen during the year 2002. The analysis of the patents filed by the assignee after 2005 reveals that the assignee's focus of filing patents shifted towards developing formulations incorporating the bioactive enriched fractions and on processess to synthesize the bioactives.

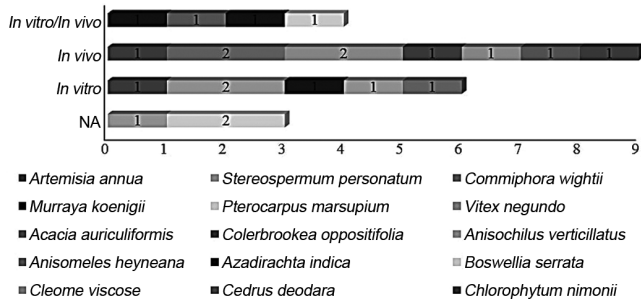


Fig. 1 — Plant vs. Bio-evaluation study type.

Bioactives

Each of the patents under consideration was analyzed in detail in order to enlist the bioactive and the nature of the bio-active constituents on the basis of their chemical structure. The main chemical classes included alkaloid, boswellic acids, coumarins, fatty acid ester, flavonoid compounds, lignan, glycosides, steroids, methyl ether, phenol derivative, polyphenol, saponins, sesquiterpene lactone, terpenes etc. The details of the bioactives as disclosed in the patent documents are enlisted in Table 1 and Fig. 3. The distribution of the patent filings by the firm amongst the chemical classes is depicted in Fig. 4.

Pharmacological evaluation

Each of the patents was further analyzed based on the therapeutic application of the bioactives and their derivatives thereof. These therapeutic applications included; anti-microbial, anti-cancer, anti-inflammatory, anti-asthmatic, immunomodulatory, anti-diabetic, hepatoprotective, anti-oxidant, bio-enhancers, anti-ulcer and miscellaneous applications.

Anti-microbial actives

Included under this category were patent documents disclosing the effects of the bioactive fractions or bioactive constituents from the medicinal plants against microorganisms which cause infections or harmful effects to animals or human. These were further grouped on the basis of the efficacy of the bioactive constituents against the specific micro-organisms and are highlighted below.

Anti-bacterial actives

Artemisia annua was the most investigated medicinal plant by the inventors from CSIR India. There were 3 patent documents disclosing the pharmacological effects of the bioactive constituents

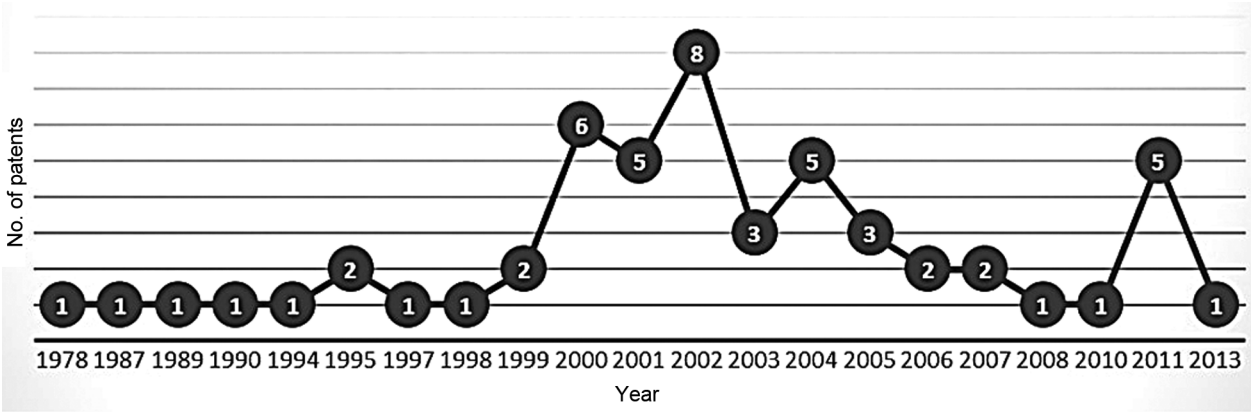


Fig. 2 — Year-wise patent filing activity by CSIR and disclosing medicinal plants and its bio-evaluation studies.

Table 1 — List of patents filled under CSIR-INDIA showing medicinal effects of plant bioactives or bioactive enriched fractions

S. No.	Publication number	Bioactive compounds	Activity	Study type	Cell line/ Animal model	Reference No
1	US6127405A	Alpha arteether	Anti-bacterial	*In-vitro*	*E. coli* strain DH 5alpha	7
2	US6451356B1	3,5-dihydroxy-4-pent-4'-enoyl-1'-oxymethyl benzoic acid (Oenostacin)			*Staphylococcus epidermis*	8
3	US6824795B2	Thymol			Disk diffusion assay	9
4	US9024043B2, IN-DEL-2011-02226A	Pimarane diterpene compounds, 2S,4aS,4bS,8aR,9R,10aS)-2,4b,8,8-tetramethyl-2-vinyltetradecahydrophenanthrene-4a,8a,9,10a-tetraol	Anti-tubercular	*In-vitro*	Human acute leukemia cell (THp-1).	10
5	IN172689B	Piperine	Anti-tubercular/ Antileprotic	NA	NA	11
6	WO2013021258A1	Corosolic acid (triterpene), 5-Hydroxy-6,7,3',4'-tetramethoxyflavone (flavonoid)	Anti-mycobacterial	NA	NA	12
7	US6214864B1	Dihydroartemisinin	Anti-malarial	*In-vivo*	Swiss mice	14
8	US6713504B2	2-(3,4-dimethyl-2,5-dihydro-1H-pyrrol-2-yl)-1-methylethyl pentanoate	Anti-fungal	*In-vitro*/ *In- vivo*	Balb/C mice	15
9	US2016046611A1, IN-DEL-2013-01077A	5,7-dihydroxy-6-(3-hydroxy-1-methylpiperidin-4-yl)-2-methyl-4H-chromen-4-one,Dysoline	Anti-cancer	*In-vitro*	Colo 205, HCT116 (Colon); HT1080 (Fibrosarcoma); NCIH322, A549 (Lung) and MOLT-4, HL-60 (Leukemia)	16
10	US8637679B2, IN-DEL-2011-00690A	Mahanine Mahanimbine			NA	17
11	US6893668B2	Camptothecin		NA	NA	18
12	IN225144B	Brevifoliol		*In-vitro*	COLO-320DM, KB-403, WRL-68, PA-1, MCF-7 , CaCO2	19
13	US2015051277A1, IN2011DE02222	Ovatodiolide or phyllocladan-16-alpha,17-dihydroxy-19-oic acid			Human acute monocytic leukemia cell line (Thp-1) cell line	20
14	US7435433B2	Oleane compounds (Arjunic acid)			Human cancer cell line, ovarian (PA-1), colon (Caco-2), breast (MCF-7) and liver (WRL-68)	21
15	US7767798B2	Loganin, 2′,3′,4′,7-tetra-O-acetyl-6′-O-propionylloganin			Human cancer cell lines, breast (MCF-7), Ovary (PA-1), Liver (WRL), Colon (COLO-320, CaCo2) cancer cells.	22
16	IN191205B	Pectic polysaccharide	Antitumor	NA	NA	23
17	US5629351A	B-Boswellic acid	Anti-inflammatory	*In-vitro*/ *In-vivo*	Guinea-pig serum, rats and mice	24
18	IN236525B, IN200403499P1, 3499/DELNP/2004	Imperatorin		NA	NA	25
19	US2008227854A	3-(1,1-Dimethyl-Allyl)-6-Hydroxy-Chromen-2-One		*In-vitro*/ *In-vivo*	Mice	26

