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Phytochemistry and pharmacological activities of genus Abutilon: a review (1972-2015)

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Abstract

Abutilon Miller is a genus belonging to family Malvaceae comprises about 150 species. The plants of this genus are annual or perennial herbs, shrubs or even small trees. It is native to the tropical and subtropical countries of America, Africa, Asia and Australia. The genus has a significant importance, which is attributed to valuable insoluble fibers obtained from different species of the genus such as *Abutilon theophrasti* and also due to several species grown as garden ornamental plants such as *A. ochsenii* and *A. vitifolium*. Reviewing the available literature on genus Abutilon revealed the presence of a diversity of secondary metabolites such as flavonoids, phenolic acids, sterols, triterpenes, quinones, coumarins, alkaloids, sphingolipids, megastigmanes, iridoids and others, which are responsible for its biological activities such as anti-inflammatory, analgesic, antipyretic, hepatoprotective, antioxidant, anti-hyperglycemic, gastroprotective, cytotoxic, antifungal, antibacterial, antiviral, anthelmintic, anti-malarial, anti-leishmanial, CNS activity, anti-stress, immunostimulant, anti-venom, anti-hyperlipidemic, anti-hypertensive, aphrodisiac, abortifacient, antidiarrhoeal, diuretic, anti-urolithiatic, and wound healing activities. This review showed that some species of genus Abutilon including *A. pannosum*, *A. mauritianum*, *A. crispum*, *A. grandiflorum*, *A. bidentatum*, *A. figarianum*, *A. ochsenii* and *A. vitifolium* need further phytochemical and pharmacological investigation to develop new drugs from natural sources.

Key words
Malvaceae, Abutilon, phytochemistry, biological activities

1. Introduction

Malvaceae (Mallow Family) is the family of flowering plants containing about 243 genera and 4225 species. The plants of this family are herbs, shrubs and trees. It is widely distributed throughout the world and particularly in tropical regions, mainly in South America [1, 2]. Abutilon is a large genus of family Malvaceae, containing 150 species. The plants of this genus are annual or perennial herbs, shrubs and small trees, native to tropical and subtropical regions. The leaves are alternate, unlobed or palmately lobed and the flowers are mostly pink, orange or yellow with five petals [3]. Abutilon is the ancient Greek name for the mulberry tree and to be given to this genus due to resemblance in the shape of the leaves [4]. The genus has a significant importance, which is attributed to valuable insoluble fibers obtained from different species of the genus such as *Abutilon theophrasti* and also due to several species grown as garden ornamental plants such as *A. ochsenii* and *A. vitifolium* [3, 5, 6]. The collected data were obtained from the following databases: PubMed, Science Direct, ChemWeb and Google Scholar. This review potentiates the researchers for carrying out further studies on this genus to isolate and develop new drugs from natural sources with wide margin of safety and understanding their effects and possible mechanism of actions. The literature was collected from 1972 to 2015 using various databases including PubMed, Science Direct, ChemWeb and Google Scholar.

2.1. Phytochemistry

Genus Abutilon contains various phytochemical constituents such as flavonoids, phenolic acids, sterols, triterpenes, coumarins, alkaloids, lactones, megastigmanes and iridoids. Their structures, **1–112** are shown below and their names and the corresponding plant sources are collected in the **(Table 1)**.

2.1.1. Sterols

Nine phytosterols **(Figure 1)**, β-Sitosterol (**1**), β-sitosterol glucoside (**2**), stigmasterol (**3**), 20, 23-dimethylcholesta-6, 22-dien-3β-ol (**4**), cholesterol (**5**), E-24-ethylidene-23-methyl-5α-cholest-20(22)-ene (**6**), pakisteroid-A (**7**), pakisteroid-B (**8**) and (24R)-5α-stigmastane-3,6 dione (**9**) have been isolated from genus Abutilon [3, 7-14].

2.1.2. Flavonoids

Flavonoids are the predominant secondary metabolites of Abutilon. Thirty seven compounds (**10 – 46**) **(Figure 2)**, were obtained from genus Abutilon. Quercetin and kaempferol and their glycosides are the most common flavonols isolated from different Abutilon species [15-17]. In addition to, the flavones luteolin, apigenin and chrysoeriol were obtained from

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Table 1: A list of the isolated compounds from genus Abutilon.

Classification	No	Compound Name	Source	Part used	Ref.
1) Sterols	**1**	β-Sitostrol	*A. indicum*	Leaves	[7, 112]
				Whole plant	[3, 8, 9]
				Aerial parts	[23]
				Roots	[132]
			A. pakistanicum	Whole plant	[10]
			A. muticum	Whole plant	[11]
	2	β-Sitostrol-3-*O*-β-D-glucopyranoside	*A. indicum*	Whole plant	[8]
			A. muticum	Whole plant	[11]
	3	Stigmasterol	*A .indicum*	Leaves	[7, 12]
				Whole plant	[9, 11]
			A. muticum	Whole plant	[23]
	4	20, 23-Dimethylcholesta-6, 22-dien-3β-ol	*A. indicum*	Stems	[13]
	5	Cholesterol	*A. indicum*	Leaves	[12]
			A. muticum	Whole plant	[23]
	6	*E*-24-Ethylidene-23-methyl -5α-cholest-20(22)-ene	*A. pakistanicum*		[10]
	7	Pakisteroid-A	*A. pakistanicum*	Aerial parts	[14]
	8	Pakisteroid-B	*A. pakistanicum*	Aerial parts	[14]
	9	(24R)-5α Stigmastane-3,6 dione	*A. indicum*	Whole plant	[8]
2) Flavonoids					
2.1) Flavonols	**10**	Kaempferol	*A. hirtum*	Non-flowering aerial parts	[15]
			A. pakistanicum	Aerial parts	[18]
	11	Kaempferol-3-*O*-α-L-rhamnopyranoside	*A. pakistanicum*	Aerial parts	[18]
	12	Tiliroside	*A. theophrasti*	Flowers	[133]
	13	4',6-Dimethoxy kaempferol	*A. indicum*	Aerial parts	[23]
	14	3,5,5'-Trihydroxy-4' methoxy flavone-7-*O*-β-D glucopyranoside	*A. indicum*	Aerial parts	[23]
	15	3,4',5,6,7-Pentahydroxy flavone	*A. muticum*	Whole plant	[23]
	16	Kaempferol-3-*O*-β-glucopyranoside	*A. grandiflorum*	Leaves	[16]
			A. theophrasti	Flowers	[133]
	17	Kaempferol-3-*O*-β-(6"-*Z*/*E* -*p*-coumaroyl)-glucopyranoside	*A. grandiflorum*	Leaves	[16]
	18	Quercetin	*A. hirtum*	Non-flowering aerial parts	[15]
			A. indicum	Leaves	[12]
				Aerial parts	[86]
				Whole plant	[23]
			A. muticum	Whole plant	[39]
			A. theophrasti	Seed coats	[21]
	19	Quercetin-7-*O*-β-glucoside	*A. theophrasti*	Flowers	[133]
	20	Quercetin-7-*O*-β-diglucoside	*A. theophrasti*	Flowers	[133]
	21	Rutin	*A. hirtum*	Non-flowering aerial parts	[15]
	22	Kaempferol-7-*O*-β-diglucoside	*A. theophrasti*	Flowers	[133]
	23	Quercetin-3-*O*-β-D-glucopyranoside	*A. grandiflorum*	Leaves	[16]
			A. theophrasti	Flowers	[133]
			A. indicum	Flowers	[19]
				Leaves	[17]
	24	Quercetin-3-*O*-α-rhamnopyranosyl (1→6)-β-glucopyranoside	*A. grandiflorum*	Leaves	[16]
			A. theophrasti	Flowers	[133]
			A. indicum	Flowers	[19]
	25	Kaempferol-3-*O*-α-L- rhamnopyranosyl (1→ 6)-β-glucopyranoside	*A. grandiflorum*	Leaves	[16]
			A. theophrasti	Flowers	[133]
	26	Cephacoside	*A. muticum*	Whole plant	[11]
	27	Abutilin B	*A. pakistanicum*	Whole plant	[134]
	28	Pakistoside A	*A. pakistanicum*	Aerial parts	[18]
	29	Pakistoside B	*A. pakistanicum*	Aerial parts	[18]
	30	Gossypetin-7-*O*-β glucoside	*A. indicum*	Flowers petals	[22]
	31	Gossypetin-8-*O*-β -glucoside	*A. indicum*	Flowers petals	[22]
			A. muticum	Whole plant	[23]
	32	Myricetin	*A. theophrasti*	Seed coats	[21]
	33	Myricetin-3-*O*-β-glucopyranoside	*A. theophrasti*	Flowers	[133]
2.2) Flavones	**34**	Luteolin	*A. indicum*	Flowers	[19]
				Leaves	[17]
			A. pakistanicum	Aerial parts	[18]

