

Review Article

A Review: Bioactive Phytochemicals as Basic Structural Templates for the Development of Newer Medicines for Better Living Health

Anil Kumar Sharma*, Kuldeep Kumar Sharma, Tek Chand Sharma, Pratibha Payal,
Mahaveer Prasad Dobhal and Mahesh Chandra Sharma

Natural Products Laboratory, Department of Chemistry, University of Rajasthan, Jaipur-302004, India

Abstract

The present research paper comprises the significances of plant based treatment of various diseases by ancient researchers and in the present text attempts were also made to explain the various strategies and approaches employed behind the discovery plant based drugs. A collection of the literature containing various examples of secondary metabolites investigated from medicinal plants also furnished in the favor of the plant derives medicines.

*Correspondence

Anil Kumar Sharma,
Email: anilkumarsharma_008@yahoo.com



Keywords: Phytochemicals, phytonutrients, secondary metabolites, drugs, diseases

Introduction

The recent advances in bioassay techniques along with scientific and technological advancements helped the researchers to rediscover the benefits of herbs and spices that were so well known to our forefathers. These benefits are directly connected to the increasing awareness of the impact of food on the well-being and health of a person. According to the literature more than 139 drugs of conventional system of medicines owe their origin to herbs and herbal active principles. Approximately 74% drugs were discovered because of their use in traditional system of medicine.

Importance of phytochemicals for drug discovery

Though the drug industry has almost abandoned their natural products drug development programme (NPDDP) due to several reasons but now they have renewed their efforts in the search of new drugs. There are two reasons for their new fondness for natural products. First and foremost conventional medicines or synthetic molecules have already become ineffective or are in the process of becoming ineffective for the treatment of disease and human ailments, especially for infective diseases due to virus and bacteria resistance to antibiotics. Second, a large number of people throughout the world are now aware about the toxic or detrimental side effects of synthetic medicine. This is the reason that drug industry has engaged itself in the field of natural products and 23 new drugs derived from botanicals and other natural products such as marine, fungi and insects has been introduced from 2001 to 2005, in the market for the treatment of cancer, diabetes, dyslipidemia, atopic dermatitis, Alzheimer's disease, genetic diseases such as tyrosinaemia and Gaucher disease, bacterial and fungal infections.

The healing properties of plants are now exploited by the food industry too. This is the reason phytonutraceuticals, herbal health supplements, fortified food products, functional food, novel food and organic

botanicals are new buzz words. The science of botanicals as health products is well established in India, Europe and China where it has long history of rigorous scientific and regulatory practice.

In most of the European and Asian countries especially India, Germany and China, herbal medicines are an integral part of the health care system. In Europe herbal medicines are prescribed along with pharmaceuticals, in some cases outselling the proffered pharmaceutical for example St. John's Wort outsells antidepressant "prozac" in Germany. Taxol isolated from the bark of the pacific yew (*Taxus brevifolia*), is perhaps the best-publicized example of a plant derived anti-cancer agent. Besides taxol (commercially available as paclitaxel), a number of other anticancer drugs available in the market are either plant derived or synthetically modified structures of the molecules isolated from plants.

As mentioned earlier approximately 74% natural drugs mostly from temperate plants were discovered because of their traditional use. On the other hand tropical plants afforded a small number of drugs because the plants from this region were not vigorously examined phytochemically and biologically as compared to the plants growing in the temperate region. Further out of 0.3 million plants species available on the planet only 15% have been examined phytochemically. A quote from Atharvaveda "The boar knows the plants, the mangoose know the remedial herb. What the serpents, the gandharvas know, I call to aid", suggested that from the animals and birds we can learn a lot about the healing properties of herbs and may develop new medicines.

Due to this reason drug industry in collaboration with chemists, biologists and pharmacologists is working on tropical plants mentioned in ancient ayurvedic text such as Charak Samhita, Shushrut Samhita, Sharangdhar Samhita, Sahastrayogam, and Ashtanghridayam texts to isolate novel drugs from tropical plants.

Discovery and development of new therapeutic agents is a continuing process. In spite of the fact that at present we have at our command a formidable array of modern drugs, the need to discover and invent new agents from plant is genuine and urgent. It has been estimated that satisfactory therapy is available only for about one-third of all presently known human ailments and several diseases, such as cancer, AIDS, senile dementia, auto-immune diseases, to mention just a few, continue to evade reasonable solution. In addition, in the case of infective diseases, causative organisms continue to develop strains refractory to the medicinal agents, to which they were susceptible earlier. It is also predicted that due to several other reasons including global warming etc., infectious diseases may become one of the main scourge of mankind in the near future. Thus, fight against disease must be carried on relentlessly by drugs isolated from natural products [1-3].

Basic strategy behind the discovery of a drug having phytochemicals origin

Several strategies have been or are being exploited to discover and invent new therapeutic agents. However, following three approaches are usually considered i.e. (i) screening (ii) probing human or mammalian biochemistry, physiology and (iii) rational drug design.

Historically, pharmacological screening of the compounds of natural or synthetic origin has been the source of innumerable therapeutic agents. Random screening as a tool in discovering new biologically-active molecules has been most productive in the area of antibiotics [4-10].

Chemotaxonomic considerations and target-directed rapid screening played crucial role in this effort. For a successful outcome the main requirements are to access a large library of molecules/extracts and well-targeted screens. Recent advances in generation of molecular diversity, in molecular biology and instrumentation have provided a special cutting edge to this approach. Now through combinatorial chemistry, it is possible to build up extensive libraries of certain classes of organic compounds [11,12].

