JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Bioactive Phytochemicals from Acanthaceae – Mini Review.

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Abstract : **The leaves of the species of Acanthceae have been traditionally used as herbal medicines by the native and nomadic communities mainly to alleviate the poisonous bites of insects and reptiles and for the treatment of external wounds and ulcers. The pharmacological activities reported from these species are antibacterial, antifungal, anti-pyretic, hepatoprotective, anti-inflammatory, cytotoxic, antioxidant, anti-platelet aggression and insecticidal. The traditional use, chemical constituents and pharmacological activities from family *Acanthaceae* have been selected for study. In literature, from this family phytochemicals mainly flavonoids, alkaloids, lignans, saponins, triterpenoids, steroids and fatty acids are recorded. The species of *Acanthaceae* has emerged as good source of traditional medicines. The chemical compounds isolated from these species have been reported for their pharmacological effects. Although, few experimental studies validated their traditional claim, but uncharacterized crude extract was employed in most of the activities. Such species need to be explored properly for their bioactive principle and exploited as potential drug. The review will help the researchers to select medicinally potential species of *Acanthaceae* for future research.**
IndexTerms-Acanthaceae, **Flavonoids, Alkaloids, Lignans, Triterpenoid Saponins.**

INTRODUCTION

Plants are potential source of herbal medicines beside as resource of food and shelter. The medicinal plants have been the raw base for preparation of medicines in all the pharmacopeias including Chinese, Ayurveda, Unani, Siddha and native and ethnic communities. India is considered as gold mine of well recorded traditional practiced herbal medicines [1]. However, among the 250,000-400,000 plant species only 6% have been screened for biological potential and 15 % for phytochemical exploration [2]. The lack of systematic research, effectiveness, efficacy, disease specific formulations and place of natural product in primary healthcare system are the primary concerns. Still, it is estimated that about 25% drugs prescribed in modern medicines are derived from plants. In the essential list of WHO, out of 252 drugs 11% have plants origin. Despite of advanced treatment through modern medicines, 85 to 90% of world population consumes plants or plants derived medicines due to one reason or other [3]. The plants defense mechanism against the herbivorous animals and pathogens to biosynthesize defensive compounds particularly secondary metabolites have attracted the attention to isolate, characterize and lab scale formulation of these compounds for various biological effects. At the present time, over 12,000 bioactive compounds are identified in science. The recognized active compounds are screened from secondary metabolites. It is an important source with a variety of structural arrangements and properties. Pharmaceutical herbs have a wealthy source of secondary metabolites with fascinating biological activities [4].

Acanthaceae is a large family comprising of 4300 species and 346 genera. This family is cosmopolitan and distributed mostly in tropical and subtropical regions of the world. They are found in the equinoctial regions of both old and new world, with few species extending north into south of Europe, Pennsylvania and Japan and southwards to the Cape of Good Hope and southern coast of New Holland [5]. In India, many of the genera of *Acanthaceae* are peculiar to southern parts, Malayan Peninsula and Indian Archipelago. The species are spreaded from the forest of Silhet to the banks of Sutlej. Some genera have extended to the elevations of 7000 to 8000 feet of Himalayas [6]. All members of this family are shrubs, under shrubs, annual and perennial herbs [7]. Many species of *Acanthaceae* have been used traditionally as herbal drugs for the treatment of various ailments by the native and nomadic communities. The species have been investigated for extraction and isolation of chemical compounds responsible for various pharmacological effects. In the present review, phytochemicals mainly flavonoids, alkaloids, lignans, saponins, triterpenoids, steroids and fatty acids are recorded from the different genera of the family *Acanthaceae* have been selected for the study with the main focus on their structure and pharmacological effects reported in literature. Databases used for study were: Google scholar, PubMed, Scopus-Elsevier, AGRICOLA and Shodhganga.