Classification	No	Compound Name	Source	Part used	Ref.
	35	Luteolin-7-*O*-β-glupyranoside	*A. indicum*	Flowers	[19]
				Leaves	[17]
	36	Chrysoeriol	*A. indicum*	Flowers	[19]
				Leaves	[17]
	37	Chrysoeriol-7-*O*-β-glupyranoside	*A. indicum*	Flowers	[19]
				Leaves	[17]
	38	Apigenin-7-*O*-β-glupyranoside	*A. indicum*	Flowers	[19]
	39	Apigenin-7-*O*-β-D(6"-p-coumaroyl) glucopyranoside	*A. pannosum*	Whole plant	[20]
	40	5,7,4'-Trihydroxy-3'-methoxy flavone-4'-*O*-*β*-D-(2"-*O*-acetyl) glucopyranoside	*A. pakistanicum*	Whole plant	[134]
	41	Scutellarein-4'-*O*-α-L-[5"-*O*-(*E*)-*p*-coumaroyl] arabinofuranoside	*A. pakistanicum*	Whole plant	[28]
2.3) Flavanols	**42**	(+)-Catechin	*A. theophrasti*	Seed coats	[21]
	43	(-)-Epicatechin	*A. theophrasti*	Seed coats	[21]
2.4) Anthocyanins	**44**	Cyanidin	*A. theophrasti*	Seed coats	[21]
	45	Delphinidin	*A. theophrasti*	Seed coats	[21]
	46	Cyanidin-3-*O*-rutinoside	*A. indicum*	Flower petals	[22]
3) Phenolic acid derivatives	**47**	Benzoic acid	*A. indicum*	Whole plant	[9]
			A. muticum	Whole plant	[23]
	48	*P*-Hydroxybenzoic acid	*A. indicum*	Whole plant	[3, 9, 24, 135]
					[23]
				Aerial parts	
	49	Vanillic acid	*A. indicum*	Whole plant	[8, 9]
				Aerial parts	[135]
	50	Glucovanilloylglucose	*A. indicum*	Aerial parts	[135]
	51	4-Hydroxyacetophenone	*A. indicum*	Whole plant	[9]
	52	4-Hydroxybenzaldehyde	*A. indicum*	Whole plant	[9]
	53	Vanillin	*A. indicum*	Whole plant	[9]
	54	Syringaldehyde	*A. indicum*	Whole plant	[9]
	55	Methyl-4-hydroxybenzoate	*A. indicum*	Whole plant	[3, 9]
			A. muticum	Whole plant	[11]
	56	Eudesmic acid	*A. indicum*	Leaves	[25]
	57	Gallic acid	*A. indicum*	Roots	[23]
				Aerial parts	[132]
			A. hirtum	Non-flowering aerial parts	[15]
	58	2,6-Dihydroxy-4-methoxyacetophenone	*A. indicum*	Whole plant	[3]
	59	4-*O*-β-Glucosylbenzoic acid	*A. indicum*	Whole plant	[3, 24]
				Aerial parts	[135]
	60	2,6-Dihydroxy-5-methoxy-(3-*C*-glucopyranosyl) benzoic acid	*A. indicum*	Whole plant	[3]
	61	*P*-Coumaric acid	*A. indicum*	Whole plant	[9]
				Aerial parts	[135]
			A. hirtum	Non-flowering aerial parts	[15]
	62	Caffeic acid	*A. indicum*	Whole plant	[3, 24]
				Leaves	[24]
				Aerial parts	[135]
			A. hirtum	Non-flowering aerial parts	[15]
	63	Ferulic acid	*A. indicum*	Leaves	[25]
	64	4-Hydroxy-3-methoxy-*E*-cinnamic acid methyl ester	*A. indicum*	Whole plant	[9]
	65	Methyl 4-hydroxyphenylacetate	*A. indicum*	Whole plant	[9]
	66	Methylcoumarate	*A. indicum*	Whole plant	[9]
	67	Syriacusin A	*A. theophrasti*	Whole plant	[26, 27]
	68	Abutilin A	*A. indicum*	Whole plant	[9]
	69	Fumaric acid	*A. indicum*	Aerial parts	[135]
	70	Mutiniside	*A. muticum*	Whole plant	[11]
	71	Dibutyl phthalate	*A. theophrasti*	Roots	[26]
4) Triterpenes	**72**	β-Amyrin	*A. indicum*	Aerial parts	[23]
	73	β-Amyrin-3-palmitate	*A. indicum*	Leaves	[7]
	74	Oleanic acid	*A. indicum*	Whole plant	[8]
	75	α-Amyrin	*A. pakistanicum*	Whole plant	[10]
	76	Taraxasterol	*A. pakistanicum*	Whole plant	[10]
	77	Urs-12(13)-en-24β-ol (Pakistanol)	*A. pakistanicum*	Whole plant	[10]
	78	Ursolic acid	*A. muticum*	Whole plant	[11]
	79	Lupeol	*A. muticum*	Whole plant	[11]
			A. indicum	Aerial parts	[23]

Classification	No	Compound Name	Source	Part used	Ref.
	80	Squalene	*A. indicum*	Leaves	[7]
5) Quinones	**81**	2,6-Dimethoxy-1,4 benzoquinone	*A. indicum*	Whole plant	[8]
	82	Lapachol	*A. pakistanicum*	Whole plant	[28]
6) Coumarins	**83**	Scoparone	*A. indicum*	Whole plant	[9]
	84	Scopoletin	*A. indicum*	Whole plant	[9]
	85	3,7-Dihydroxychromen-2-one	*A. indicum*	Whole plant	[9]
7) Alkaloids and amides	**86**	Aurantiamide acetate	*A. indicum*	Whole plant	[9]
	87	(R)-N-(1'-Methoxycarbonyl-2'-phenylethyl)-4-hydroxybenzamide	*A. indicum*	Whole plant	[9]
	88	N-Feruloyl tyrosine	*A. indicum*	Whole plant	[9]
	89	1-Lycoperodine	*A. indicum*	Whole plant	[9]
	90	1-Methoxycarbonyl-β-carboline	*A. indicum*	Whole plant	[9]
	91	Methyl indole-3-carboxylate	*A. indicum*	Whole plant	[9]
	92	Vasicine	*A. indicum*	Aerial parts	[23]
8) Sphingolipids	**93**	Pakistamide A	*A. pakistanicum*	Whole plant	[29]
	94	Pakistamide B	*A. pakistanicum*	Whole plant	[29]
	95	Pakistamide C	*A. pakistanicum*	Whole plant	[30]
9) Lactones	**96**	Alantolactone	*A. indicum*		[31]
	97	Isoalantolactone	*A. indicum*		[31]
	98	Taraxacin	*A. muticum*	Whole plant	[11]
10) Ionones	**99**	3-Hydroxy-β-damascone	*A. indicum*	Whole plant	[9]
	100	3-Hydroxy-β-ionol	*A. indicum*	Whole plant	[9]
11) Vitamins:	**101**	Riboflavin	*A. indicum*	Whole plant	[9]
12) Nitrogenous bases	**102**	Adenosine	*A. indicum*	Whole plant	[9]
	103	Adenine	*A. indicum*	Whole plant	[9]
	104	Thymine	*A. indicum*	Whole plant	[9]
13) Waxes:	**105**	Methyl triacontanoate	*A. indicum*	Aerial parts	[23]
	106	Triacontylpalmitate	*A. muticum*	Whole plant	[23]
	107	Tetradecanyltriacontanoate	*A. pakistanicum*		[10]
14) Long chain alcohol	**108**	1-Tricosanol	*A. muticum*	Whole plant	[23]
15) Megastigmanes	**109**	(6*S*,9*R*)-Roseoside	*A. theophrasti*	Aerial parts	[32]
	110	(6*S*,9*S*)-Roseoside	*A. theophrasti*	Aerial parts	[32]
16) Iridoid glycosides	**111**	Pakiside A	*A. pakistanicum*	Whole plant	[28]
	112	Pakiside B	*A. pakistanicum*	Whole plant	[28]

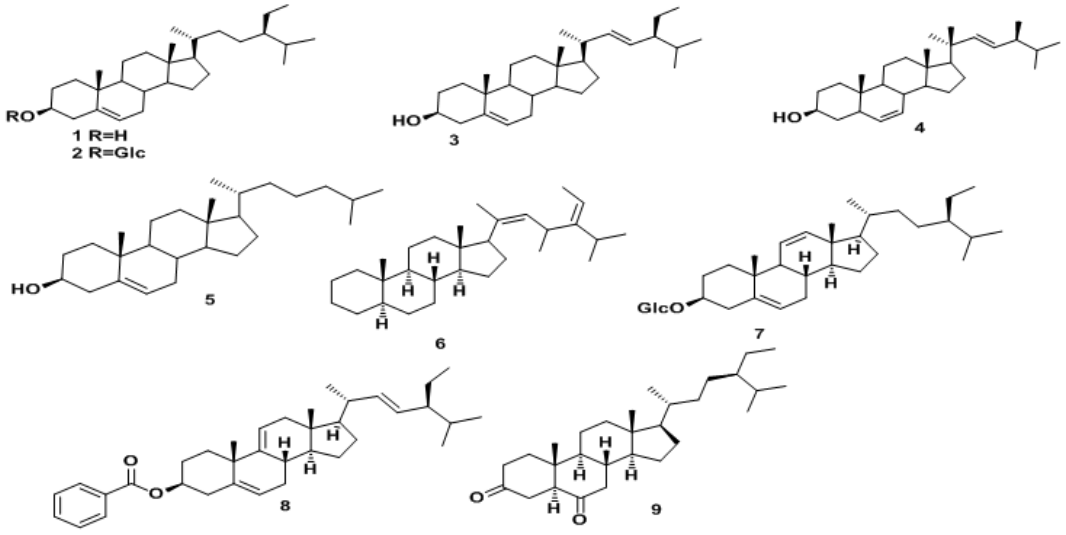


Figure 1: Chemical structures of sterols isolated from Abutilon.

A. indicum, A. pakistanicum and *A. pannosum* [18-20]. Besides, two flavanols; (+)-catechin (**42**) and (-)-epicatechin (**43**) were found in *A. theophrasi* [21]. Three anthocyanin derivatives **(44 – 46**) were obtained from genus Abutilon [21, 22].

2.1.3. Phenolic acid derivatives

Genus Abutilon is rich in phenolic acid derivatives, about 25 components were found (**47 – 71**) (**Figure 3**), mainly from the whole plant and aerial parts of *A. indicum* [3, 9, 23-27].

2.1.4. Triterpenes

Nine triterpenes (**72 – 79**) (**Figure 4**), were isolated from genus Abutilon. Most of the triterpenoids are pentacyclic, three compounds (**72 – 74**) belong to oleanane type, four compounds (**75 – 78**) belong to ursane group and one compound (**79**) belong to lupane skeleton, in addition to onesqualene triterpenoid (**80**) was found in *A. indicum* leaves [7, 10, 11, 23].

2.1.5. Quinones

Only two quinones 2,6-dimethoxy1,4-benzoquinone (**81**) and lapachol (**82**) (**Figure 5**), were isolated from *A. indicum and A. pakistanicum*, respectively [8, 28].

2.1.6. Coumarins

Only three coumarins (**Figure 5**), have been reported (**83 – 85**) in *A. indicum* [9].

2.1.7. Alkaloids

Eight alkaloids (**86 – 93**) (**Figure 6**),were isolated from *A. indicum* [9, 23].

2.1.8. Sphingolipids

Sphingolipids constitute a class of lipids defined by their eighteen carbon amino-alcohol backbones. Three sphingolipids pakistamide A (**94**), pakistamide B (**95**) and pakistamide C (**96**) (**Figure 7**), were obtained from the whole plant of *A. pakistanicum* [29, 30].