The chemistry of natural products has been developed as a major field of scientific endeavor during the last few decades. Now this field has much advanced due to the modernization and computerization of traditional scientific techniques i.e. column chromatography, thin layer chromatography [13], HPLC and spectroscopy. The phytochemists are now exploiting these sophisticated tools for isolation and investigation of structure of compounds available even in small quantities with the help of modern separation and spectroscopic techniques.

Examples of some recently discovered biologically active Phytochemicals

The discovery of some of the recently isolated biologically important plant constituents is being summarized below. Kyroda *et al.*, have isolated a novel polyoxygenated 5 β -cholestane diglycoside, i.e., galtonioside A (**1**) from the bulbs of *Galtonia candicans* which was found active against HL-60 leukemia cells and various other cancer cell lines [14]. *Fissistigma bracteolatum* chat. (Arrnonaceae) and its other species mostly grown in Vietnam and south East Asia are used in the traditional medicine, especially to stop wound bleeding for treatment of infection and for enhancement of blood circulation [15].

A class of linear antibiotic peptides e.g. peptaibols were biosynthesized by soil fungi such as *Trichoderma*, *Hypocrea*, *Emericellopsis* and *Boletus* genus. Some of them were able to induce various biological activities such as uncoupling of oxidative phosphorylation in mitochondria, enhancements of Ca⁺² dependent catechol amine release from adrenal chromaffin cells, hemolysis, cell fusion and to inhibit amoeba cell multiplication [16].

Oenothera biennis (Onagraceae) commonly known as evening primrose, cultivated in Indian gardens, and seeds of this plant are of great pharmacological importance as dietary source for the formation of prostaglandins and related hormones [17]. Besides this, the plant is reported to possess antitumour and antithrombic properties [17]. Ethyl acetate fraction of the root of *Oenothera biennis* yielded gallic acid and possessed antibacterial activity against *Klebsiella pneumoniae* and *Streptococcus mutans*, while n-butanol fraction was found active against *Escherichia coli* [17].

The root of *Vitex negundo* Linn. (Verbanaceae), for the showed anti-inflammatory activity and is comparable to diclofenac sodium [18]. Similar chloroform extract of the seeds of the *Vitex negundo* containing 3 β -acetoxyolean-12-en-27-oic acid; 2 α , 3 α -dihydroxyolean-5,12-dien-28-oic acid and 2 β , 3 α -diacetoxyolean-5,12-dien-28-oic acid exhibited significant anti-inflammatory activity [19].

Caffeine (**2**), theobromine (**3**) and theophylline (**4**) isolated from tea, coffee, coca and cola have several common pharmacological properties. They stimulate central nervous system (CNS) relax cardiac muscle and produce diuresis by acting on kidney. Caffeine stimulates CNS and has a weak diuretic action where as theobromine acts in reverse way. Theophylline has more powerful diuretic action than caffeine. It also relaxes involuntary muscles more effectively than theobromine or caffeine. Theophylline is the prototype drug of this class used to manage asthma and apnea [20].

The wood of *Helicteres isora*, a large shrub found in India, south east Asia and China is used as anthelmintic, colic and aphtha, while fruits are used as colic, anticonvulsant and abdominalgia [21]. Hattori and co-workers have reported an inhibitory activity of water extract of fruits of the *H. isora* against reverse transcriptase from avian myeloblastosis virus (AMV-RT) and anti human immuno deficiency virus type-I (anti HIV-I) activity [21].

Ryu and co-workers have isolated three steroidal glycosides viz. wondosterol (A-C) from a Korean marine sponge which were found moderately cytotoxic against P-308 murine leukemia cells and showed antibacterial activities against *Pseudomonas aeruginosa* and *Escherichia coli* [22].

Thara *et al.* have isolated new phenolic glycosides named eriosemasides, eriosematin and four known phenolic constituents from the n-BuOH soluble fraction of the root of *Eriosema tuberosum*. All the phenolic compounds were

found fungitoxic. All these isolates were tested for their antifungal activity against the growth of *Cladosporium herbarium* using bioassay technique. 3,4-Dihydro-4-methoxy naphtha quinone-2-carboxylic acid (**5**) was found to be responsible for this activities [23].

The new nor-triterpene quinines, amazo-quinone (**6**) and (7*S*,8*S*)-7-hydroxy-7,8-dihydro-tingenone (**7**) and the new nor phenolic triterpenes 7,8-dihydro-6-oxo-tingenol (**8**), 23-nor-6-oxo-tingenol (**9**) and 23-oxoiso-tingenone (**10**) were isolated from *Maytenus amazinica* which showed antitumor activity against cancer cell lines [24].