(*Contd.*)

Table 1 — List of patents filled under CSIR-INDIA showing medicinal effects of plant bioactives or bioactive enriched fractions (*Contd*.)

S. No.	Publication number	Bioactive compounds	Activity	Study type	Cell line/ Animal model	Reference No
20	US8519154B2, IN2011DE00267	9H-carbazole compound,(1-methoxy-3-formylcarbazole)	Anti-asthmatic	*In-vitro/ In-vivo*	Rat heart, Mice	27
21	IN-DEL-2010-02363A	Dianthoside tetraacetate (2-methyl-pyran-4-one-3-0-ß-D-2",3",4",6"-tetra-O-acetyl glucopyranoside (MPTAG))		*In-vitro/ In-vivo*	Mouse/murine model	28
22	CN101365444B, IN-DEL-2005-03278A	Cleomiscosin A, Cleomiscosin C, Coumarinolignoids	Immunomodulatory	*In-vivo*	Red blood cell	29
23	IN183822B	Polysaccharide		NA	NA	30
24	US8729034B2	Acaciaside-A, Acaciaside-B	Spermicidal	*In-vitro/ In-vivo*	Sander & Cramer assay/ Rat, Mice, Rabbit	31
25	US6617313B1	Marsuposide (2,6-dihydroxy-2-(P-hydroxybenzyl)-3(2H) benzofuran-7-C-beta-D-glucopyranoside)	Anti-diabetic	NA	NA	32
26	US6562791B1	Pteroside (6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C-beta-D-glucopyranoside)		NA	NA	33
27	US7160866B2	Tigogenin pentaglycoside (Tigogenin-3-O-[alpha]-L-rhamnopyranosyl-1-3-[beta]-D-xylopyranosyl-1->4-[beta]-D-glucopyranosyl-1-3-[beta]-D-xylopyranosyl-1->4-[beta]-D glucopyranoside)	Anti-hyperglycemic	*In-vivo*	Rats	34
28	US7276258B2	Lupinoside PA (LPA4)	Anti-diabetic	*In-vitro*	3T3-L1 cell line, 3T3L1 adipocytes	35
29	IN167498B	Ionositolmonomethylether		NA	NA	36
30	US6896901B2	Gugulipid	Anti-hyperglycemic	*In-vivo*	Male swiss mice, rats	37
31	IN179769B	Swerchirin (1,8-dihydroxy 3,5-dimethoxy xanthone)	Hypoglycemic	NA	NA	38
32	IN232584B	Oleanolic acid	Hepatoprotective	*In-vivo*	Rat/mice	39
33	US6989162B2	Acteoside			Wistar and swiss albino mice	40
34	US6537593B2	(-)-wikstromol (4,4<1>,8-trihydroxy-3,3<1>-dimethoxyliganan-9,9<1>-olide)			Male Wistar rats	41
35	IN235713B	10-O-P-Hydroxybenzylaucubin (agnuside)			Rats	42
36	US7259148B2	2'-p-hydroxybenzoylmussaenosidic acid (negundoside)			Rats	43
37	US6309678B1	Silymarin		NA	NA	44
38	US6592911B2	(-)-Olivil	Anti-oxidant	*In-vitro*	NA	46
39	US6562381B2	(+)-Cycloolivil			NA	47
40	IN220681	(-)-Secoisolariciresinol		NA	NA	48
41	IN217147B	Bergenin			NA	49

(*Contd*.)

Table 1 — List of patents filled under CSIR-INDIA showing medicinal effects of plant bioactives or bioactive enriched fractions (*Contd.*)

S. No.	Publication number	Bioactive compounds	Activity	Study type	Cell line/ Animal model	Reference No
42	IN242799B	Cambogin			NA	50
43	IN241827B	3',5-Dihydroxy flavone 7-0-P-D-galacturonide-4'-0-(3-D-glucopyranoside	Bio-enhancer	NA	NA	52
44	US6979471B1	Glycyrrhizin and glycyrrhizic acid		*In-vitro*	Breast cancerous cell line MCF-7	53
45	US6858588B2	Nitrile glycoside NIAZIRIDIN			Assays	54
46	IN233906B/ WO 2003080059	Lysergol			Disk diffusion assay	55
47	US8383690B2	Oenothein C	Anti-ulcer	*In-vivo*	Rat	58
48	IN188667B	Phenolic glycoside		*In vitro/ In-vivo*	Isolated gastric glands/Rat	59
49	US7855200B2	Oroxylin A, Chrysin, Baicalein		*In-vivo*	Rat	60
50	IN191415B	Z and E gugulsterones	Hypolipidemic	*In-vivo*	Rat	61
51	US8921417B2	Diterpene (16[alpha]-hydroxycleroda-3,13(14)Z-dien-15,16-olide	Anti-dyslipidemia		Male golden Syrian hamster	62
52	US6638546B2	Methyl palmitate	Anti-muscarinic	*In-vitro/ In-vivo*	Atria, ileum and bladder tissues of guinea pig	63
53	IN148265B	guggul resin	anti-platelet aggregation , hypolipidemic	*In -vitro*	NA	68

from this medicinal plant. The bioactive constituents were evaluated for its effects on drug-resistant bacterial infections either alone or in combinations with other bioactives. For example, the bioactive alpha-arteether semi synthetic drug from *A. annua* was evaluated for its efficacy against gyrase mutant bacteria which are resistant to quinolone drugs and can be used as a therapeutic agent for treating drug-resistant bacterial infections, and also act as an antifungal agent[7].