2.1.9. Other metabolites

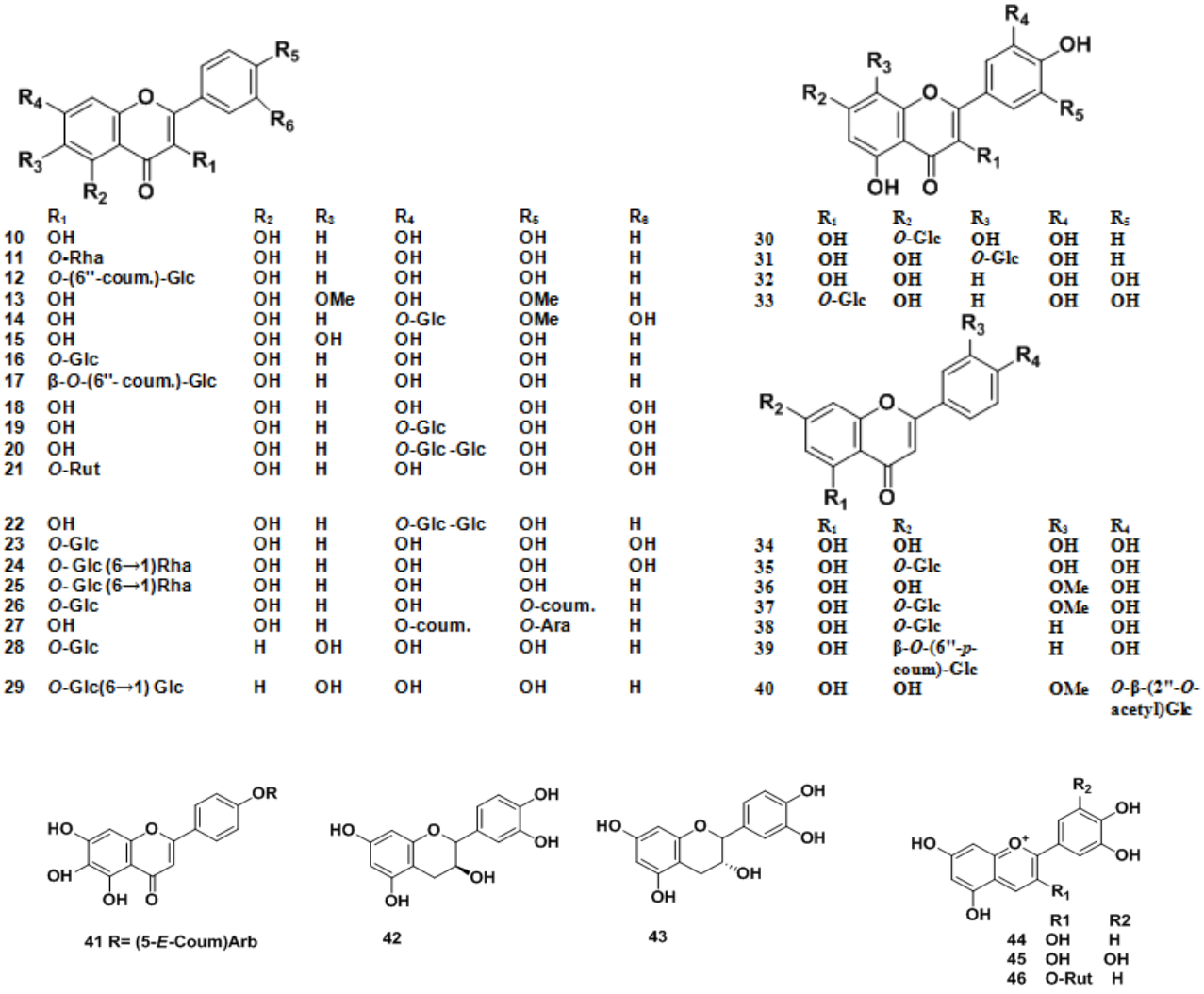
They including lactones **(97 – 99**), ionones (**100 – 101**), vitamins (**102**), (**103 – 104**), waxes (**105 – 107**), long chain alcohols (**108**), megatigmanes (**109 – 110**) and iridoid glycosides (**111 – 112**) were isolated from genus Abutilon [9-11, 23, 28, 31, 32] (**Figure 7-9**).

2.2. Pharmacological activities

Different extracts and isolated compounds of genus Abutilon exhibited various pharmacological activities as following:

2.2.1. Anti-inflammatory and analgesic activities

The petroleum ether, chloroform, methanol and aqueous extracts of whole plant of *A. indicum* were administrated orally at dose level of 400 mg/kg. The methanol and the aqueous extracts exhibited a significant analgesic activity. Besides, the two latter extracts showed also significant anti-inflammatory activity against carrageen an induced rat paw oedema at a dose level of 400 mg/kg in comparing with diclofenac sodium (10mg/kg) [33]. The ethanolic extract of the whole plant of *A. indicum* was evaluated for its anti-inflammatory activity at doses 250, 500and 750 mg/kg using the carrageenan-induced paw oedema in wistar albino rats. The extract of the different doses showed significant reduction in the oedema volume(37.00%, 49.00% and 65.65%, respectively) after 3 hrs of the treatment comparable to ibuprofen (76.34%)(10mg/kg) [34]. The ethanolic and aqueous extracts of whole plant of *A. indicum* displayed significant analgesic effects in the tail flick and formalin induced paw licking methods in wistar albino rats. In addition to, the ethanolic extract showed significant suppression of the inflammation in the carrageen an induced paw oedema [35]. The ethanolic extract of *A. indicum* and *Pedalium murex* leaves were evaluated for their anti-inflammatory effects at doses of 200 and 400 mg/kg using carrageen an induced paw oedema in albino rats. Both the plants possessed anti-inflammatory activity and *Pedalium murex* showed more anti-inflammatory activity, when compared with *A. indium* [36]. The ethanolic leaf extract of *A. indicum* was found to have high anti-inflammatory activity, when investigated using 5-lipoxygenase (5-LOX) inhibition assay. It showed a potent inhibition of 5-LOX with IC_{50} value at 8.89 µg/ml in comparison with curcumin (IC_{50}=8.14 µg/ml) as standard drug [37]. The 75% methanolic extract of *A. indicum* leaves was tested against carrageenan induced paw oedema in wister rats. The extract produced a significant effect at the early phase of the inflammation. It showed maximum oedema inhibition effect after 1st and 3rd hr of treatment at a dose of 100 (47.36% and 42.62%, respectively) and 200 mg/kg (50.25% and 66.12%, respectively) compared to 15.38% and 40.79% of indomethacin (10 mg/kg). This effect was probably attributed to the presence of phenolic compounds especially flavonols, which have a potent anti-inflammatory activity through blocking the action of COX, LOX and AT enzymes preventing the formation of the inflammatory mediators [38]. Quercetin was isolated from the ethanolic extract of whole plant of *A. indicum*. It was investigated for its antinociceptive effects using acetic acid and formalin induced nociception and for anti-inflammatory activities by using carrageen an induced paw oedema in rats. It showed significant dose dependent anti-nociception in all tested nociceptive models. It also exhibited potent significant anti-inflammatory effects compared to dexamethasone [39]. Eugenol analgesic principle from *A. indicum* displayed significant analgesic effects in the acetic acid-induced writhing and radiant heat method in mice at dose of 10, 30 and 50 mg/kg [40]. The petroleum ether and benzene extracts of *A. indicum* leaves exhibited good significant analgesic activities, when the different extracts (petroleum ether, benzene, ethanol and aqueous) were screened for analgesic activity using radiant heat analgesiometer at dose of 400mg/kg that probably attributed to the steroidal constituents of the petroleum and benzene extracts

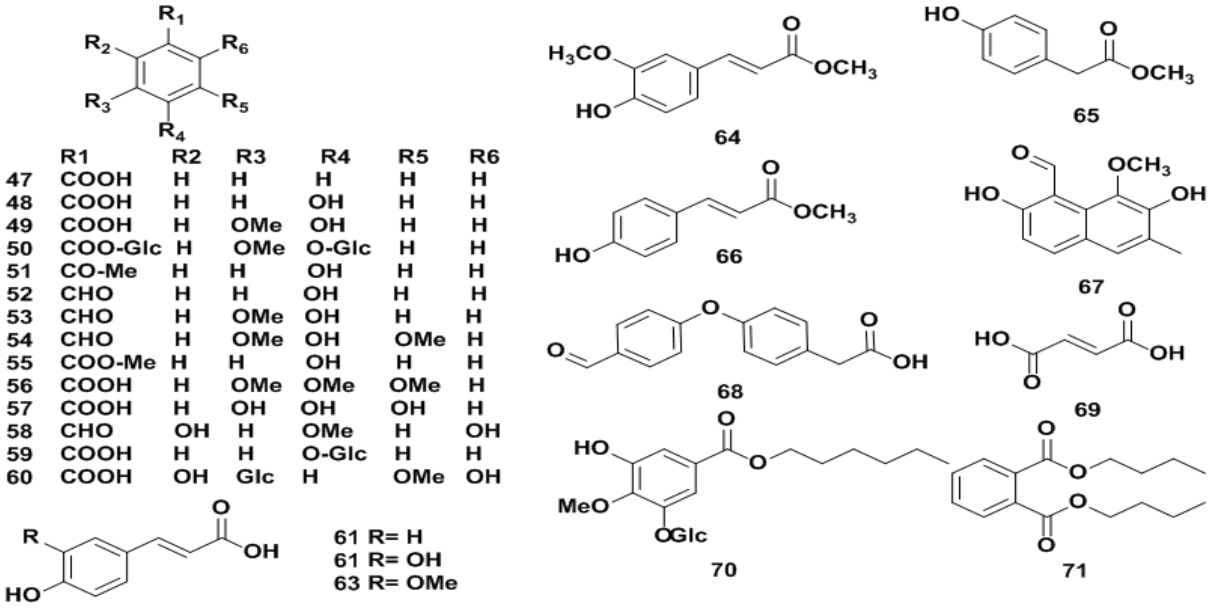


	R_1	R_2	R_3	R_4	R_5	R_6
10	OH	OH	H	OH	OH	H
11	*O*-Rha	OH	H	OH	OH	H
12	*O*-(6''-coum.)-Glc	OH	H	OH	OH	H
13	OH	OH	OMe	OH	OMe	H
14	OH	OH	H	*O*-Glc	OMe	OH
15	OH	OH	OH	OH	OH	H
16	*O*-Glc	OH	H	OH	OH	H
17	β-*O*-(6''- coum.)-Glc	OH	H	OH	OH	H
18	OH	OH	H	OH	OH	OH
19	OH	OH	H	*O*-Glc	OH	OH
20	OH	OH	H	*O*-Glc -Glc	OH	OH
21	*O*-Rut	OH	H	OH	OH	OH
22	OH	OH	H	*O*-Glc -Glc	OH	H
23	*O*-Glc	OH	H	OH	OH	OH
24	*O*- Glc (6→1)Rha	OH	H	OH	OH	OH
25	*O*- Glc (6→1)Rha	OH	H	OH	OH	H
26	*O*-Glc	OH	H	OH	*O*-coum.	H
27	OH	OH	H	O-coum.	*O*-Ara	H
28	*O*-Glc	H	OH	OH	OH	H
29	*O*-Glc(6→1) Glc	H	OH	OH	OH	H