Plants of *Solanum* species are useful as tonics, antirheumatics, remedies for colds, fevers, dizziness and anticonvulsants. They are also used as vegetables for their high nutritive values. Some of the *Solanum* species have been reported for their antiviral, anticancer, anticonvulsant, and anti-infective activities [25,26]. Thus *Solanum* species have attracted the attention of researchers as they are rich source of steroid drugs [27] or precursor for the steroid drugs. Steroidal raw materials have been found useful in cardiovascular therapy [28], human abortifacients, anti-inflammatory agents [29], menopause regulants and are now known to influence the CNS. Many researchers have investigated *Solanum* species for their steroidal sapogenin [30] and alkaloidal content. Recently fruit of *Solanum wrightii* were examined chemically for its solasodine content. Pharmaceutically important compounds diosgenin and solasodine (**11**) were isolated from *Solanum verbascifolium* in appreciable amount [31]. The leaves of *S. mammosum* were found to contain solasodine, tomatidine, solaverbascine, progesterone, 16-pregnenolone, and other compounds. Telek *et al.* reported good yield of crude solasodine, which is important for the commercial synthesis of 3 β -acetoxy-5,16-pregnadiene-20-one [32]. The berries of *Solanum nigrum* was investigated for solasodine content [33] and it was found that the ripe berries and unripe berries contains 5 to 6% and 4 to 5% solasodine respectively. Thus *S. nigrum* could be exploited for the commercial synthesis of new drugs. Tigogenin, diosgenin and sitosterols (**12**) have also been reported from the plant [34-36]. The unripe berries of *Solanum nigrum* possess anticancer activity [35]. Chemical investigation afforded 3-O- β -lyco-tetraoside, desgalactotigonin, and solamargine (**13**) from berries and showed inhibitory activity against JTC-26. It has also been shown that the crude alkaloid fraction isolated from the leaves of *Solanum melongena* exhibited significant analgesic effect [36] and some CNS depressant action in mice.

Acanthospermum species [37-40] have led to the isolation of *cis,cis*-germacranolides (**14**) and melampolides⁴¹ (**15**). These compounds showed *in vivo* anticancer activity [42]. Bioassay-guided fractionation of the ethyl acetate soluble portion of the stem of *Tephrosia toxicaria* [43-45] led to the isolation and characterization of a new butenylated flavanone (**16**) and a new retinoid (isoliquiritigenin), isoflavone (genistein), the flavone (chrysoeriol) and the rotenoid- α -toxicarol by using the enzyme quin-red (QR) induction assay. All of these isolates were evaluated for their potential cancer chemopreventive properties [46].

The roots of *Withania somnifera* commonly known as Ashwagandha showed antitumor and bacteriostatic activities [47]. It is a rejuvenating herbal drug which controls the synthesis of α -2-macroglobulin during inflammation [48,49]. Extracts of the roots of this plant have also shown neuro-pharmacological [50] and anti-stress activity [51]. The plant is also used as an adjuvant during radiation therapy [52]. α -Arasone isolated from *Acorus calamus* was found to exhibit anticarcinogenic [53], strong sedative and antispasmodic activities [54].

Lapachol (**17**) isolated from bark of the *Acacia calamus*, was shown active against different types of tumors and anti-inflammatory activity [53]. Naphtho[2,3,b]furan-4,9-dione (**18**) and 2-(1-hydroxyethyl)naphtho[2,3,b]furan-4,9-dione (**19**) were active against tumor cells and these compounds were also found to have immunomodulatory effect on human granulocytes and lymphocytes. -Lapachone (**20**) showed anti-inflammatory activity comparable to that of the antipsoriatic drug anthralin, 2-acetyl-8-hydroxynaphtho[2,3,b]furan-4,9-dione (**21**) was the most potent inhibitor among the known lapachol related compounds [55]. Betulin and betulinic acid isolated from *Zizyphus* species was also recognized as potent antitumor agents [56].

Ferestin-A (**22**), a labdane type of diterpenoid, isolated from *Hedychium forreslii* have shown anti-neoplastic activity [57]. The methanolic extract of *Tabernaemontana calcarea* [58] resulted in the isolation of the new cytotoxic

indole alkaloids viz. vocangine, isovocangine, coronaridin, voarcristin. All these compounds exhibited cytotoxic activity against the ovarian cancer cell line.

Two new flavanone glucoside, (2*R*) and (2*S*)-5-O--D-glucopyranosyl-7,4'-dihydroxy-3',5'-dimethoxyflavone (pervianoside) and a new flavanol glycoside quercetin 3-O-(-D-glucopyranosyl)-(1-2)-(α-L-rhamnopyranosyl)-(1-6)-galactopyranoside were isolated from leaves of *Thevetia peruviana* [59,60].

A new iridoid citrifolinoside have been isolated from the leaves of *Morinda citrifolia* [61]. The leaves and fruit extract of this plant exhibited anticancer activity. Gaddipati *et al.* have reported that picroliv, a purified iridoid glycoside isolated from root of *Picrorhiza kurrooa*, protect cells and regulates the gene expression during hypoxia or reoxygenation [62]. Picroliv have also shown protective effect against chemical carcinogenesis in mice [63,64].

Methanolic extract of leaves and twigs of *Guatteria cardoniana* have been investigated chemically for the alkaloid the contents which showed *in vitro* anticancer properties [65]. Illurdins (**23**), a group of sesquiterpene antibiotics isolated from fungus *Coprinopsis episcopalism* [66] was investigated as antitumor agents.