Bioactives from *Oenothera biennis, Trachyspermum ammi*, and *Plectranthus mollis* were investigated for their anti-bacterial effects. For example, a pharmaceutical composition comprising an effective amount of 3.5-dihydroxy-4-pent-4'-enoyl-1'-oxymethylbenzoic acid (Oenostacin) and a phenolic acid derivative isolated from alcoholic extract of root from plant *Oenothera biennis* was found to be effective against *Staphylococcus epidermis*. The formulation comprising an effective amount of the bioactives can be in the form of powders, ointments, drops, buccal/nasal spray or suppository form[8]. Another formulation comprising thymol in the range of 20 to 50% w/w obtained from *Trachyspermum ammi*, mint oil in the range of 0.1 to 0.5% w/w obtained from a hybrid of *Mentha spicata* and *Mentha arvensis* along with pharmaceutically acceptable additives was found to be effective in the treatment of drug-resistant bacterial infections. The anti-bacterial activity was tested by Disk diffusion assay[9].

Anti-tubercular actives

Bioactives belonging to the class of diterpernes and alkaloids were also found to be effective against *Mycobacterium tuberculosis*. For example the diterpene 2S,4aS,4bS,8aR,9R,10aS)-2,4b,8,8-tetramethyl-2 vinyltetradecahydrophenanthrene-4a,8a,9,10a-tetraol isolated from aerial parts of *Anisochilus verticillatus* was found to prevent and inhibit the growth and progression of tuberculosis in mammals[10]. Further, a formulation comprising piperine along with pharmaceutically accepted excipients was found to be effective in treating tuberculosis and leprosy when investigated in humans[11]. A pharmaceutical formulation consisting of corosolic acid and/or 5-Hydroxy-6, 7, 3', 4'-tetramethoxyflavone from *Plectranthus mollis was* found to be effective against infections caused by *M. tuberculosis*. The bioactives were found to possess a half maximal inhibitory concentration in the range of 4.37 to 4.93 μg/mL[12].

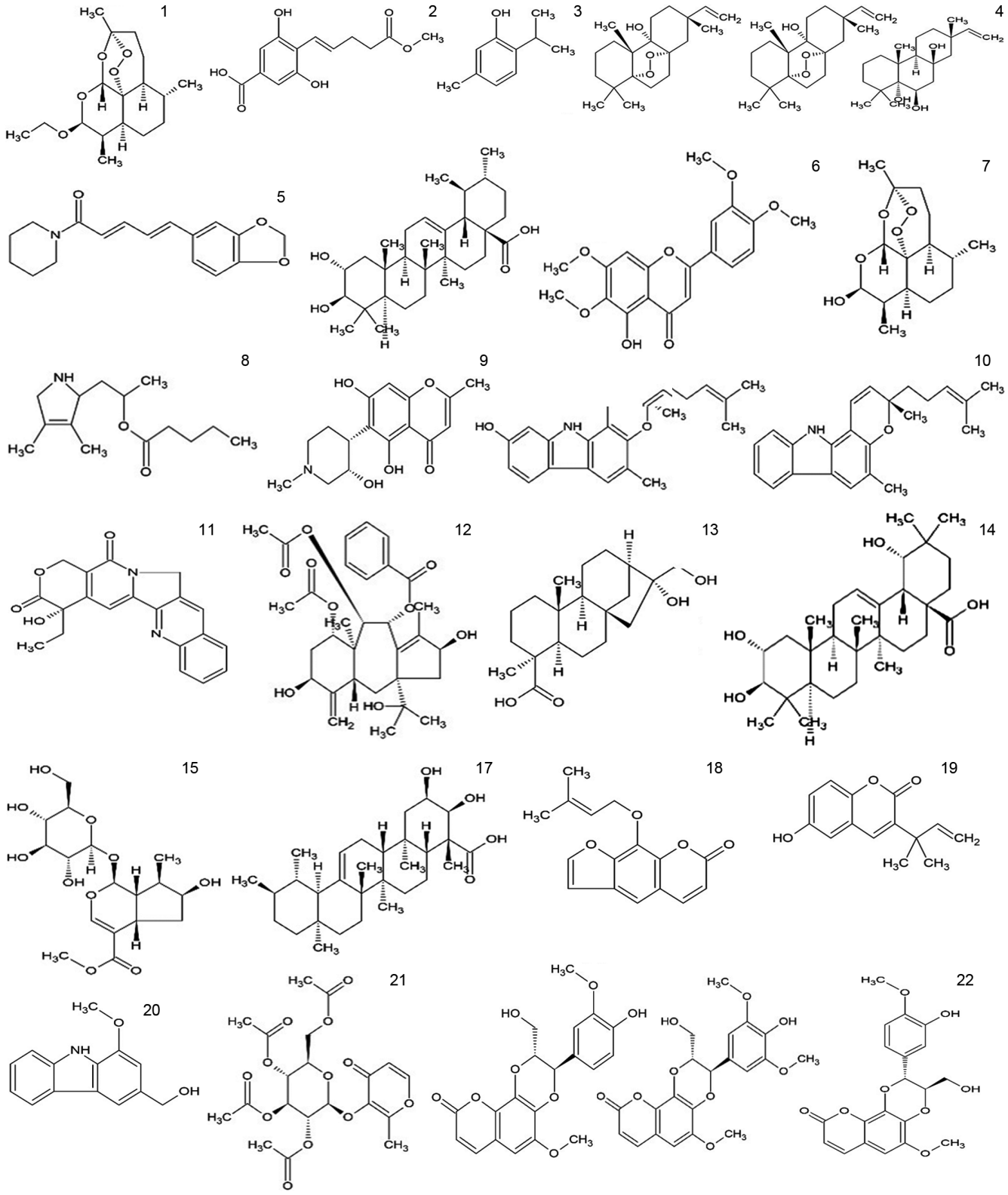
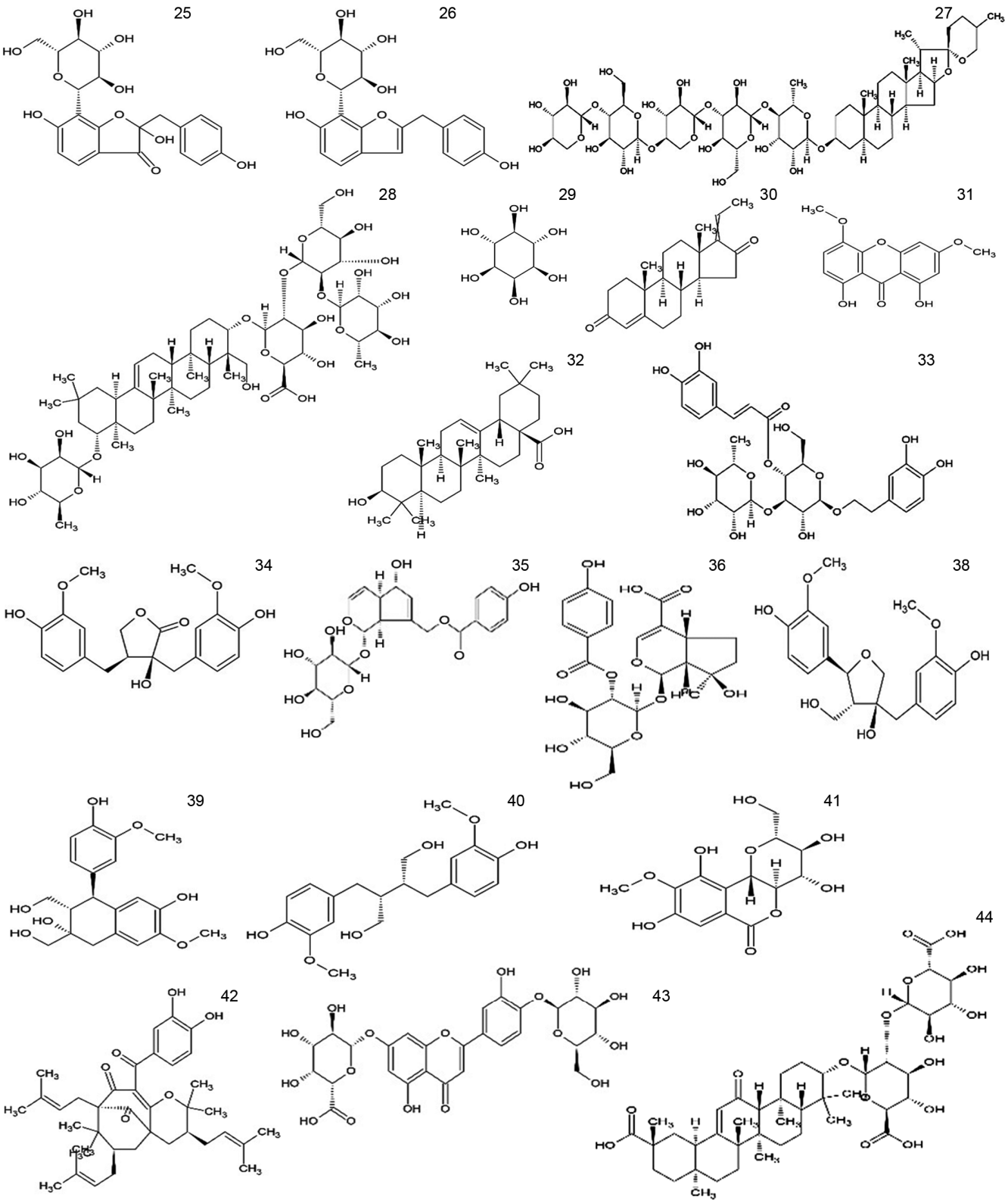