Traditional uses of family Acanthaceae:

Mostly, leaves of the plants of *Acanthaceae* have been used for traditional purpose. Leaves of *Andrographis peniculata* are used to alleviate bites of poisonous insects and reptiles and for wounds and ulcers [8]. Paste of leaves of *Barberia grandicalyx* is used for snake bites [9]. The paste of onion bulbs and leaves of *Blepharis maderaspatens* are used for cuts and wounds [10]. Leaves part of the plant *Justicia gendrarussa* are used for fever, headache, vertigo and wounds [11]. *Justicia adhatoda* plant is used for rheumatism, fever, pneumonia, asthma, tuberculosis, expectorant, antiseptic and to relieve pain [12]. Decoction of whole plant of *Rungia linifolia* is used for ulcers [13]. Leaves of *Hygrophila auriculata* and *Justicia transquebariensis* are used for cough [11]. Infusion of two or three species is also used for various ailments. Ash of leaves of Justicia betonica, Acathus pubescens and Justicia flava has been used for cough, ulcers and flu [10]. The leaves of the species *Acanthus eminens, Aystasias chimperi, Dyschoristethum bergiiflora, Thunbergiaalata, Dyschoris teradicans* and *Lepidagathis scariosa* are infused to treat cough, skin

diseases, wounds, eye infections, anti-diarrhea, edema, pneumonia [10]. *Andrographis paniculata, Hygrophila spinosa, Barleria prionitis* and *Adhatoda vasica* are used traditionally as antiviral, antipyretic, antiasthmatic and in respiratory diseases [14].

Chemical Composition of Acanthaceae:

Flavonoids

Flavonoids belonging to different phytochemical classes, have been isolated and identified from different parts of *Acanthaceae.* From the genus Blepharis the isolated flavonoids belong to the classes flavones- apigenin, blephariside and dihydro flavones- naringenin, rutin aglycones glycosylated with D- glucose sugar and rarely esterified with coumaroyl moieties. The major flavonoids are apigenin 7-(3"-acetyl-6"-*E*-pcoumaroyl)-glucopyranoside, genistein-7-*O*-(6″- *O*-E-caffeoyl)-*β*-D glucopyranoside, naringenin-7-*O*-(3″-acetyl-6″-*E*-*p*coumaroyl)-*β*-D-glucopyranoside were isolated from Blepharis *ciliaris, B. scindica* and *B. maderaspatensi* species.