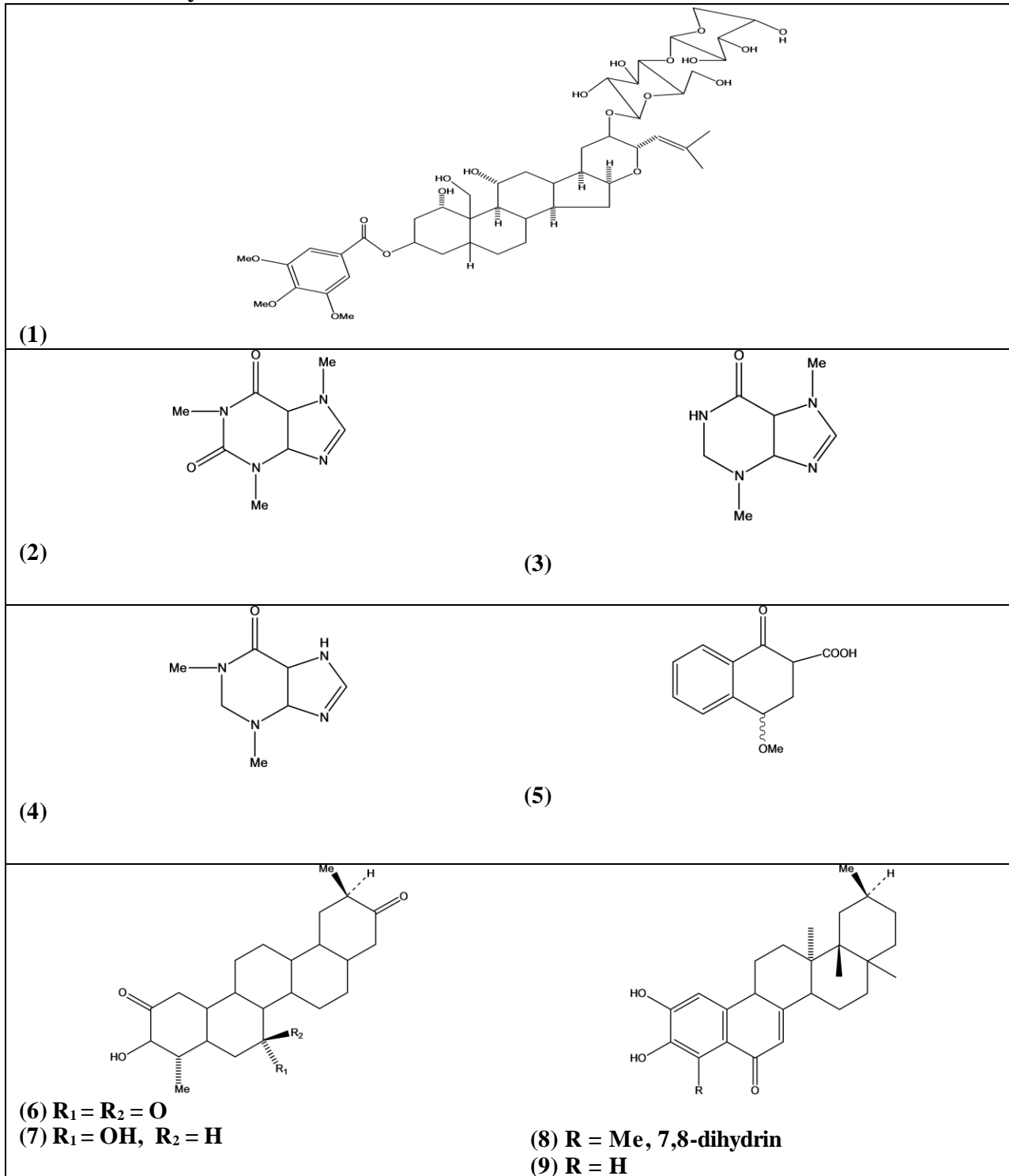
In our laboratory plumieride isolated from *Plumeria biocolar* in our laborites was synthetically modified to get various plumieride based derivatives, which showed significant antitumor activity [67-69].

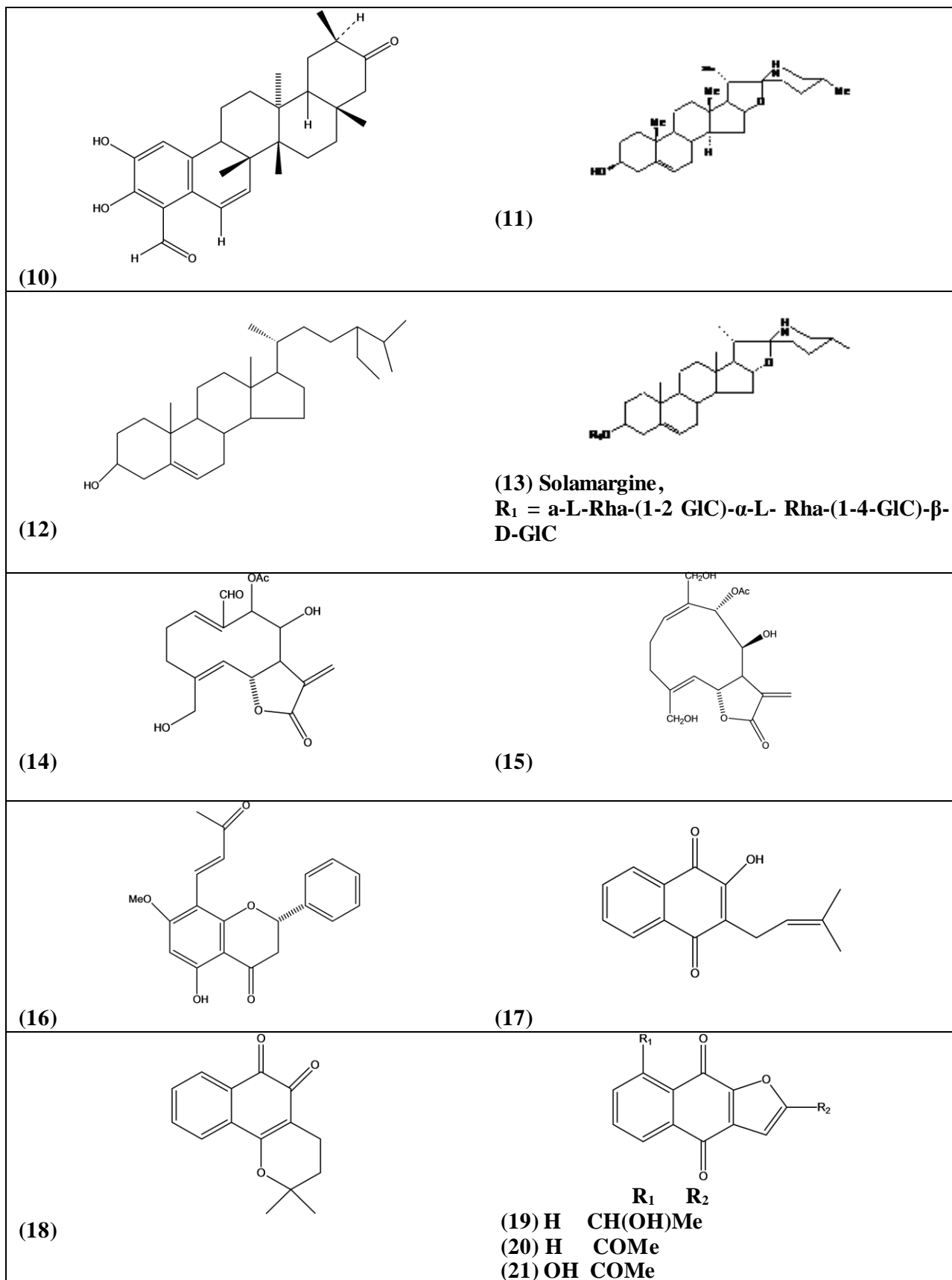
Capparenol-13, isolated from *Capparis spinosa* have shown anti-inflammatory activity [70-72]. Ethanolic extract of the leaves of *Bouchea fluminensis* afforded an active compound lamide which to showed anti-inflammatory activity [73]. A new iridoid, pedunculariside, isolated from *Vitex peduncularis* showed significant anti-inflammatory activity [74]. An attempt has been made to locate the biologically active fraction of plant *Verbena officinalis* (verbenaceae) for its anti-inflammatory activity [75]. The prenylisoflavone characterized as warangalone (**24**) was isolated from the bark of *Erythrina addisoniae*. It was found a powerful inhibitor of protein kinase and also showed marked anti-inflammatory activity [76]. Volutamides (**25-28**), halogenated alkaloid of amino acid origin have been isolated from the *Convolvula lamouroux* [77] having anti-inflammatory activity. Tanetin (**29**), designated as 6-hydroxykaempferol-3,7,4'-trimethyl ether a new flavanol has been isolated from leaves, flowers and seeds of *Tanacetum parthenium* and showed remarkable anti-inflammatory activity [78].