Fig. 3 — Chemical structures of bioactives enlisted in Table 1. (*Contd*.)



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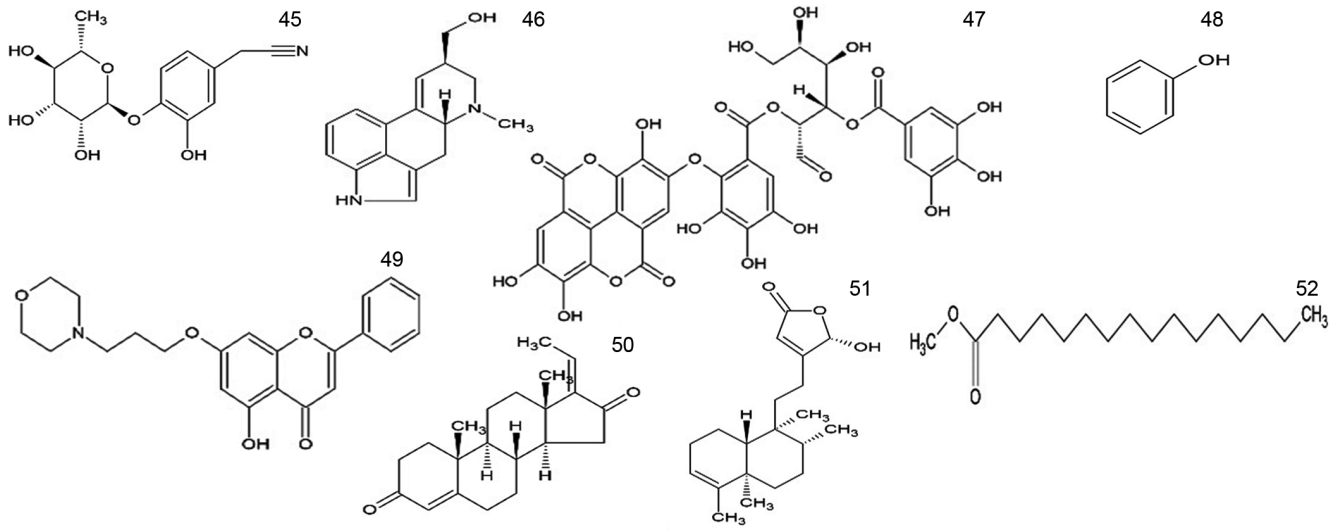

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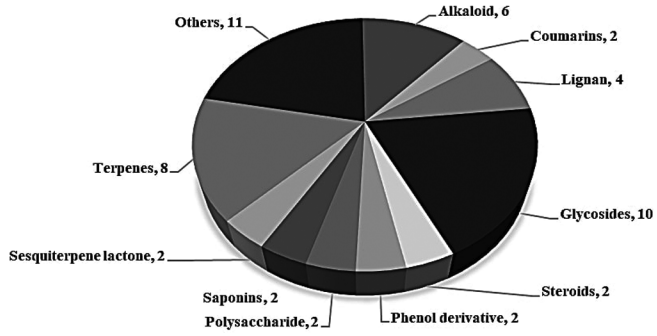

Fig. 4 — Analysis based on chemical classification of bioactives.