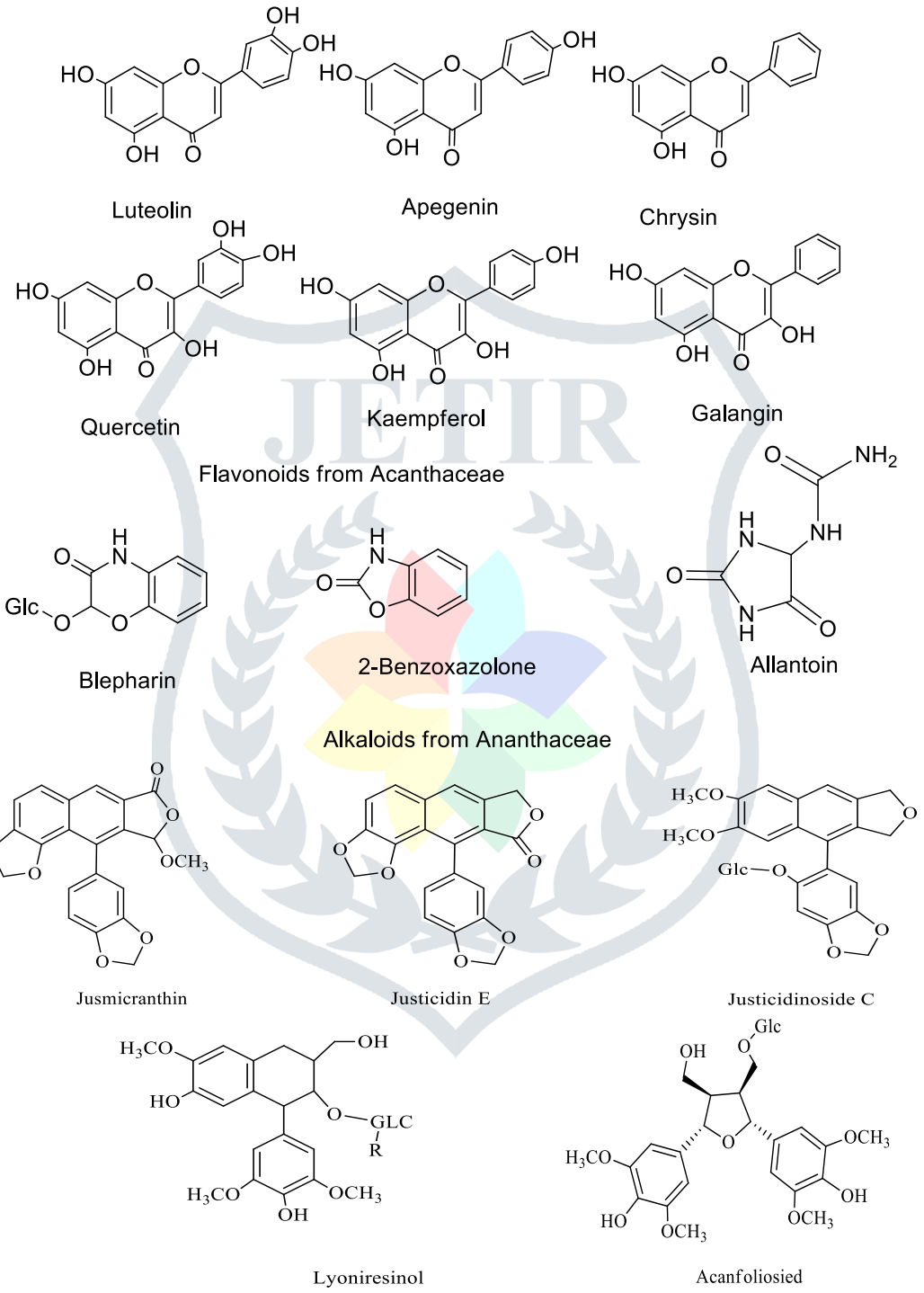

Fig-1 Common Flavonoids, Alkaloids, Lignanas from Acanthaceae.

From the genus *Justicia* -flavanol and dihydroxyflavonols – kaempferitrin, vitexin, 3′,4′-Dihydroxyflavonol were identified from the species- *Justicia cataractae, J. gendarussa* and *J. spicigera* [14]. The species *Andrographis paniculata* [15]of *Acanthacea* led to identify flavones and isoflavones and other class of polyphenyl compounds - andrographolide, 14-deoxy-ll,12-dedihydro Andrographolide,14-Deoxyandrographolide, 7-*O*-methyl dihydro wogonin, (2S)-5,7,2',3'-tetramethoxyflavanone, 12-Didehydro-andrographolide, 14-Deoxy-11-hydroxyandro grapholide, Neoandrographolide, andrographoside, 5-hydroxyl -7,8,2',5'-tetramethoxy-flavone, 5-hydroxy-7,8,2',3'-tetra methoxyflavone, 5-hydroxy-7,2',6'-trimethoxyflavone, 5-hydroxy-7,2',3'trimethoxyflavone. Different classes of flavonoids were identified from the genus *Ruellia*- Luteolin, Luteolin 7-*O*-glucoside, Apigenin 7-*O*-glucuronide, Cirsimaritin, Cirsimarin, Cirsiliol 4′-glucoside, Sorbifolin, Pedalitin, Apigenin, Apigenin 7-*O*-glucoside, Apigenin 7-*O*-glucuronide, Hispidulin 7-*O*-β-D-glucuronopyranoside , Comanthoside B, Hispidulin 7-*O*-*α*-L-Rha-

(1'''→2'')-*O*- β -D-glucuronopyranoside, Pectolinaringenin 7-O- *α* -L-Rha-(1'''→2'')-*O*- β -D-glucuronopyranoside, Nepetin 7-*O*-β-D-glucopyranoside, Demethoxycentaureidin 7-*O*-β-D-glucopyranoside, Pectolinarigenin 7-*O*- β-D-glucopyranoside, 7-*O*-Acetyl apigenin, Quercetin, Quercetin 3-*O*-glucoside, 5, 2′, 3′ -trihydroxy 7-*O*-glucoflavone, 5, 7, 4′ -trimethoxy 3-*O*Rhamnopyranoside, 2, 2′, 4′, 6′-tetrahydroxy-chalcone from the species- *Ruellia tuberose, R. prostrate* and *R. brittoniana* [16] .

Alkaloids

Few alkaloids including derivatives of hydroxamic acids have been also identified in some *Blepharis* species [17]. The bitter glucoside blepharin was first isolated from the *B. edulis* and its structure was later confirmed as blepharin i.e. *N*-deoxy-2,4-

Table1-Pharmacological activities from Acanthaceae.