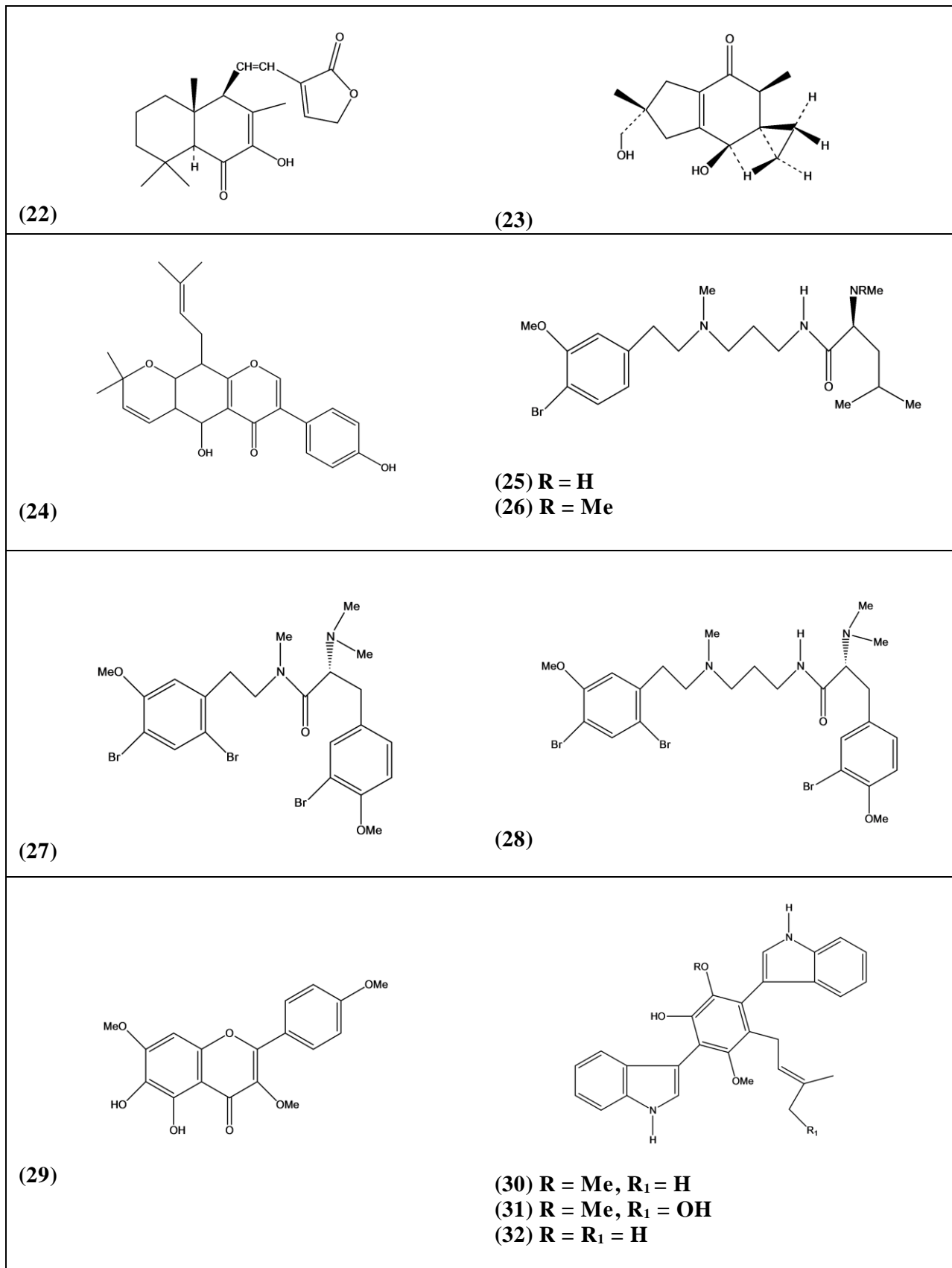
Anti-inflammatory activity was detected in the dichloromethane extract of the aerial part of *Eupatorium buniifolium*. Three compounds were isolated from this extract, by using bioassay-guided fractionation and afforded 5,7,5'-trihydroxy-3,6,2',4'-tetramethoxyflavone, scopoletin and centaureidin. These compounds were found to inhibit the odema by 67.3%, 59.8% and 49.7% respectively. Several species of the *Epacridaceae* family showed inhibitory activity against multiresistant *Staphylococcus aureus*. A new compound kaempfero, 3-(2,4-di-E-p-coumaroylrhmnoside) was isolated from *Pentachendra pumila* and showed significant antimicrobial activity [79]. Four new prenylated bis-indolyl benzenoid metabolites ochrindoles (**30-33**) were isolated from *Aspergillus ochraceus*.