Anti-malarial actives

The natural product based anti-malarial therapy comprising from *A. annua* is a well-known and the bioactive was first isolated in 1972[13]. Chemically, artemisinin is a sesquiterpene lactone with a rare peroxide bridge linkage. CSIR's patent portfolio in this area mainly includes improved process for the synthesis of *arteether, artemisinin* and hence, the details were excluded from further discussion. However, the analysis reveals that a formulation comprising an effective amount of dihydroartemisinin and a vegetable oil selected from groundnut, sesame, and tea oil was effective against multi-drug resistant *Plasmodium yoeliinigerienses* parasite. The ratio of dihydroartemisinin and vegetable oil in the formulation was 0.022-0.33:1 w/w and was suitable for oral, intrarectal, and intramuscular routes. It provided maximum bio-availability in comparison to other artemisinin derivatives such as artemether and arteether[14].

Anti-fungal actives

The bioactive 2-(3, 4-dimethyl-2, 5-dihydro-1h-pyrrol-2-yl)-1-methylethyl pentanoate isolated from *Datura metel* was found to possess anti-fungal activity when tested in mice[15].

Anti-cancer actives

There were around 8 patents disclosing the efficacy of bioactive constituents against cancer and associated conditions. Most of the bioactives which were found to be effective against certain tumours when evaluated in *in-vitro* assay models were alkaloids and terpenoids. For example a formulation consisting of chromone alkaloid dysoline (5,7-dihydroxy-6-(3-hydroxy-1-methylpiperidin-4-yl)-2-methyl-4H-chromen-one) isolated from bark of *Dysoxylum binectariferum* was evaluated on different cancer lines such as human colon (Colo 205, HCT116) cell line, human fibrosarcoma (HT1080) cell line, human Lung cancer (NCIH322, A549) cell line and human Leukemia (HL-60) cell line[16]. The formulation was found to inhibit cell growth, proliferation and also inhibited the pro-inflammatory cytokines.

The alkaloids, mahanine, and mahanimbine present in the ethanolic extracts of *Murraya koenigii* leaves were found to be effective in inhibiting cell proliferation against seven different types of cancer such as glioma, cervical carcinoma, lymphoid leukaemia, myeloid leukaemia, pancreatic cancer, colon cancer and lung cancer. The bioactives were found to effective at a dose range between

50-150 mg/kg body weight for a period of 0 to 9 days in the treatment of cancer[17]. The alkaloid camptothecin from twigs and stems of *Nothapodytes foetida* was also found to be effective against cancer[18].

Brevifoliol a diterpenoid found in the chloroform extract in the leaves of *Taxus wallichiana* was found to inhibit cancer cell growth when evaluated in human colon (COLO-320DM) cell line, breast cancer (MCF-7) cell line, oral cancer (KB-403) cell line, WRL-68, ovarian PA-1, colon (Caco-2)[19]. The diterpenoid ovatodiolide or phyllocladan-16-alpha, 17-dihydroxy-19-oic acid present in the aerial parts of *Anisomeles heyneana* were found to be effective against Human acute monocytic leukaemia cell line (Thp-1) at a concentration of 0.1-99 wt/wt of the composition[20].

Alcoholic extracts rich in triterpenoids such as Arjunic acid from the barks of *Terminalia arjuna* tested were found to be effective against Human cancer cell lines, breast (MCF-7), ovary (PA-1), liver (WRL) and colon (COLO-320, CaCo2) cancer cells at a concentration of about 0.2-0.04% of the composition[21].

The glycoside loganin, 2′, 3′, 4′, 7-tetra-O-acetyl-6′-O-propionylloganin from the aqueous fruit pulp extract of *Strychnos nux-vomica* and its semi-synthetic analogues[22], pectic polysaccharide from *Feronia limionia* were also found to possess anti-tumour properties[23].

Anti-inflammatory actives

Bioactives from *Boswellia serrata*, *Aegle marmeloscorrea* and *Ruta graveolens* L were found to possess anti-inflammatory activity. Boswellic acids isolated from gum resin extract of *B. serrata* showed anti-inflammatory effects when evaluated in Guinea-pig serum and rats[24]. Imperatorin, which is a furocoumarin was found to be present in mature fruits (3.12%) immature fruits (0.89%) and ripe fruits (1.71%) of *A. marmeloscorrea.* Studies revealed that Imperatorin was effective in inhibiting nitric oxide synthase in inflammatory conditions[25]. The coumarin, 3-(1, 1-Dimethyl-Allyl)-6-Hydroxy-Chromen-2-One (Coumarins) isolated from *R. graveolens* diethyl ether fraction was also found to be effective in suppressing LPS induced inflammatory condition like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) when administered at a dose ranging from 40 to 160 mg/kg body weight or 5 μg/mL in mice. Its elucidated mode of action related to the inhibition of nitric oxide synthase[26].

Anti-asthmatic actives

The analysis reveals that bioactives from *Punica granatum* and *Murraya koenigii* were evaluated for their anti-asthmatic effects. The bioactive 1-methoxy-3-formylcarbazole isolated from the bark of *Murraya koenigii*[27] and 2-methyl-pyran-4-one-3-0-ß-D-2", 3", 4", 6"-tetra-O-acetyl glucopyranoside (MPTAG) isolated from leaves of *P. granatum* were found to be safer and more effective for treating asthma[28]. Formulations comprising effective dose of the bioactive along with pharmaceutically accepted excipients were evaluated using rat models for treating asthma and COPD and found to exhibit 73.1% inhibition of phosphodiesterase-4 enzyme.

Immunomodulatory actives

Amongst the evaluated medicinal plants, bioactives from cleome viscose and *Picrorhiza kurroa* were found to possess immunomodulatory effects. A pharmaceutical formulation consisting of coumarinolignoids was found to act as an immunomodulator for initiating both humoral and cell mediated immunity at a dose of 25-100 mg/kg body weight in mouse. The coumarinolignoids was found to be present in the seed extract of cleome viscose[29]. Further the bioactive enriched fraction from picrorhiza containing polysaccharide was found to possess significant immunomodulatory and anti-complimentary properties. This bioactive fraction was devoid of cucurbitacin iridoids and their glycosides[30].