Activity	Isolate/ extract	Species	Animals/ Species	Ref.
Antioxidant	Methanol, Aqueous	Juticia spicigera, Ruellia kerrrii, Barleria cristata, Justicia procumbens, Strobilanthes aureculata, Rhinacanthus nasutus	DPPH/In vitro	[43,44]
Antibacterial	Methanol, Aqueous, chloroform,	Andrographis paniculata, Asteracantha logifolia, Andrographis paniculata, Rhinacanthus nasutus, Andrographis affinis	*B. subtilis, S. aereus, E. coli, B. pseudomallei, P. vulgaris, P. aeruginosa*	[45,46]
Antifungal	Acetone, Chloroform Dichloromethane	Hypoestes serpens, Andrographis paniculata, Rhinacanthus nasutus	*C. cucumerinum C. albicans, A. niger, P. oryzae*	[47,44]
Cytotoxic	Methanol, Elanoside, Justifortinol, Justicinol, Patentiflorin, 4-O-acetyl patentiflorin, Andrographolide, 14-deoxy andrographolide, 14-deoxy -11, 12-di hydroandrographolide, Rhinacanthin-A, B, C, D	Justicia hysssopifolia, Justicia petentifolia, Andrographis paniculata, Rhinacanthus nasutus	Human cancer cells, Tumor cell lines, Human cervix adenocarcenoma	[48,45,44]
Anti-inflammatory	Ethanol, Aqueous, Methanol	Hygrophila spinosa,Dicliptera verticillata, Justicia grandrarussa, Barleria prionitis, Andrographis paniculata	Male Wister rats, key enzymes used for inflammation	[49,47,46]
Antiviral	Rhinacanthin-E, Rhinacanthin-F	Rhinacanthus nasutus	Varity of DNA and RNA virus.	[44]
Hepato protective	Andrographolide	Andrographis paniculata	Male Wister rats	[51]
Immuno modulatory	Aqueous	Rhinacanthus nasutus	Male rats	[44]
Anti-platelet aggregation	Rhinacanthin-A, B, C, G, H, I, K, M, Q	Rhinacanthus nasutus	Rabbits	[44]
Insecticidal	B-sitosterol-3-O-β-glucoside, Palmitic acid, Linaroside, Acetoside	Acanthus montanus	*Aedesaegypti*	[52]

dihydroxy-1,4- benzoxazin-3-one glucoside (N-deoxyDIBOA). Blepharigenin (N-deoxy-DIBOA) and blepharin were reported from *B. scindica* and 2-benzoxazolinone (BOA) has been isolated from the roots of *B. edulis*. Allantoin and betaine hydrochloride were isolated from *B. scindica*. Macrocyclic polyamine alkaloids are found in several plant families. The principal basic unit of these alkaloids

is the polyamine spermidine or spermine, which is connected with one or two molecules of a 4-hydroxycinnamic acid. The roots of *Aphelandra species* contain as the major alkaloid the macrocyclic spermine alkaloid, aphelandrine, Aphelandarine, N1,N5-Di-*p*-coumaroylspermidine, N5,N10]-di-*p*coumaroylspermidine, N1,N5,N[10]-tri-*p*coumaroyl spermidine, 18-*O*-Methylchaenorpine, iso-18-*O*-methylchaenorpine from *Aphelandra tetragona* and 6-hydroxy-aphelandrine, 6-acetoxy-aphelandrine from *Aphelandra fuscopunctata*. Polynuclear quinolinic based alkaloids are isolated from the methanol and ethyl acetate extract of the species of *Justicia*. 5*H*,6*H*-Quinindolin-11-one, 10*H*-Quindoline, Jusbetonin, Vasicine, Vasicinone, Allantoin, 6*H*-Quinindoline alkaloids from *J. betonica* and Vasicinol alkaloid from *J. adhatoda*. The alkaloids were tested for their pharmacological effects- Antitumor, bronchodilator, uterotonic, anti-inflammatory and anti-ulcer effects [18]. Indole based indole-3-carboxaldehyde bioactive alkaloids were isolated from *Ruellia* species [19]. A tryptophan derived alkaloid 6-hydroxyluteolin,6-hydroxyluteo lin-7-apioside (cristatin) was isolated form ethanol extract of Lepidagathis *cristata*[20]. Cytotoxic 2- Benzoxazolinone alkaloid and derivatives which were glycosylated in few cases were isolated from *Acanthus ilicifolius*- Acanthicifoline, Trigonellin, 2-benzoxazolinone,