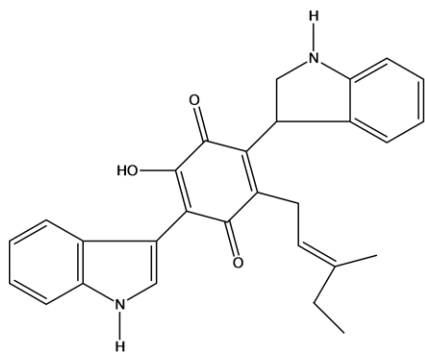
Shizuo and co-workers [80] isolated three novel catechin derivatives, pilosanols (**34-36**) which showed antibacterial activity against *Staphylococcus aureus*. A novel alkaloid, purpurone having ATP-citrate lyase inhibitory activity was isolated from the marine sponge (*Iotrochota* species). Purpurone was the first example of a new class of marine product [81]. The root bark of *Turraea nilotica* contain nilotin (**37**), a new limonoil which showed significant activity as an antifeedant against larvae of the Colorado potato beetle *Leptonotrasra deemlineata* [82]. Griffonilide (**38**), lithospermoside (**39**) and agnoflorine (**40**) isolated from the roots of *Semiaquilegia adoxoides*, were found to induce diuresis and may be used for treating stranguria, swelling and detoxication [83]. A new naturally occurring polyhydroxylated piperidine alkaloid α-1-C-ethylgagomine (**41**) was isolated from *Adenophora triphylla* [84].

Structure of some Phytochemicals

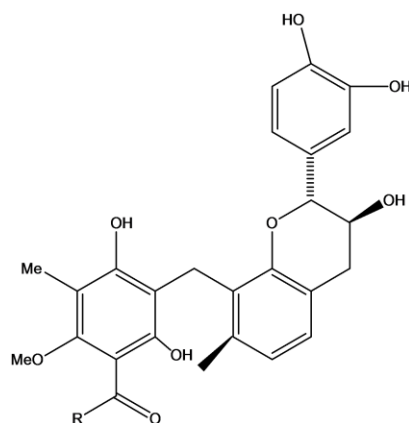








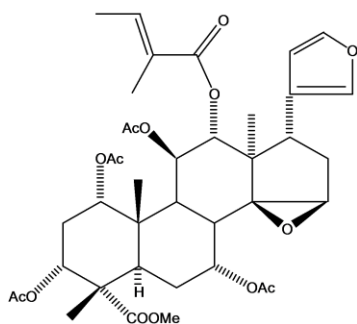
(33)



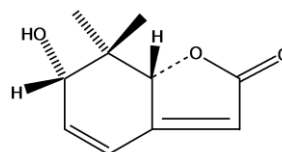
(34) $R = \text{CH}(\text{Me})\text{CH}_2\text{-Me}$

(35) $R = \text{CH}(\text{Me})_2$

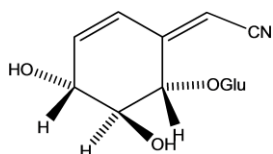
(36) $R = \text{CH}_2\text{-CH}_2\text{-Me}$



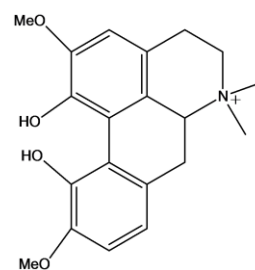
(37)



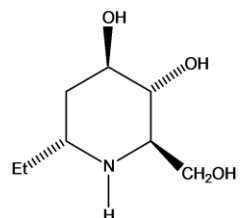
(38)



(39)



(40)



(41)

Conclusion

Encouraged by these remarkable achievements in the field of plant chemistry, the investigation were therefore, undertaken to isolate and characterize the active principles of the medicinally important and widely used plants for the healthy life of the livings.

Acknowledgement

Authors wish to thanks Head, Department of Chemistry, University of Rajasthan for providing library facilities.