Spermicidal active

A formulation comprising of acaciaside-A, acaciaside-B (acylated bisglycoside saponins) was found to be effective for their spermicidal activity when investigated in rat models using sander and cramer assay. The bioactives were present in the seeds of *Acacia auriculiformis* and extracted using methanolic extract. Such composition consisting of the said bioactive was found to be useful in lubricated condoms, jelly-filled plunger-type applicators, pessaries, films, foams, squeezable tubes, cervical rings, sponges and acts as a viral envelope lipid peroxidation stimulator, sperm membrane lipid peroxidation stimulator etc[31].

Anti-diabetic actives

Evaluation of the anti-diabetic effects of the bioactives from the medicinal plants was one of the major focus by the inventors from CSIR India.

For example glycosides of glucopyranosides present in the alcoholic extract of *Pterocarpus*

marsupium heartwood were found to be effective anti-diabetic agents. These actives included 2, 6-dihydroxy-2-(P-hydroxybenzyl)-3(2H) benzofuran-7-C-.beta.-D glucopyranoside and 6-hydroxy-2-p hydroxybenzylbenzofuran-7-C-beta-D-glucopyranoside. These bioactive constituents mainly lowered the blood glucose levels[32,33].

The saponins, tigogenin pentaglycoside, tigogenin-3-O-[alpha]-L-rhamnopyranosyl-1-3-[beta]-D-xylopyranosyl-1->4-[beta]-D-glucopyranosyl-1-3-[beta]-D-xylopyranosyl-1->4-[beta]-D glucopyranoside isolated from the aerial parts of *Chlorophytum nimmonii* were found to be effective as anti-hyperglycemic agents when tested in rat models[34].

Formulation comprising lupinoside PA (LPA4) isolated from the roots of *Pueraria tuberose* showed anti-diabetic activity when examined on 3T3-L1 cell line, and 3T3L1 adipocyte cells. The actives were found to be effect when administered at a dose concentration ranging from 1 to 40 mg/kg body weight. The study further revealed that the bioactive enhances insulin signal in a signal transduction pathway mainly by acting on the augment glucose transporter-4 (Glut4) phosphorylation and Glut4 translocation[35].

The bioactive inositol monomethyl ether isolated from *Bougainvillaea spectabilis*[36], gugulipid isolated from aerial branches *Commiphora wightii* was found to be effective in preventing and controlling hyperglycemia along with cognitive dysfunction and skin infections[37]. Swerchirin (1, 8-dihydroxy 3, 5-dimethoxy xanthone) isolated from *Swertia chirayita* also showed hypoglycaemic activity[38].

Hepatoprotective actives

The triterpenoid oleanolic acid and the terpene acteoside showed hepatoprotective effects in rat study models. Oleanolic acid present in the roots of *Lantana camara* was found to be effective against hepatitis, arthritis and oedema when administered orally[39]. On the other hand acteoside present in the aqueous/alcoholic extract of aerial parts of *Colebrookea oppositifolia* showed hepatoprotective effects by acting on serum glutamine transferase (GPT), serum glutamine transferase (GOT), serum alkaline phosphatase (ALP), serum bilirubin, serum triglycerides (TG), lipid peroxidase (LP). The bioactive was found to be effective even at a low-dosage ranging from 1.25 to 5 mg/kg body weight when administered orally to mice[40]. Composition containing pheol(-)-wikstromol (4, 4<1> and 8-trihydroxy-3, 3<1>-dimethoxyliganan-9, 9<1>-olide) isolated from bark and leaves of *Cedrus deodara* showed hepatoprotective activity when evaluated in male rats[41].

The bioactive component; 10-O-P-Hydroxy–benzylaucubin (agnuside) &2'-p-hydroxybenzoyl mussaenosidic acid (negundoside) present in the aqueous alcoholic extracts of *Vitex negundo* were also found to be effective as a hepatoprotective agent when evaluated in rat models[42,43]. These bioactives reduced elevated levels of serum glutamin-pyruvic transaminase (GPT), serum glutamin-oxalo acetic transaminase (GOT), serum alkaline phosphatase (ALP), serum tryglycerides, and bilirubin in the hepatic associated conditions. The bioactive Silymarin found in the *Silybum marianum* seeds improved the defense of hepatic cells against different toxic substances by counteracting the oxidative stress[44].

Anti-oxidant actives

Natural products have played an important role as drugs due to their unique mechanism of action and general safety. Among the various mechanisms exhibited by substances originating from natural products, anti-oxidant effects have been one of the most studied and pursued mechanisms. Given the importance of oxidative stress and the deleterious effects of reactive oxygen species in several diseases, it is very important to evaluate the potential anti-oxidant activity of a compound or extract in a given therapeutic condition and its effective dosage[45].

The analysis reveals that CSIR, India as the assignee had quite a number of patent filings which disclosed the bioactives responsible for their anti-oxidant activity. The effective anti-oxidants belonged to polyphenols, lignins, isoprenylated benzophenone derivative and trihydroxybenzoic acid glycosides. For example (-)-olivil[46], (+)-cycloolivil[47] and secoisolariciresinol[48] obtained from *Stereospermum personatum* wood were found to be an effective free radical scavenger. (+)-Cycloolivil was effective as an anti-oxidant at a dosage of 300 to 380 mg per dose when taken orally, twice a day while (-)-olivil was effective at a dosage of 300 to 400 mg when taken twice a day.

Formulations containing bergenin isolated from the stems of *Tinospora crispa* showed anti-oxidant effects by inhibiting 38.54% DPPH at a concentration of 200 µg/mL and 57.03 per cent inhibition of NO production[49].

On the other hand, other phytoconstituent such as cambogin which is an isoprenylated benzophenone derivative present in the rinds of *Garcini*a *cowa* also possessed anti-oxidant activity[50].

Bio-enhancers

Bio-enhancers are defined as substances that increase the bioavailability and bio-efficacy of active substances with which they are combined without having any activity of their own at the dose used[51]. There were four patents focusing on compositions for enhancing bioavailability of drugs or neutraceuticals from plants and granted to CSIR.

The analysis reveals that the bioactives from *Cuminum cyminum*, *Glycyrrhiza glabra, Moringa oleifera*, *Rivea corymbosa*, *Ipomoea violace* were found to act as a bioenhancer for different drugs.