	R_1	R_2	R_3	R_4	R_5
30	OH	*O*-Glc	OH	OH	H
31	OH	OH	*O*-Glc	OH	H
32	OH	OH	H	OH	OH
33	*O*-Glc	OH	H	OH	OH

	R_1	R_2	R_3	R_4
34	OH	OH	OH	OH
35	OH	*O*-Glc	OH	OH
36	OH	OH	OMe	OH
37	OH	*O*-Glc	OMe	OH
38	OH	*O*-Glc	H	OH
39	OH	β-*O*-(6''-*p*-coum)-Glc	H	OH
40	OH	OH	OMe	*O*-β-(2''-*O*-acetyl)Glc

Figure 2: Chemical structures of flavonoids from genus Abutilon.



	R1	R2	R3	R4	R5	R6
47	COOH	H	H	H	H	H
48	COOH	H	H	OH	H	H
49	COOH	H	OMe	OH	H	H
50	COO-Glc	H	OMe	O-Glc	H	H
51	CO-Me	H	H	OH	H	H
52	CHO	H	H	OH	H	H
53	CHO	H	OMe	OH	H	H
54	CHO	H	OMe	OH	OMe	H
55	COO-Me	H	H	OH	H	H
56	COOH	H	OMe	OMe	OMe	H
57	COOH	H	OH	OH	OH	H
58	CHO	OH	H	OMe	H	OH
59	COOH	H	H	O-Glc	H	H
60	COOH	OH	Glc	H	OMe	OH

Figure 3: Chemical structures of phenolic acid derivatives from genus Abutilon.

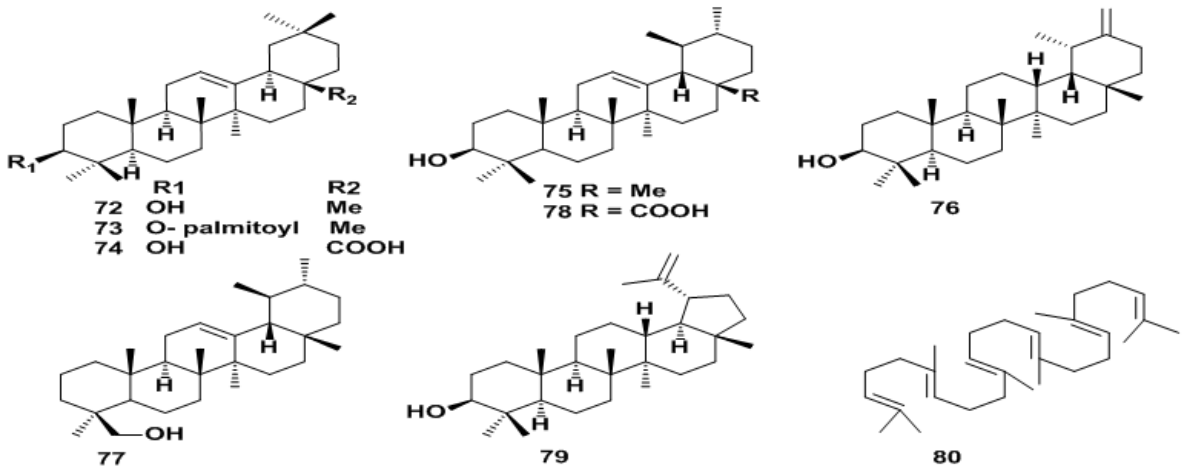


Figure 4: Chemical structures of triterpenes isolated from Abutilon.

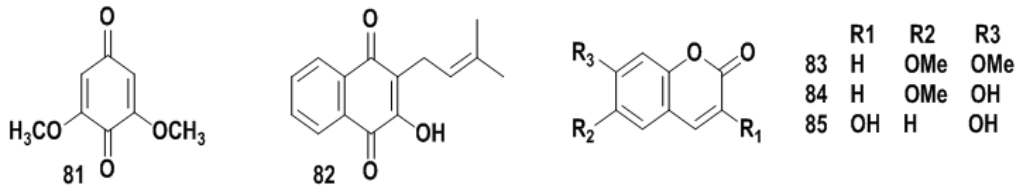


Figure 5: Chemical structures of quinones and coumarins isolated from Abutilon.

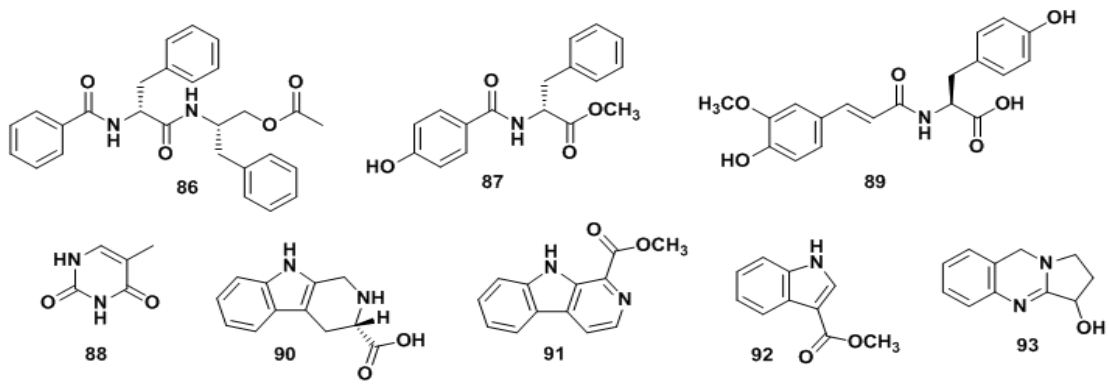


Figure 6: Chemical structures of alkaloids isolated from Abutilon.

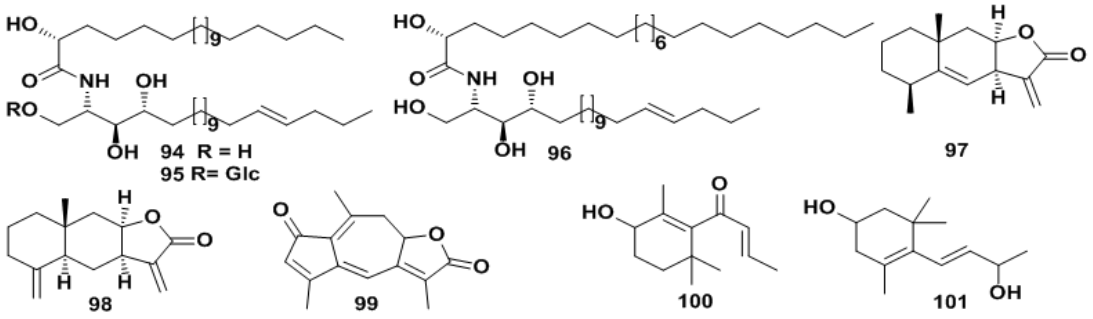


Figure 7: Chemical structures of sphingolipids, lactones and ionones isolated from Abutilon**.**

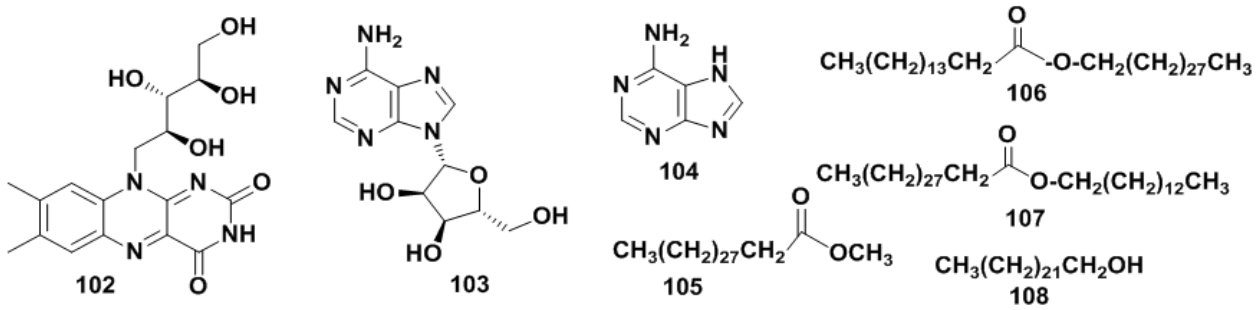


Figure 8: Chemical structures of vitamins, waxes and fatty alcohols isolated from Abutilon.

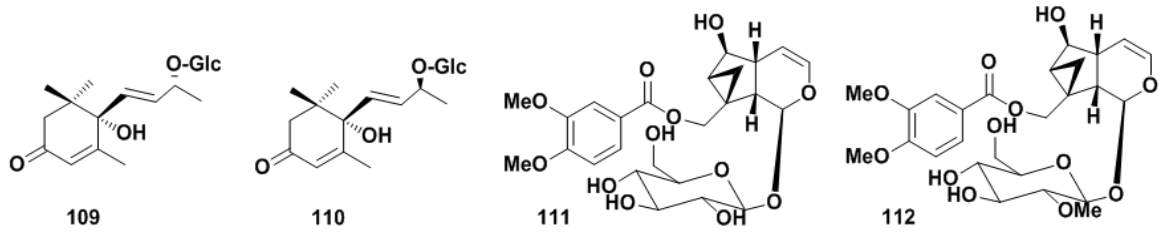


Figure 9: Chemical structures of megastigmanes and iridoids isolated from Abutilon.