References

- [1] Vidyalankar S, *The Holy Vedas*, Clarion Books, Delhi 1983, 385.
- [2] Mullar JM, Schlitter E, Bein HJ, *Experiential* 1952, 8, 338.
- [3] Bentley KW, *Endeavor* 1964, 23, 97.
- [4] Serturner FAW, *Trommsdorffs Journal Der Pharmazie* 1805, 13, 234.
- [5] Colman & Green G, *Nature (London)* 1946, 157, 465.
- [6] Sukh Dev, *Proc. Indian Natl Sci Aacad* 1988, 12, 54.
- [7] Hileman B, *C & EN* 1996, 22, 9.
- [8] Wolf ME, *Burger's Medicinal Chemistry and Drug Discovery*, Wiley-Interscience, NY 1995, 2.
- [9] Gerhartz W, Yamamoto YS, Compbell FT, Prefferkorn R, Rounsaville IF, *Ullmann's Encyclopedia of Industrial Chemistry* 1985, 467.
- [10] Kroschwitz JI, Howe-gran M, *Ommer Enclopedia of Chemical Technology* 1992, 2, 893.
- [11] Nisbet LJ, Westley JW, *Annu. Rep Med Chem* 1986, 21, 149.
- [12] Dower WJ, Fodor SPA, *Annu Rep Med Chem* 1991, 26, 271.
- [13] Stanhl E, *Chemiker* 1958, 82, 323.
- [14] Kyroda M, Mimaki Y, Sashides Y, Yamori T, Tsuruo T, *Tetrahedron Letters* 2000, 41, 251.
- [15] Prozel A, Lien TP, Schmidtm J, Wagner C, Muzweiler K, Surg VT, Adam G, *Tetrahedron* 2000, 56, 865.
- [16] Oh SU, Lee SJ, Kim JH, You ID, *Tetrahedron Letters* 2000, 41, 61.
- [17] Shukla YN, Srivastava A, Kumar STR, Khanuja SPS, Kumar S, *Indian Drugs* 2000, 37, 60.
- [18] Valamathi R, Sundari SKK, Puratchikory A, Jayakar B, *Indian Drugs* 2000, 37, 42.
- [19] Kapuridi M, Warin R, Delude C, *Bull Soc Chem Belg* 1992, 101, 283.
- [20] Dharma PJ, Maninder M, Raja C, *Indian Drugs* 2000, 37, 1.
- [21] Yasuhiro T, Terazono M, Kusumoto TI, Kawashima Y, Hatanaka Y, Kadota S, Hattori M, Bamba T, Kikuchi T, *Helv Chem Acta* 1999, 82, 408.
- [22] Ryu G, Choi BW, Ho LB, Hwang K-H, *Tetrahedron* 1999, 55, 1317.
- [23] Wei GMFY, Ducrey B, Hosteltmann K, Tahara S, *Phytochemistry* 1999, 51, 1087.
- [24] Chaver H, Estever-Braun A, Ravelo AG, Gonzalez AG, *J Nat Prod* 1999, 62, 434.
- [25] Gbile ZO, Adesina SK, *Annals of The Missouri Botanical Garden* 1988, 75, 862.
- [26] Telek L, *Planta Med* 1979, 37, 92.
- [27] Bose B, Ghosh C, *J Inst Chem (India)* 1980, 52, 83.
- [28] Segal R, Milo-Goldzweig I, Zaitschek DV, *Lloydia* 1977, 40, 604.
- [29] Jain SC, Sahoo SL, *Pharmazie* 1981, 36, 714.
- [30] Jain SC, Sahoo SL, *Chem Pharm Bull* 1981, 29, 1765.
- [31] Roychoudhury R, *Acta Bot Indica* 1980, 8, 91.
- [32] Vohora SB, Ishwar K, Khan MSY, *J. Ethnopharmacol* 1984, 11, 331.
- [33] Ojewole JAO, Adesina SK, *Planta Med* 1983, 49, 99.
- [34] Ojewole JAO, Adesina SK, *Planta Med* 1983, 49, 46.
- [35] Ojewole JAO, Marquis VO, *J African Med* 1981, 4, 27.
- [36] Kumar S, Bagchi GD, Darokar MP, *Pharmaceutical Biology* 1977, 35, 179.