For example, the bioactive 3', 5-Dihydroxy flavone 7-0-P-D-galacturonide-4'-0-(3-D-glucopyranoside isolated from the seeds of *Cuminum cyminum* using water extract was found to enhance the activity of antibiotics such as ciprofloxacin, macrolides such as erythromycin and amoxicillin, anti-fungal drugs such as fluconazole and amphotericin B, antiviral drugs such as acyclovir and zidovudine, anticancer drugs such as methotrexate, 5-fluorouracil, doxorubicin and cisplatin, cardiovascular disorder drugs such as alprazolam and haloperidol[52].

Glycyrrhizin and glycyrrhizic acid isolated from roots of *G. glabra* using aqueous/alcoholic extract were found to enhance the activity of antibiotics or anti-bacterial agents such as nalidixic acid, norfloxacin, ciprofloxacin and sparfloxacin[53].

Niaziridin isolated from fruit pods of *Moringa oleifera* were found to enhance the bioactivity of commonly used antibiotics such as rifampicin, tetracycline, and ampicillin. Niaziridin was found to enhance the biological activity and the bioavailability of the anti-bioactive through the gastro-intestinal membrane and hence can be useful as a combination therapy with drugs and nutrients. These effects in turn may play a role in reduced drug associated toxicity and duration of therapy[54].

A pharmaceutical composition consisting of lysergol as a bio-enhancer in combination with an antibiotic such as rifampicin, tetracycline & ampicillin showed synergistic effects. Lysergol was isolated from seeds of *R. corymbosa* or *I. violace* using methanol as the solvent. Lysergol provides synergy by aiding the absorption of antibiotics across the cell membrane in animal cells and was effective at a dose ranging from l-10 µg/mL[55].

Anti-ulcer actives

Proton pump inhibitors are the class of drugs currently available for treating recurrent gastric and duodenal ulcers caused by *Helicobacter pylori* infections[56]. The well know proton pump inhibitors include omeprazole, lansoprazole, pantoprazole and rabeprazole[57]. However, these small molecule entities are associated with gastrointestinal ulcers, insufficient gastric mucous membrane protecting action and other related side effects. The analysis reveals that the research activity relating to proton pump inhibitors from natural products resulted into the finding that oenothein C (polyphenol) and phenolic glycoside (glycoside) bioactives acted as potential proton pump inhibitors. Oenothein from the flowers of *Woodfordia fruticosa* was found to be effective in inhibiting gastric proton pump activity and specific anti *H. pylori* activity in rat models[58].

The phenolic glycoside (Glycoside) from the leaves and flower of *Azadirachta indica* was found to control gastric hyperacidity and gastric ulceration by inhibiting H.sup. + -K.sup. + -ATPase in isolated rat gastric glands[59]. Other bioactives such as oroxylin A, chrysin and baicalein isolated from the stem bark of *Oroxylum indicum* was found to be effective in treating gastric-ulcer induced by aspirin in rats. These phtyoconstituents showed up to 77.84% mucoprotective property at dose level of 50 mg/kg of body weight in gastric ulcers induced by aspirin[60]. The activity was around 4 times higher in comparison with the synthetic drug ranitidine for the same dosage level.

Miscellaneous therapeutic agents

Patents disclosing other pharmacological uses of the bioactive constituents such as hypolipidemic, anti-dyslipidemic, and anti-muscarinic activities were grouped under this category. For example Z, Eguggulsterones from the aerial branches of *C. wightii* and guggul-resin were found to impart hypolipidemic effects when administered orally[61]. 16[alpha]-hydroxycleroda-3, 13(14) Z-dien-15, 16-olide from the leaves of *Polyalthia longifolia* was found to show anti-dyslipidemic activity when evaluated in golden syrian hamster[62]. Methyl palmitate obtained from stems, leaves and flowers of *Salvadora persica* L., a mangrove showed anti-muscarinic activity in atria, ileum and bladder tissues

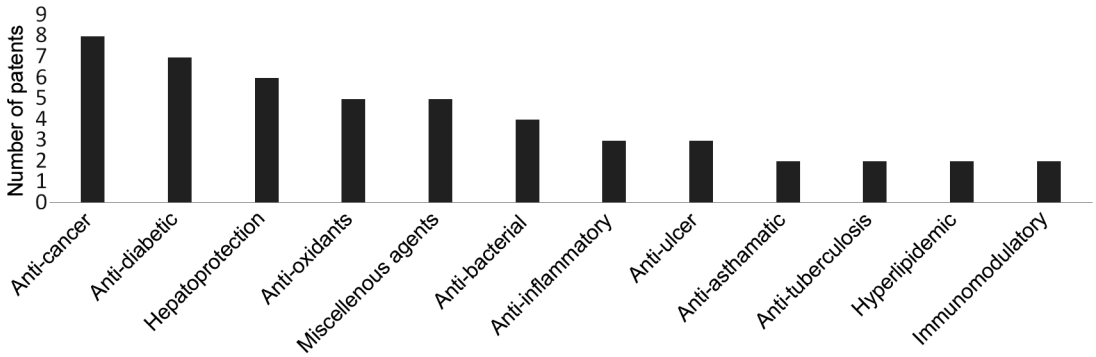

Fig. 5 — Pharmacological activity trend analysis.

of guinea pig and prevented renal colics, bronchial asthma, abdominal cramps, motion sickness and premature delivery by acting as a muscarinic receptor antagonists[63].

The number of the patent filings in each of the above enlisted therapeutic category is depicted in Fig. 5.

Discussion

CSIR-lndia is amongst the top enlisted assignees in terms of filing and securing patents in India as well as worldwide. It has to its credit greater than 90% of the US patents filed by any Indian publicly funded R&D organization and has a wide portfolio of patents in its armory. Amongst CSIR's patent portfolio 67% patents are focused on inventions involving medicinal plants. The data when refined resulted into around 30% patents which disclosed the bio evaluation of different bioactives mainly for therapeutic applications. Indicator variables like the level of activity amongst the natural product types, therapeutic areas, research study designs and patent citation characteristics were examined to gain a general understanding of the extent to which CSIR is active in the area.

Prevalence of diseases such as diabetes, cancer, cardiovascular diseases and obesity is mainly due to alterations in several factors such as lifestyle, pathological, physiological and environmental changes. Earlier research and development pertaining to determine the therapeutically active molecules revolved around developing new molecule which acts on a single target[64]. This discovery resulted into the identification of lead molecules which undergoes a series of drug optimization, pre-clinical and clinical evaluation process. The process involving the identification of active molecule for a specific therapeutic condition to the final approval of the drug product in the market is very complex involving time and cost.