[41]. The petroleum, ethanol and aqueous extracts of *A. indicum* root showed significant analgesic activities in the tail flick and acetic acid induced writhing test in swiss albino mice [42].

2.2.2. Anti-arthritic activity

The different extracts of *A. indicum* (whole plant) were investigated for its anti-arthritic activity using Freund's adjuvant induced arthritis in albino rats. The extracts were administrated orally at doses of 100, 200 and 400 mg/kg. The methanolic extract (400 mg/kg) exhibited significant anti-arthritic effects and showed significant reduction ($P<0.01$) in paw volume on both 7^{th} and 14^{th} day in comparison with methotrexate (0.75 mg/kg) [43].

2.2.3. Antipyretic activity

The ethanolic extract of *A. mauritianum* roots significantly reduced yeast and lipopolysaccharide induced pyrexia in rats at doses of 150 and 300 and 600 mg/kg, respectively. The higher dose of extract (600 mg/kg) exhibited the most significant antipyretic activity compared to the lower one. Possible mechanism for this activity was inhibition the release of inflammatory mediators [44].

2.2.4. Antioxidant activity

The chloroform fraction of alcoholic extract of *A. indicum* (whole plant) displayed antioxidant effects, when investigated using reducing power assay and DPPH free radical scavenging method. It showed 87.6% inhibition at a concentration of 500 µg/ml in case of DPPH free radical scavenging method compared to butylated hydroxy anisole (BHA) and ascorbic acid [45]. The ethanolic extract of *A. indicum* (whole plant) exhibited a significant in vivo antioxidant activity using CCl_4 induced toxicity in ratsat 500 mg/kg in comparison with Liv-52 (56 mg/kg). The extract showed a significant improvement in the glutathione, SOD, catalaseand peroxidase levels that probably were attributed to the phenolic compounds(flavonoids) present in the extract [46]. The Methanolic extracts of *A. indicum* and *Blumea mollis* (whole plant) possessed strong antioxidant properties when investigated using FRAP, DPPH and nitric oxide radical scavenging methods. The two plants were potent free radical scavengers in DPPH assay especially *A. indicum* showed 62.5% of inhibition activity comparable to ascorbic acid (57.5%) [47]. The *n*-hexane, chloroform, ethyl acetate, and *n*-butanol fractions of *A. indicum* and *A. muticum* aerial parts and roots were investigated for their antioxidant activities using ABTS, FRAP, DPPH and linoleic acid peroxidation methods. The butanol fraction of roots of *A. muticum* and ethyl acetate fraction of aerial parts of *A. muticum* showed the highest ABTS radical scavenging activity, while the ethyl acetate and *n*-hexane fractions of different parts of both plant species showed a significantly stronger DPPH scavenging activity than the *n*-butanol and chloroform fractions. The FRAP assay showed that the root fraction of *A. muticum* exhibited greater activity than the other fractions. Besides, all fractions of both plant species exhibited inhibition of peroxidation of linoleic acid and the root fractions of both species gave the highest activity this was attributed to the presence of phenolic and flavonoidal components [48]. The petroleum ether, chloroform, ethyl acetate, *n*-butanol, ethanol and water extracts of *A. indicum* were evaluated for their antioxidant activities correlated with their total phenol and flavonol contents. The ethyl acetate showed potent antioxidant activity in lipid peroxidation method, hydrogen peroxide scavenging activity, deoxiribose, ABTS, nitric oxide and total antioxidant capacity, but didn't show high phenol and flavonolic contents. On the other hand, a significant

total phenolic content and total flavonolic content were found only in ethanol extract of A. indicum, but it didn't show a higher antioxidant activity [49]. The chloroform fraction of *A. indicum* leaves possessed a good antioxidant property and it was investigated using the nitric oxide and superoxide radical scavenging tests. It showed maximum scavenging of nitric oxide and superoxide radical at (28.74% and 49. 62% inhibition, respectively) [50]. The ethanolic extract of *A. indicum* leaf possessed antioxidant activity, when compared with vitamin C. It possessed total phenolic content of 22.34 mg gallic acid equivalent /gm extract. It showed IC_{50} of 5.4 µg/mlin comparison with vitamin-C (IC_{50}=1.9 µg/ml) in DPPH assay [51].The methanol extract of *A .indicum* leaf was found to have strong antioxidant activity when screened using ferric reducing antioxidant power (FRAP) assay. The reducing power of the extract was markedly enhanced with the increasing concentrations [52]. The leaf extract of *A. indicum* showed strong antioxidant effects with total protein content of 12.5±3.6 mg/g of fresh leaves. The antioxidant activities of the extract were evaluated using superoxide dismutase, catalase and peroxidase assay [53]. The different extracts of *A. indicum* stem exhibited a significant phenolic content and possessed free radical scavenging effect of DPPH in a concentration dependant manner. The aqueous extracts showed more potent total phenolic content (35.45 mg gallic acid equivalent/g extract) and exhibited a significant scavenging activity (IC_{50}=1154.20µg/ml) than methanolic and hydro-alcoholic extracts [54]. The 70% ethanolic extract of *A. indicum* flowers was tested for in vitro antioxidant activity by reducing power, superoxide and hydroxyl radical scavenging assay. The extract exhibited a significant antioxidant activity and at higher concentration (100 µg). It was more potent than the standard drug in case of superoxide and hydroxyl radical scavenging activity but less potent than the standard drug in reducing power activity [55].

The seed oil of *A. indicum* and *A. muticum* exhibited strong antioxidant activity when assayed by ABTS, FRAP, DPPH and linoleic acid peroxidation. *A. muticum* seed oil showed stronger antioxidant activity than *A. indicum* seed oil. The total phenolic content of the extracts obtained from seeds of *A. indicum* and *A. muticum* were 13.770 and 38:815 mg gallic acid equivalents/g of seed oil, respectively, which explained the higher antioxidant activity of *A. indicum* seed oil [56]. *In vitro* free radical scavenging activity of various extracts (petroleum ether, chloroform, ethyl acetate, ethanol and aqueous) of *A. hirtum* were determined using DPPH, FRAP and reducing power assay. The aqueous extract exhibited the highest activity in DPPH assay with IC_{50} value of 120 µg/ml, followed by ethyl acetate and ethanol extracts (202 and 270 µg/ml, respectively).While, the ethyl acetate extract showed the highest FRAP value, followed by aqueous and ethanol extracts. The reducing power of aqueous and ethanol extracts at 100 µg/ml was 0.454 and 0.428, respectively, which remained slightly lower than that of ascorbic acid (0.532) at the same concentration [57].

2.2.5. Hepatoprotective activity

The aqueous extract of *A. indicum* leaves showed a dose-dependent hepatoprotective activity against CCl_4 and paracetamol-induced hepatotoxicities in rats. The pretreatment with the extract at doses of 100 and 200 mg/kg reduced the depletion in GSH level and reduced the elevated levels of SGOT, SGPT, ALKP and bilirubin [58].

The ethanolic extract of *A. indicum* leaves was investigated for its hapatoprotective activity in rats. Liver damage was induced by 30% alcohol. Orally administrated of the ethanolic extract at doses of 100 and 200 mg/kg for 21 days showed a significant hepatoprotection and maintained the hepatic antioxidant enzymes level (SOD, CAT, GPx, GR and GST) close to normal. Possible mechanism for this hepatoprotective activity was the synergistic effects of the isolated flavonoids from the extract (luteolin, chrysoeriol, luteolin-7-*O*-β-glucopyranoside, chrysoeriol-7-*O*-β-glucopyranoside and quercetin-3-*O*-β-glucopyranoside [17]. The aqueous extract obtained from *A. crispum* leaves exhibited a significant hepatoprotective activity when tested against CCl_4 induced hepatotoxicity. The extract was orally administrated at doses of 100 and 200 mg/kg. Liver tissue showed slight necrosisat 100mg/kg and in 200 mg/kg showed lesser vacuole formation comparable to CCl_4 [59]. The 70% ethanolic extract of *A. indicum* flowers displayed a potent protective action against CCl_4 induced liver damage. It showed a potent significant reduction in the elevated levels of SGPT, SGOT, ALP, ACP and bilirubin at dose of 500 mg/kg. This effect was probably attributed to the flavonoidal content of the extract [55]. The 80% methanolic extract of *A. bidentatum* (aerial parts) was found to have a potent hepatoprotective action against CCl_4 and paracetamol induced hepatic damage in rabbits. It showed a significantly decrease in serum enzymes (SGPT, SGOT, ALKP and direct bilirubin) in comparison with silymarin [60]. The aqueous extract of *A. hirtum* leaves possessed a significant hepatoprotective activity against CCl_4 induced hepatotoxicity in rats. It showed significant reduction in the elevated serum enzyme levels (SGOT, SGPT, ALP and total bilirubin content) in addition to, the histopathological investigation of liver tissue proved the hepatoprotective effect of the extract. These results confirmed the folk use of the plant as a hepatoprotective agent [61].

2.2.6. Antihyperglycemic activity

The aqueous extract of *A. indicum* (whole plant) exhibited important anti-diabtic activity in streptozotocin-induced diabetic rats. The extract was more effective in moderately diabetic rats than severely diabetic one as the oral administration of the extract at doses of 0.5 and 1.0 g/kg caused a significant reduction in plasma glucose levels in 30 min after the administration in moderately diabetic rats this was at a faster rate than glibenclamide while, in severely diabetic rats 1.0 g/kg of the extract showed a significant reduction in the plasma glucose level [62].