Benzoxazin-3-one, 5,5'-bis-benzoxazoline-2,2'-dione,Benzoxazinoid glucosides, 4-O-β-D-glucopyranosyl-benzoxazolin-2(3H)-one, (2R)-2-D glucopyranosyloxy-2H-1,4-benzoxazine-3(4H)-one, (2R)-2-glucopyranosyloxy-4-hydroxy-1,4-benzoxazine-3-one), 2-hydroxy-2H-1, 4-benzoxazin 3(4H) one[21].

Lignans

Lignans have wide diversity in structure but basic skeleton contain two of more phenylpropanoid units linked through 8-8′ bonds [22]. Further investigations of more diverse skeletal units and size the term lignan is used to encompass all linkage types- 8-8′, 8-1′, 8-5′, 8-O-4′, 5-5′, 3-O-4′, 7-1′, 8-7′, 1-5′ and 2-O-3′. Out of various types of lignans, 8-8′ linked lignans are commonly found in nature. These are further subdivided as Classical Lignans and Neolignans. In *Acanthaceae* family [14]Classical lignans of type Aryl Naphthalene- Jusmicranthin , Jusmicranthin methyl ether, Neesiinoside A, Jusmicranthin methyl ether from *Justicia. Neesii* [23], Helioxanthin , (+)-Isolariciresinol, Podophyllotoxin from *J. flava* [24], Taiwanin E, Taiwanin E methyl ether Justicidin E, Neojusticin A, Diphyllin, Justicidin A, Chinensinaphthol, Justicidinoside A, Justicidinoside C, Justicidinoside B, Procumbenoside A, Diphylin apioside , Diphyllin apioside-5-acetate from *J. procumbens* [25,26], Justicidin B, Cleistanthin B, Justalakonin, Juspurpurin, Sesamin, Xanthoxylol, Juspurpurin , Sesamin, Xanthoxylol from *J. purpurea* [27], 4´´-*O*-Acetylpatentiflorin B, Patentiflorin A, Patentiflorin B, Carinatone, Justiflorinol from *J. patentiflora*, Tuberculatin, Chinensinaphthol methyl ether, 4´-Dimethyl chinensinaphthol methyl ether, Neojusticin B, Ciliatoside A, Cilinaphthalide A, Cilinaphthalide B, Heliobuphthalmin from *J.ciliata* [28,29], (+)-Lyoniresinol 3a-[2-(3,5-dimethoxy-4-hydroxy)-benzoyl]-O-β -glucopyranoside, dihydroxymethyl-bis (3,5-dimethoxy-4-hydroxyphenyl)tetrahydrofuran-9(or9')-*O*-β -D-gluco pyranosid, (8R,7'S,8'R)-5,5'-dimethoxylariciresinol 4-*O*-β -D-glucopyranoside [30], Acanfolioside, Alangilignoside C, (+)-syringaresinol-*O*-β -D-glucopyranoside (+)-lyoniresinol3 -O- -D-glucopyranoside, (+)-lyoniresinol 2a-O-β -D-galactopyranosyl-3a-O-β -D-glucopyranoside, (+)-lyoniresinol 3a-O-β-D-galactopyranosyl-(1-6)- β-D-glucopyranoside, (-)-lyoniresinol 3 -O-β -D-glucopyranoside from the species *Acanthus ilicifolius* [21].

Saponins

The triterpenoid based saponins 3-β-O-[(-α-L-rhamnopyrano syl(1→4)-O-β-D- glucopyranosyl]16-α-hydro- xy-olean-12-en(13)-28-oic acid from *Lepidagathis hyaline* Nees [31], 16,28-dihydroxy 22-acetyl-21-tigloylolean-12-ene-3-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-(1→3)-[β-D-glucopyranosyl-(1→2)]-β-D–glucopyranosi duronic acid (Cuspidate A), 3-O-α-L-arabinopyranosyl-(1→3)-α-L- rhamnopyrano syl-(1→2)-α-L-arabinopyranoside hedera genin (Clemontanoside C) from *Lepidagathis cuspidata*[32]. α-L-Arabinofuranosyl-(1/4) -β -D-glucuronopyranosyl-(1→3) -3 -hydroxylup-20-ene from Acanthus ilicifolius [21].