On the other hand, traditional medicinal systems belonging to all cultures have used medicinal plants or herbs as main therapeutic agents. It is considered as safer, generally slow acting, permits long term use, more effective against long standing degenerative diseases, simultaneously treats and protects human body, partially uses body's immune system. Literature survey reveals that a lot of research is being conducted worldwide outside India on herbal medicines. Further, the National Institute of Health in United States has a separate National Center for Complementary and Alternative Medicine. They have specifically funded clinical investigations of alternative plant-based medicines for arthritis, cardiovascular diseases, immunology, digestive and infectious diseases.

Over the past decade, a number of leads from natural resources such as medicinal plants, marine sources, and insects have been explored, which are important for the ongoing multi-target drug discovery[65]. The bioactives from the medicinal plants are being used widely as single-agent or combination formulations in prescription drugs[66]. For example, atropine from *Atropa belladonna* is used as an anticholinergic agent, codeine from *Papaver somniferum* is used as a cough suppressant, colchicine from the genus Colchicum as an antigout active, ephedrine from Ephedra species as a bronchodilator, pilocarpine from *Pilocarpus jaborandi* as a parasympathomimetic and physostigmine from *Physostigma venenosum* as a cholinesterase inhibitor[66].

The correlation between the therapeutic usages of the phytoconstituents from medicinal plants has been investigated by CSIR. Based on the review of around 53 patents filed by CSIR, around 45 medicinal plants

have been explored in terms of their bioactive constituents responsible for around 18 therapeutic conditions. More than 60 bioactive constituents and combinations thereof have been investigated for their therapeutic activity in different study designs. They belonged to alkaloids, glycosides, lignan, sesquiterpene lactone, terpenes etc. The phytoconstituents from *Stereospermum personatum, A. annua* and *Commiphora wighitii* were widely investigated.

A patent to product search for the patents under consideration was also carried out. The search revealed that few of the inventions were actively pursued for product development and now available as herbal-based products in the market. For example alpha arteether from *A. annua* is sold as an anti-malarial drug under the trade name E-Mal. It is protected by the US patent 6127405A. Gugulipid from *Commiphora mukul* is available as cholesterol lowering drug under the brand name Guglip and protected by the patent IN148265B[67]. A hepatoprotective formulation consisting of bioactives from *Picrorhiza kurrooa* is marketed under the brand name PICROLIV. The formulation/bioactive is protected by the patent IN183822B.

A number of bioactives were found to be useful as anticancer agents. They included chromone alkaloid dysoline (5,7-dihydroxy-6-(3-hydroxy-1-methylpiperidin-4-yl)-2-methyl-4H-chromen-one) isolated from bark of *Dysoxylum binectariferum,* mahanine and mahanimbine from the leaves of *Murraya koenigii*, brevifoliol from the leaves of *Taxus wallichiana,* ovatodiolide or phyllocladan-16-alpha, 17-dihydroxy-19-oic acid from the aerial parts of *Anisomeles heyneana*, Arjunic acid from the barks of *Terminalia arjuna.*

The anti-diabetic agents included glucopyranosides from alcoholic extract of heartwood of Pterocarpus marsupium, tigogenin pentaglycoside, Tigogenin-3-O-[alpha]-L-rhamnopyranosyl-1-3-[beta]-D-xylopyranosyl-1-4-[beta]-D-glucopyranosyl-1-3-[beta]-D-xylopyranosyl-1-4-[beta]-Dglucopyranoside isolated from the aerial parts of *Chlorophytum nimmonii*, lupinoside PA (LPA4) isolated from the roots of *Pueraria tuberose,* inositol monomethyl ether isolated from *Bougainvillea spectabilis* and Swerchirin (1, 8-dihydroxy 3, 5-dimethoxy xanthone) isolated from *Swertia chirayita.*

The newly validated biological activities of the bioactives, bioactive enriched fractions or extracts thereof that have been protected by patents are discussed in this review. Few of them are currently being investigated for their use against corona viruses and more specifically against COVID-19 strain. This is mainly because the conventional drugs viz hydroxychloroquine, ritonavir are not as effective as expected and hence the researchers started screening potential active components from traditional herbal medicine in addition to antivirals, biologics and vaccines. In April 2020, Chinese officials also announced the effectiveness of traditional herbal medicines for the treatment of COVID-19 patients.

Drug Controller General of India (DCGI), has for the first time approved the phytopharmaceutical drug repurposed by CSIR, for clinical trial for Covid-19. In collaboration with Sun Pharma, CSIR has repurposed the Phytopharmaceuticals formulation, ACQH (developed for dengue) for coronavirus.

CSIR in collaboration with Ministry of AYUSH, have started clinical trials on four traditional herbal medicines viz *Glycyrrhiza glabra*, *Tinospora cordifolia, Withania somnifera* and Ayush-64 (four-herb formulation comprising of *Alstonia scholaris*, *Picrorhiza kurroa*, *Swertia chirayita*, and *Caesalpinia crista*) for coronavirus. These medicines were proposed to be administered as prophylactic, symptom management, and add-on interventions to modern medicine treatments[68].

The citation analysis reveals that a number of multinational health and personal care companies have cited CSIR's patents revealing the high technical potential of the patents filed by CSIR, India in this area. Some of these MNC companies include Vital Healthcare Pvt Ltd, Janssen Pharmaceutica NV, Progenics Pharmaceuticals, Inc., Affinium Pharmaceuticals Inc, and L'Oreal SA.

Conclusion

Natural substances from plants are an important source of medicines, specifically with respect to their extensive *in-vivo* and *in-vitro* safety testing with no adverse effects, high compatibility in formulating with other ingredients and can be used as an active agent in tablets, capsules, liquids, powders, bars and other delivery systems. This review reveals that continuous R&D efforts to identify and validate new therapeutic or cosmetic applications of the extracts and bioactives from medicinal plants have been made by one of the largest publicly funded organization in India. Further, an attempt to evaluate the mode of action of the identified bioactives, conduct animal

studies, clinical toxicological has resulted in to the development, approval, and launch of herb based therapeutics as well as dietary supplements. Similarly, there exist a large number of prior art literatures disclosing the *in-vitro* bio evaluation data for bioactives from natural sources such as marine organisms, micro-organisms, fungi etc. Such *in-vitro* bio evaluation data on bioactives can be harnessed and considered for further investigation in animal models and clinical research. Additionally, investigations to understand the mechanism of action of intracellular signal transductions of these bioactives can aid in the development of newer herbal based drugs, dietary supplements and cosmeceuticals.

Conflict of interest

The authors declare that there is no conflict of interest.

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