The anti-diabetic effect of the aqueous extract of *A. indicum* (whole plant) was tested in streptozotocin- induced diabetic rats. The extract was administrated orally at doses of 250 and 500mg/kg for 14 days. The extract significantly lowered

($P<0.05$) 2 hrs postprandial plasma glucose [63]. The chloroform fraction of the ethanolic extract of *A. indicum* plant at dose of 50 mg/kg was evaluated for its anti-diabtic effects in streptozotocin-induced diabetic rats. It showed a significant reduction in blood glucose level, especially at the 14th and 21st day compared to glipizide (350 mg/kg). It also showed a significant increase in serum insulin levels this attributed to its hypoglycemic activity [64]. The ethanolic and aqueous extracts of *A. indicum* leaves showed significant hypoglycemic effect in normal rats 4 hrs after the administration of a dose of 400 mg/kg. They showed a significant reduction in blood glucose level (23.10% and 26.95%, respectively). On the other hand, the petroleum ether and chloroform extract of *A. indicum* leaves didn't show a significant hypoglycemic activity. The flavonoids and glycosides contents of the extracts regenerated the damaged pancreatic β-cells and stimulated the secretion of insulin in β-cells of pancreas were attributed to their activity [65]. The different extracts (petroleum ether, benzene, ethanol and aqueous) of *A. indicum* leaves were found to possess a significant hypoglycemic activity. All the extracts exhibited a significant reduction in blood glucose level at dose of 400 mg/kg in normoglycemic rats. The aqueous extract showed the highest activity (53.55%) followed by benzene extract (46.33%), petroleum ether extract (34.68%) and ethanolic extract (30.30%) in comparison with tolbutamide (55%) [41].

The methanolic extract of *A. indicum* leaves was investigated for hypoglycemic effect in normal and streptozotocin-induced diabetic rats. The oral administration of the extract at a dose of 500 mg/kg significantly decreased the blood glucose concentrations in both normal and diabetic rats after 2 hrs administration but it didn't have any significant effect on plasma glucose concentrations in both diabetic at dose of 250 mg/kg and normal rats while, metformin reduced the blood glucose only in diabetic rats. In addition to, the extract showed a potent sucrose inhibitory activity with IC_{50} of 2.45±0.13 mg/ml, while it was less potent on the maltose inhibition [66]. *In vitro* α-amylase and α-glucosidase inhibitor activity of methanolic extract of *A. indicum* leaves were evaluated. The extract showed a significant inhibitory effect at concentration of 160 µg/ml against α-amylase (41.31%) and α-glucosidase (36.13%), therefore the extract had a potant inhibitory activity against α-amylase more than α-glucosidase this delayed the carbohydrate digestion and reduced glucose absorption confirming the traditional use of this plant extract for diabetes treatment [67].

2.2.7. Gastroprotective and antiulcer activity

The ethanolic extract of *A. indicum* leaves was evaluated for antiulcer activity using aspirin and pylorus ligation induced ulceration in rats. The extract at 100 and 200mg/kg (p.o) significantly reduced pH level, formation of lesions and acid secretion compared with rantidine (50 mg/kg) [68].

The ethanolic and aqueous extracts of *A. indicum* plant showed anti-ulcerogenic effects against aspirin, pylorus ligation and alcohol induced ulcer models in rats. The extracts were administrated orally at doses of 200 mg/kg twice daily for five days. The two extracts significantly inhibited the gastric lesions and reduced the gastric volume and total acidity. The ethanolic extract exhibited more gastroprotective effect (50.22% protection) than the aqueous extract (42.26% protection) [69].

The hydro-alcoholic extract of *A. indicum* leaves exhibited dose-dependent antiulcer effects against ethanol and pyloric ligation induced gastric ulcer in rats using omeprazole (20 mg/kg,p.o) as the standard drug. Oral administration of the extract at 200 and 400 mg/kg showed a significant reduction the ulcer index in both ulcer induced models [70]. Pretreatment of the methanolic extract of *A. indicum* leaves at doses of 250 and 500 mg/kg exhibited a significant antiulcer properties in pylorus ligated and ethanol induced ulceration in the albino rats. The extract showed a significant inhibition the of ulcers formation and reduced the total acidity, number of ulcers and ulcer index especially at the higher dose. This activity was attributed to the presence of flavonoids (quercetin), alkaloids and tannins in the plant [71].

2.2.8. Anti-diarrhoeal activity

The different leaf extracts (petroleum ether, methanol and aqueous) of *A. indicum* were evaluated against castor oil-induced diarrhoea and prostaglandin E2 -induced enteropooling in rats. The methanolic extract and aqueous extracts possessed a significant antidiarrhoeal activity as they inhibited significantly the frequency of defecation, faecal droppings compared to loperamide. While, the petroleum ether extract didn't show any significant activity [72].

2.2.9. Respiratory activity

The dried powder of *A. indicum* aerial parts was investigated on patients with moderate bronchial asthma with and without antiasthmatic medication. The plant was orally administrated at dose of 1.0 g three times daily with water for 4 weeks. It didn't show any significant change when taken without any antiasthmatic drugs. But it exhibited significantly decrease in the symptoms of bronchial asthma (wheezing, cough and chest tightness) when given with antiasthmatic medication. For this reason, there was decrease in requirement of antiasthmatic medicine preventing their serious side effects [73]. The methanolic extract of *A. indicum* aerial parts was evaluated to determine the mechanism of action of the plant in the treatment of bronchial asthma using histamine and acetylcholine induced bronchospasm in guinea pigs and egg albumin induced rat peritoneal mast cell degranulation. The extract didn't show bronchodilating activity against histamine and acetylcholine induced bronchospasm. While, it exhibited a significant a mast cell stabilizing effect and also displayed a significant anti-inflammatory activity when estimated using carrageenan induced rat paw oedema. The possible mechanism of action of *A. indicum* in the treatment of bronchial asthma was its mast cell stabilizing and anti-inflammatory activity [74].

2.2.10. Anticonvulsant activity

The ethanolic and aqueous extracts of *A. indicum* leaf were tested against pentylene tetrazole and maximal electro shock

induced convulsions in rats. The extracts were orally administrated at doses of 100 and 400 mg/kg. The ethanolic extract exhibited a significant anti-convulsant effect. It increased latency, onset of clonic convulsion and decreased onset of tonic seizures in case of pentylene tetrazole induced convulsions. While, both extracts showed a highly anti-convulsant effect in case of maximal electro shock induced convulsions [75].

2.2.11. Diuretic activity

The ethanolic extract of *A. indicum* plant was found to have a protective effect against acetaminophen-induced nephrotoxicity in rats. The extract was orally administered at 400 mg/kg that exhibited greater protective effects than the extract at 200 mg/kg. It showed significant reduction in serum creatinine, alkaline phosphatase and uric acid levels. In addition to, the nephroprotective effects the extract were confirmed by the histopathological examination of the kidney tissue that showed a significant improvement of the renal cellular damage [76].
The aqueous extract of *A. indicum* seeds possessed significant diuretic and natriuretic activities. Oral administration of the extract at doses 200 and 400 mg/kg produced significant diuresis and increased sodium elimination but had no effect on the urinary potassium excretion in comparison with furosemide (20 mg/kg) [77]. The aqueous and ethanol extracts of *A. indicum* leaves showed a significant increase inurine volume and urinary electrolytes (Na^+, K^+ and Cl^-) excretion when administrated orally at doses of 200 and 400 mg/kg in rats. The aqueous extract at 400 mg/kg showed marked increase in urine volume and urinary Na^+, K^+ and Cl^- levels similar to that of furosemide (25 mg/kg) that supported the folklore use of *A. indicum* for its diuretic actions [78]. The ethanolic extract of *A. indicum* plant was investigated against cisplatin induced nephrotoxicity in rats. The extract was administered orally at doses of 200 and 400 mg/kg for 7 days before cisplatin injection. It significantly prevented the increase of serum creatinine, blood urea nitrogen, uric acid, total proteins, total cholesterol, alkaline phosphatase and albumin levels and markedly decreased cisplatin-induced renal damage that was confirmed by histopathological studies of the rat kidney [79].

2.2.12. Anti-urolithiatic activity

Preventive and curative anti-urolithiatic activity of ethanolic extract of *A. indicum* (400 and 800 mg/kg p.o) was evaluated by calcium oxalate calculi induction using CPD (Calculi Producing Diet- 5% ammonium oxalate in rat feed) and gentamicin (40 mg/kg; s.c.). It showed a significant decrease in the deposition and excretion of calcium oxalate urinary stones, in addition to, it showed a significant decrease in the kidney weights [80].

2.2.13. Cytotoxic activity

The methanolic extract of *A. indicum* was tested for its cytotoxic activity using human melanoma (SK-MEL28) and lung adeno carcinoma (NCI-H23) cell lines. It showed good inhibition effects on cancer cells with IC_{50} value of 4.71 mg/ml on SK-MEL 28 and IC_{50} value 15.8 mg/ml on NCI-H23 cell lines[47].
The ethanolic leaf extract of *A. indicum* showed good anti-proliferative activity against lung cancer cell line (A549). It exhibited a high percentage of cell inhibition (72.1%) at concentration (200 µg/ml) in comparison with cisplatin that showed percentage cell inhibition 91.1% at the same concentration. It also showed shrinkage and lysis in lung cancer cells [45]. The different fractions (petroleum ether, ethyl acetate and aqueous) of *A. grandiflorum* roots were tested for their cytotoxic effects using the human colon carcinoma cell line HT29. All three fractions showed only moderate cytotoxic effects with IC_{50} value at 130,36 and 800 µg/ml, respectively [81]. The chloroform fraction of *A. indicum* leaves showed strongly significant cytotoxicity using brine shrimp lethality bioassay in addition to, the *n*-hexane, carbon tetrachloride and aqueous extracts demonstrated moderate cytotoxic activity [82].
The ethanolic and aqueous extracts leaves of *A. indicum* leaves were investigated for their cytotoxic activity against Ehrlich Ascites Carcinoma (EAC) and Dalton's Ascitic Lymphoma Cell Lines (DAL). Both extracts showed more activity against EAC than DLA. The ethanolic extract exhibited greater cytotoxic activity than aqueous extract particularly at the concentration of 200 µg/ml. It showed 60% of cell death in case of EAC, while the aqueous extract exhibited 42% cell death at the same concentration [83]. The petroleum ether, defatted alcohol, alcohol and aqueous extracts of *A.hirtum* leaves showed various cytotoxic activities against Ehrlich Ascites Carcinoma (EAC) at different concentrations (25, 50 and 100 µg/ml). The petroleum ether extract exhibited the highest activity particularly at doses 50 and 100 µg/ml it showed 100% viability inhibition of (EAC) cells while, the defatted alcohol and alcohol extracts showed only 40% and 20% viability inhibition of (EAC) cells, respectively at dose 100 µg/ml and the aqueous extract was found to be inactive [84]. The cytotoxic activity of the aqueous extract of *A. hirtum* plant was investigated against human breast cancer cell lines (MCF-7). It exhibited a high cell inhibition rate of 43.71% at 300 µg concentration with IC_{50} value of 368.7 µg/ml on MCF-7 cell line [57].