- [37] Unny R, Chauhan AK, Joshi YC, Dobhal MP, Gupta RS, *Phytomedicine* 2003, 10, 233.
- [38] Herz W, Lalyanaraman PS, *J Org Chem* 1975, 40, 3486.
- [39] Bohlmann F, Jakupovic J, Zdero C, King RM, Robinson H, *Phytochemistry* 1979, 18, 625.
- [40] Jakupovic J, Barauh RN, Bohlmann F, Msonthi JD, *Planta Med* 1986, 52, 154.
- [41] Macias FA, Molinillo JMG, Fischer NH, *Phytochemistry* 1993, 32, 127.
- [42] Cartagena E, Bardon A, Catalan CAN, Hernandez LP, Nathan PJ, *J Nat Prod* 2000, 63, 1323.
- [43] Saleh AA, Cordell AG, Farmsmoron NR, *Lloydia* 1976, 39, 456.
- [44] Clark EP, *J Am Chem Soc* 1930, 52, 2461.
- [45] Harper SH, *J Am Chem Soc* 1940, 62, 1178.
- [46] Pezzuto JM, song LL, Lee SK, Shamon LA, Matagreen WE, Jang M, *In Chemistry Biological and Pharmacological properties of Medicinal plants from the Americas* 1999, 81.
- [47] Kinghorn AD, Lee D, Pezzuto JM, *Curr Org Chem* 2003, 7, 213.
- [48] Granda MM, *Dun. Rev. Cubana Fausm* 1984, 18, 405.
- [49] Anbalayan K, Sadique J, *Int J Crude Drug Res* 1985, 23, 177.
- [50] Sudhir S, Budhiraya RD, Miglani GP, Arora B, Gupta LC, Garg KN, *Planta Med* 1986, 1, 61.
- [51] Yidya PM, Rao A, Karanth KS, *Fitoterapia* 1990, 61, 237.
- [52] Roy U, Mukhopadhyay S, Poddar MK, Mukerjee BP, *International Seminar on Traditional Medicine, Calcutta* 1992, 141.
- [53] Kuttan G, *Indian J Exp Biol* 1996, 34, 854.
- [54] Hu B, Ji Y, *Chin J Integ Trad West Med* 1986, 6, 480.
- [55] Muller K, Selloner A, Weigrebe W, *J Nat Prod* 1999, 62, 1134.
- [56] Mourya SK, Devi S, Panday VB, Khosa RL, *Fitoterapia* 1989, 60, 468.
- [57] Zhao Q, Hao XJ, Chen YZ, Zou C, *Yaoxue Xuebao* 1995, 30, 119.
- [58] Chaturvedula P, Sprague S, Shcilling JK, *J Nat Prod* 2003, 66, 528.
- [59] Tewtrakul S, Nakamura N, Hattori M, Fuguwara T, Supavita T, *Chem Pharm Bull* 2002, 50, 630.
- [60] Calis I, Heilmann J, Tasdemir D, Linden A, Ireland CM, Sticher O, *J Nat Prod* 2001, 64, 961.
- [61] Sang S, He K, Liu G, Zhu N, Cheng X, Wang M, Zheng Q, Dong Z, Ghai G, Rosen RT, Ho CT, *Org Lett* 2001, 3, 1307.
- [62] Gaddipati JP, Madhavan S, Sidhu GS, Singh AK, Seth P, Maheshwari RK, *Molecular Cell Biochem* 1999, 194, 271.
- [63] Rajesh K, Kutan R, *Teratog carcinogen* 1991, 21, 303.
- [64] Wilkinson HH, Siegel MR, Blankenship JD, Mallory AC, Bush LP, Sechadi CL, *Mol Plant Microbe* 2000, 13, 1027.
- [65] Paredes A, Hasegawa M, Prieto F, Merdez J, Rodriguez M, Ortega M, *J Ethnopharmacol* 2001, 78, 128.
- [66] Matias R, Junan C, Azucena G, *Phytochemistry* 2004, 65, 381.
- [67] Rini JM, Annu T, *Biophys Biomol* 1995, 24, 551.
- [68] Hirabayashi J, Hashidate T, Arata Y, Nishi N, Nakamura THM, Urashima T, Oka T, *Biochemica Biophysica Acta* 2002, 232, 1572.
- [69] Brewer CF, Miceli MC, Baum LG, *Current Struct Biol* 2002, 12, 616.
- [70] Al Said MS, Abdelsattar EA, Khalita SL, El Faraly FS, *Pharmazie* 1988, 43, 640.
- [71] Gadgoli C, Mishra SH, *J. Ethanopharmacol* 1999, 66, 187.
- [72] Denetzos C, Dimas KS, *Studies in Natural Products Chemistry, (Bioactive Natural Products Part-I)* 2001, 25, 235.
- [73] Delaposte R, Sanchez G, Cuellar A, Giuliani A, Palazzo de Mello J, *J Ethanopharmacol* 2002, 82, 82.
- [74] Suksamrarn A, Kumpun S, Kistikara K, Yingyongarongkul B, Suksamrarn S, *Planta Med* 2002, 68, 72.
- [75] Deepak M, Handa SS, *Phytotherapy Res* 2000, 14, 463.
- [76] Talla E, Njamen D, Mbafor TJ, Fomum TZ, Kamanyi A, Giner MR, *J Nat Prod* 2003, 66, 891.
- [77] Montanari AM, Liridquist N, Lee YA, Clardy J, *Tetrahedron* 1996, 52, 5371.
- [78] Williams JRSH, Jeffery BH, Jenny G, John E, *Phytochemistry* 1995, 38, 267.
- [79] Bloor SJ, *Phytochemistry* 1995, 38, 1033.

- [80] Shizuo K, Sayaka W, Iun K, Satoshi T, Jaya M, *Phytochemistry* 1992, 31, 787.
- [81] Chan GW, Francis T, Thureen DR, Offen PH, Pierce NJ, Westley JW, Johanson RK, Faulkner DJ, *J Org Chem* 1993, 58, 2544.
- [82] Youngwan S, Rho JR, Jongheon S, *Tetrahedron* 1995, 51,2497.
- [83] Han Q, Jiang B, Mei S, Ding G, Sun HD, Xie J, Liu Y, *Fitoterapia* 2001, 72, 86.
- [84] Asana N, Nishida M, Miyauchi M, Ikeda K, Yamamoto M, Kizu H, Kameda Y, Watson AA, Nash RJ, Fleet GWJ, *Phytochemistry* 2000, 53, 379.

© 2014, by the Authors. The articles published from this journal are distributed to the public under “**Creative Commons Attribution License**” (<http://creativecommons.org/licenses/by/3.0/>). Therefore, upon proper citation of the original work, all the articles can be used without any restriction or can be distributed in any medium in any form.

Publication History

Received 27th Sep 2014
Revised 16th Oct 2014
Accepted 10th Nov 2014
Online 30th Nov 2014