Steroids, triterpenoids and fatty acid derivatives- Pentacyclic triterpenes- β-amyrin, α–amyrin[33], lupeol, oleanolic acid and ursolic acid [34]. Steroids- Cholesterol, campesterol, stigmasterol[50], β–sitosterol[35], stigmast-7-en-3 -ol, stigmasteryl -D-glucopyanoside[36],28-isofucosterol, octacosyl alcohol[36], β-sitosterol-3-O-β -D glucopyranoside, stigmasterol-3-O-β -D-glucopyranoside[37] from *Acanthus ilicifolius* [21]. Oleanolic acid, *β*-Sitosterol, 9-Hydroxydodecanoic acid from *B. scindica* [38], (2*S*,3*S*,4*R*)-2[(2′*R*)- 2′-(Hydroxyeicosanoyl amino) octadecane-1,3,4-triol, *β*-Sitosterol -3-*O*-*β*-Dglucopyranose, Stigmasterol, Stigmasterol-3-*O*-*β*-Dglucopyranose, Stigmasterol tetracosanoate from *B. ciliaris* [39]. From *Justicia flava* steroids campesterol, stigmasterol, sitosterol, and sitosterol-D-glucoside were isolated [17] Sterols-β-Sitosterol, β-sitosterol glucoside , stigmasterol , campesterol and stimat-6-en-3-β-ol, Triterpenes-Lupeol, Betulin, β-Amyrin, 1-Methyldammar-22-en-3β,18,27-triol, Coumarins - 7-Hydroxy-4-Methyl Coumarin, Dicoumarol have been isolated from the genus [17]. Fatty acid derivatives Palmitic acid, octadecanoic acid, stigmasterol octadecanoate, -sitosterol octadecanoate, tetracosanol, octacosanol[37] from *Acanthus ilicifolius*.

Miscellaneous (2R)-2-*O*-β -D-glucopyranosyl-4-hydroxy-*2H*-1,4-benzoxazin-3(4H)-one, (2R)-2-*O*-β -D-glucopyranosyl-7-hydroxy-*2H*-1,4-benzoxazin-3(4H)-one, 7-chloro-(2R)-2-*O*- β-D-glucopyranosyl-*2H*-1,4-benzoxazin-3(4H)-one[41], betaine, vanillic acid[42], luteolin-7-O-b-D-glucuronide, uridine, uracil[40].

Pharmacological activities of family Acanthaceae

The methanol extract of the species of Acanthaceae have expressed strong antioxidant potential under standard pharmacological conditions using DPPH/ in vitro. The crude extracts from the genera *Andrographis*, *Asteracantha*, *Rhinocanthus* and *Hypoestes* have exhibited strong antibacterial and antifungal activities against respective bacterial and fungal strains in disc diffusion method/ in vitro. The chemical compounds Justifortinol, Justicinol, Patentiflorin, 4-O-acetyl patentiflorin, Andrographolide, 14-deoxy andrographolide, 14-deoxy -11, 12-di hydroandrographolide isolated from *Justicia petentifolia* and Rhinacanthin-A, B, C, D from *Rhinacanthus nasutus* have expressed strong cytotoxic potential against human cell lines culture in MTT and LDH Cytotoxic Assay. The β-sitosterol-3-O-β-glucoside, Palmitic acid, Linaroside, Acetoside isolated from *Acanthus montanus* have shown remarkable efficacy against Aedesa egypti. The pharmacological effects examined from Acanthaceae species are summarized as

a) In most of the pharmacological activities crude extract was utilized. However, Elanoside, Justifortinol, Justicinol, Patentiflorin, 4-O-acetyl patentiflorin, Andrographolide, 14-deoxy andrographolide, 14-deoxy -11, 12-di hydroandrographolide, Rhinacanthin-A, B, C, D isolated compounds from the species *Justicia hysssopifolia*, *Justicia petentifolia* [47] were recorded for their cytotoxic activities.

b) Rhinacanthin-E, Rhinacanthin-F compounds from *Rhinacanthus nasutus* [48] were used to test Antiviral effects.

c) Cuspidate A, Clemontanoside C comounds from *Lepidagathis cuspidata* were tested positively for their antifungal activity [32].

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