2.2.14. Antifungal activity

The antifungal activity of essential oil of *A. indicum* leaves was screened against *Asp. niger, Asp. nidulans, R. nigricans, Cl. herbarium* and *Pe. digitatum* using disc diffusion method. The essential oil showed good effective antifungal efficiency especially against *Asp. niger* [85]. The methanolic extract of various parts (leaves, stem and flowers) of *A. indicum* were tested for antimycotic activity against *Asp. niger, Asp. flavus, Asp. fumigatus, Ca. albicans, Ca. utilis, F. oxysporum, F. solani, Micros. gypseum, Trichop. metagraphytes, Ep. floccosum and Trichop. rubrum* using minimum inhibitory concentration and disc diffusion method. All the extracts significantly and dose dependently inhibited the growth of all the fungi. The leaf and stem extracts were more effective than flower extracts at both the concentrations (12.5 and 25 µg/ml). In addition to, the leaf extract was particularly active against

Ca. utilis and *Asp. fumigatus* while, all the three extracts were less active against *Ca. albicans* than ketoconazol [86]. Quercetin isolated flavonoid from aqueous extract of *A. theophrasti* seed coats significantly inhibited growth of *Asp.niger* and *Fusarium sp.* but it had no effect on *G. roseum, Pe.diversum* and *Tricod. viride* [21]. The steroidal compound (20, 23-dimethylcholesta-6, 22-dien-3β-ol) isolated from *A.indicumstem* was tested by poison food technique against various pathogenic fungi. It exhibited a potent fungicidal and fungistatic property. It showed 100% inhibition of mycelial growth of *Asp. parasiticus var. globosus* and *Asp. terreus var. aureus* at concentration of 5000 ppm and 69.2% inhibition in case of *Asp. candidus* at the same concentration [13]. The antifungal activity of methanolic extracts (leaves, stems and roots) of *A. indicum* and *A. muticum* were investigated against *Asp. niger, R. microsporus* and *Trichod. Viride* using fluconazole and nystatin as positive control. The root extracts of both plants exhibited greater activity than the other extracts while, the leaf extract of *A. indicum* at a concentration of 1000 µg/ml and the stem extracts of both plants at concentrations of 1000 and 2000 µg/ml were found to be inactive against *Asp. niger* [87]. The methanolic extract obtained from *A. indicum* exhibited greater antifungal activity than hexane and chloroform extracts. It possessed good antifungal effects at (100 mg/ml concentration) against *Al. alternate* and *F. oxysporum* with inhibition zone 17 and 13 mm, respectively [88]. The phenolic acids (eudesmic, ferulic and caffeic acid) isolated from *A. indicum* leaves were tested against *Asp. niger* and *Ca. albicans.* The ferulic and caffeic acid exhibited high antifungal activity against *Asp. niger* and *Ca. albicans* comparable to chloramphenicol, while eudesmic acid didn't show any activity against the tested fungi [25]. The ethanolic extract of *A. indicum* leaves showed a potent antifungal activity against *Trichop. rubrum* and *Micros. canis* that were responsible for ringworm (fungal infections affected the skin). It strongly inhibited the growth of the tested fungi(30 and 28 mm)in comparison with ketoconazole (30 and 29 mm) [89]. The methanolic extract of *A. indicum* leaves exhibited high antifungl activity when investigated against *Asp. niger, Asp. flavus, Asp. fumigatus, Ca. albicans* and *Pe. chrysore*. It showed maximum activity towards *Asp. niger* and minimum activity against *Asp. fumigatus* [90].

The chloroform fraction of alcoholic extract of *A. indicum* was orally administrated at doses of 25, 50, 75 and 100 mg/ml. It showed high activity against *Ca. albicans* with a zone of inhibition (18.6 mm) greater than that of standard drug amphotericin B (13.6 mm) at concentration of 100mg/ml while, it was completely inactive at concentration of 25 mg/ml [45].

The ethanolic and aqueous extracts of *A. indicum* leaves and roots were investigated against *Micros. gypseum, Pe. chrysogenum, Asp. flavus* and *Fusarium sp.* The ethanolic leaves extract exhibited moderate activity against *Micros. gypseum* and *Pe. chrysogenum* at 500 µg/ml concentration while, the aqueous leaves extract, ethanolic and aqueous extracts of roots didn't show any antifungal activity [91].

2.2.15. Antibacterial activity

The seed oil of *A. indicum* and *A. muticum* showed a broad spectrum activity against Gram-positive (*B. licheniformis,B. subtilis, Microc. luteus* and *N. asteroids*) and Gram-negative bacteria (*E. coli, Pr. mirabilis* and *Sal. typhimorium*). Both the plant species inhibited the growth of both Gram-positive and Gram-negative bacteria but *Sal. typhimorium* was most resistant to both the seed oils. *A. muticum* seed oil was found to be more effective than *A. indicum* seed oil [56]. The petroleum ether, ethanolic and aqueous extracts of *A. pannosum* leaves were tested against *S. aureus, Pr. mirabilis, E. coli, K. pneumoniae, Sal. typhi, En. faeculis, P. aeruginosa and S. aureus.* The ethanolic and aqueous extracts had more potent antibacterial activity than the petroleum ether extract. The ethanolic extract showed the highest inhibitory activity against *E. coli.* The aqueous extract exhibited a strong inhibition effect on *E. coli, En. faeculis* and *P. aeruginosa* while, all the tested extracts didn't show any activity against *K. pneumonia* and *Sal. typhi* [92]. The methanolic extract of *A. indicum* leaves was investigated against *E. coli, S. aureus* and *B. subtilis* using disc diffusion method. It exhibited a potent inhibitory effect on *S. aureus* than the other bacteria (inhibition zone=2.6 cm at the concentration of 10 µl) [93]. The ethanolic extract of *A. indicum* flowers exhibited better antibacterial activity than chloroform, ethyl acetate and aqueous extracts when examined against *E. coli, S. aureus, P. aeruginosa, Pr. vulgaris, Sal. paratyphi, Sh. sonnei, Sal. typhimurium* and *K. pneumonia. S. aureus* was found to be more sensitive toward the ethanolic extract with inhibition zone diameter 17mm and the least antibacterial activity showed by *Sh. sonnei* with inhibition zone diameter 9 mm. while, the chloroform extract highest activity against *K. pneumoniae* with inhibition zone of 15 mm [94]. Different extracts (petroleum ether, acetone, *n*-hexane, methanol and water) of *A. pannosum* leaves were investigated against Gram-positive (*B. subtilis, S. aureus, Sar. leuka* and *B. megaterium*) and Gram-negative (*E. coli, P. aeruginosa, Pr. vulgaris* and *Sh. sonnie*) bacterial strains using agar-well diffusion method. Among all the extracts the ethanolic extract exhibited the highest significant ($P<0.001$) antibacterial activity comparable to penicillin potassium and streptomycin sulphate. It showed 23.5 mm maximum diameter of inhibition zone against *Pr. vulgaris* while, the petroleum ether showed lower activity than the other extracts [95]. The methanolic extract of *A. bidentatum* leaves was found to produce significant ($P<0.001$) anti-bacterial activity, than the other extracts (petroleum ether, acetone, *n*-hexane and aqueous) against the Gram-positive bacteria such as (*B. subtilis, S. aureus, Sar.leuka* and *B. megatherium*) and Gram-negative bacteria such as *E. coli, P. aeruginosa, Pr. vulgaris* and *Sh. sonnie*. The petroleum ether extract didn't produce any significant antibacterial activity ($P>0.05$) when compared with standards (penicillin potassium and streptomycin sulphate) [96].

The successive combined extracts (petroleum ether, acetone, ethyl acetate and ethanol) of *A. indicum* and *Phylanthus niruri* leaves were screened against *S. aureus, P. aeruginosa, E. coli, Klebsiella sp* and *B. subtilis.* The ethyl acetate showed significant anti-bacterial activity followed by the ethanolic

extract and acetone extract showed low activity, while the petroleum ether extract was found to be inactive against the all tested organisms [97]. The methanolic extracts of different parts (leaves, stems and roots) of *A. indicum* and *A. muticum* were studied against Gram-positive (*B. licheniformis, B. subtilis, Microc. luteus* and *N. asteroids*) and Gram-negative bacteria (*E. coli, Proteus mirabili* and *Sal. typhimorium*) using the agar diffusion method. *A. muticum* extracts exhibited greater activity than *A. indicum*. All extracts showed good activity against the tested microorganisms except the stem and root extracts of *A. indicum* and root extract of *A. muticum* had no activity against *Pr. mirabilis*. The leaf extract of *A. indicum* and stem extract of *A. muticum* exhibited a potent significant antibacterial activity against *Sal. typhimorium* and *B. licheniformis* in comparison with benzyl penicillin and ampicillin [23]. The methanolic extact of *A. indicum* possessed antibacterial effects greater than the aqueous one when tested against fifteen strains of *S. aureus* isolated from animals with mastitis manifestation using the disc diffusion method. The methanolic extract exhibited a promising effect on S. aureus with minimum inhibitory concentration at 0.250 mg/ml that support the possible use of the plant in the clinical management of bovine mastitis [98]. The chloroform, ethanol and aqueous extracts of *A. indicum* leaves were investigated for their antibacterial activity against *B. subtilis, S. aureus, K. pneumoniae, P. aeruginosa, E. coli* and *Sal. typhi*. The maximum bacterial growth inhibition was exhibited by ethanol extract followed by chloroform extract while aqueous extract didn't show any activity [99]. The chloroform extract of *A. indicum* leaves showed antimicrobial activity in a dose dependent manner against only on Gram-positive bacteria (*S. aureus, B. subtilis, B. pumilis* and *Microc. luteus).* It showed the highest inhibition zone diameter 19.3 ± 0.5 mm in in case of *S. aureus at* 500µg/ml. The extract showed growth inhibition zones against other strains. But it didn't show growth inhibition against Gram-negative bacteria(*E. coli, P. aeruginosa* and *Pr. vulgaris*) when compared with standard drug cefexime (10µg/ml) [100]. The ethanolic extract of *A. indicum* stem exhibited significant wide spectrum antibacterial activity against Gram-positive (*B. subtilis*) and Gram-negative bacteria (*E. coli*) compared to gentamicin. It showed higher potent activity against *B. subtilis* than *E. coli*[101]. The chloroform and methanolic extracts of *A. indicum* leaves showed inhibitory activity against Gram-negative bacteria such as *Sal. typhi, P. aeruginosa, E. coli, Pr. mirabilis, K. pneumoniae* and *Sh. flexneri*. The antibacterial activity of the extracts increased with increase in the concentration. The methanol extracts were more potent than the chloroform extracts. It showed the highest growth inhibition of *P. mirabilis* (29.3 mm), while the maximum inhibition that showed by the chloroform extract was against *E. coli*(8.9 mm) [102].

Eudesmic, ferulic and caffeic acid, three phenolic acids isolated from the methanol extract of *A. indicum* leaves were evaluated for their antibacterial activity against *B. subtilis, E. coli, S. aureus* and *P. aeruginosa*. All compounds showed moderate activity against the tested bacterial strains. Eudesmic acid showed maximum inhibition zone (15.6 mm) for *E. coli* whereas ferulic acid showed maximum inhibition zone (16.7 mm) for *P. aeruginosa*. While none of these compounds inhibited the growth *of B. subtilis* [25]. The methanolic extract of *A. indicum* leaves exhibited high inhibitory activity in a dose dependent manner against *E. coli, S. aureus, Sal. typhi, K. pneumonia* and *B. subtilis*. It showed maximum activity against *B. subtilis* and minimum activity against *Sal. typhi* with minimum inhibitory concentration at 3 mg/ml [90]. The carbon tetrachloride extract of *A. indicum* leaves exhibited moderate antibacterial activity against B. *cereus, B. megaterium, Sar. lutea, Sh. boydii, E. coli, Sal. paratyphi, Sh. dysenteriae* and *V. mimicus,* while the chloroform extract showed significant activity against only *Sar. lutea* [82]. The chloroform fraction of alcoholic extract of *A. indicum* plant was found to be are most active against Gram-positive bacteria (*S. aureus* and *B. subtilis*) than that of Gram-negative bacteria (*E. coli* and *P. aeruginosa*). It showed the maximum zone of inhibition (31.6 mm) in case of *S. aureus* compared to ciprofloxacin (26.3 mm) [45]. The methanolic extract of *A. indicum* leaves and methanolic extract of *A. indicum* loaded solid lipid nanoparticles (SLN's) exhibited effective antibacterial activity against microorganisms which were responsible for diabetic foot and urinary tract infection such as *S. aureus, Staph. epidermidis, B. subtilis, E. coli, P. aeruginosa, K. pneumonia, Pr. vulgaris, Pr. mirabilis, Strep. pyogenus* and *Strep. faecalis* by using modified agar well diffusion method. The extracts showed a high inhibitory effect against all tested microorganisms comparable to streptomycin. The nanoparticle system was an effective carrier for oral delivery of *A. indicum* as SLN's exhibited a higher antibacterial effect than that of the methanoilc extract [103]. The ethanol extract of *A. indicum* whole plant at concentration 5, 50 and 100 mg/ml displayed maximum antibacterial activity against *B. subtilis, Microc. luteus, S. aureus, E. coli, P. aeruginosa* and *Sal. choleraesuis* than the hexane, chloroform and aqueous extracts [104]. The methanloic extract of *A. figarianum* leaves was screened for its antibacterial activity against *E. coli, S. aureus* and *K. pneumonia* using cup-diffusion method. It showed the highest activity against *K. pneumonia* and *S. aureus* with inhibition zone diameter (21 and 20 mm, respectively) at concentration 200 µg/ml, while it showed moderate activity against *E. coli*[105]. The silver nanoparticles synthesized from leaf extract of *A. indicum* exhibited a great activity against *Sal. typhi* with inhibition zone diameter (32 mm) followed by *B. subtilis* (26.6 mm), *K. pneumonia* (23 mm) and *Pr. vulgaris* (22.6mm) using agar well diffusion method. The extract protein molecules reduced silver nanoparticles which acted as an anti-bacterial agent to control pathogenic microorganisms [106].

The silver nanoparticles synthesized usnig *A. indicum* leaves aqueous extract (3.5 ml) were found to have the highest antibacterial activity against *B. subtilis* (18.3 mm) and *E. coli* (17.25 mm) but low activity against *Sal. typhi* (14.5 mm) and *S. aureus* (16.8 mm), when compared to the positive control (AgNO3) which had the maximum activity against *B. subtilis* and *E. coli*(6.8 and 7.2 mm, respectively) using disc diffusion method. The antibacterial effects of AgNPs was attributed to their small size and extremely large surface are that increased

their ability to enter cell membrane and provided better contact with microorganisms [107]. The ethanolic leaf extract of *A. mauritianum* was investigated against *P. aeruginosa, K. pneumonia* and *E. coli*. It showed highest activity against *K. pneumonia* with (MIC) 15 % (w/v) while exhibiting lowest activity against *E. coli* with MIC 25% (w/v) [108].

2.2.16. Antiviral activity

The methanloic extract of *A. figarianum* leaves as found to possess a moderate activity against two animal viruses (Newcastle disease virus and the Fowl pox virus), particularly when used at dose of 100 μg/ml [105].

2.2.17. Anthelmintic activity

The ethyl acetate and aqueous extracts of *A. indicum* leaves at different concentrations (25, 50 and 100 mg/ml) were evaluated for their anthelmintic activity against earth worm *Eu. eugeniae* and round worm *As. lumbricoids*. Albendazole was used as standard drug. The extracts exhibited a higher activity on earth worm *Eu. eugeniae* more than round worm *As. lumbricoids*. The ethyl acetate extract showed better activity than the aqueous extract [109]. The comparative evaluation of anthelmintic activity of different extracts (ethyl acetate, methanol and aqueous) of *A. indicum* (whole plant) against *As. lumbricoids* and *Ph. postuma* showed that all the extracts of the plant possessed a good anthelmintic activity against both parasites. The methanolic extract was found to be the most potent extract and exhibited anthelmintic activity higher than the reference drug piperazine citrate [110]. The alcoholic extract of the stems, ethyl acetate and carbon tetrachloride fractions of aqueous extract of *A. indicum* leaves were investigated for their anthelmintic activity against *Ph. posthuma*. All tested extracts showed a significant activity at concentration of 80 mg/ml compared to albendazole [100]. The methanolic extracts of *A. indicum* stems, leaves and roots were tested against earthworms (*Ph. posthuma*) at concentration of 20 mg/ml. The methanol extract of stem was found to be most active followed by root and leaves. [111].

2.2.18. Anti-malarial activity

The different extracts of *A. grandiflorum* roots were studied for their anti-malarial *in vivo* and *in vitro* antiplasmodial effects. The extracts showed promising antimalarial effects specially; ethyl acetate extract exhibited the highest in vivo activity against *Pl. vinckei vinckei* in mice and *in vitro* against *Pl. falciparum* [81].

2.2.19. Larvicidal activity

The *n*-hexane, petroleum ether, acetone, ethyl acetate and methanol extracts of *A. indicum* leaves were assayed for their toxicity against *Cu. quinquefasciatus*. All extracts showed moderate larvicidal effects however, the highest larval mortality was found in petroleum ether extract (100% larval mortality). The potent larvicidal activity of petroleum ether extract was attributed to β-sitosterol which was a mosquito larvicidal compound isolated from petroleum ether extract [112]. The different extracts (*n*-hexane, diethyl ether, dichloromethane and ethyl acetate) of *A. indicum* leaves showed different various effects against vector mosquitoes *Ae. aegypti*, *An. stephensi* and *Cu. quinquefasciatus*. The *n*-hexane extract was found to be the most effective extract as it exhibited 100 % mortality at 1000 ppm against the larvae of *Ae. aegypti* at 24 hrs, while the diethyl ether extract showed the lowest activity against the three vector mosquitoes [113].

2.2.20. Anti-leishmanial activity

The ethanolic extract and different fractions (*n*-hexane, chloroform, *n*-butanol and aqueous of *A. indicum* seeds were examined for their anti-leishmanial effects against *L. donovani*. The ethanolic extract exhibited dose-dependent efficacy with highest activity followed by *n*-hexane and *n*-butanol fractions while, chloroform and aqueous fractions were totally inactive [114].

2.2.21. CNS activity

Various extracts (petroleum ether, chloroform, ethanol and aqueous) of *A. indicum* aerial parts were investigated for their CNS depressant activity using phenobarbitone induced sleeping time and locomotors activity testing on mice. The chloroform extract showed better CNS depressant activity more than the other extracts. It exhibited a significant reduction in the locomotor activity compared with to standard drug diazepam and potentiated phenobarbitone sodium induced sleeping time [115].

2.2.22. Anti-stress activity

The ethanolic extract of *A. indicum* was evaluated for its anti-stress activity using cold induced stress method in albino rats. It significantly reduced the WBC, lymphocytes, eosinophils and monocyte counts and showed significantly reduction in ulcer incidence (%), increase in pH of gastric juice, in addition to it exhibited a significant decrease in elevated blood glucose, cholesterol, triglyceride and plasma cortisol [116]. The pretreatment of the methanolic extract of *A. muticum* seeds at doses of 200 and 400 mg/kg (p.o) in albino rats subjected to swim endurance stress model showed that the extract exhibited a significant increase in total time swimming and significant improvement in swimming endurance. In addition to, it significant delayed the onset of immobilization. While, the 100 mg/kg of the extract was found to be inactive. The adaptogenic activity of this plant was attributed to the presences of biological active constituents such as flavonoids, fixed oils and alkaloids [43]. The anti-anxiety activity of ethanolic extract of *A. indicum* leaves was studied using Elevated Plus Maze model induced stress in mice. The extract was orally administrated at doses of 100, 200 and 400 mg/kg. The three doses significantly increased the percentage of time spent in open arms and numbers of entries into the open arms in dose dependent manner

in comparison with diazepam (2mg/kg) as the standard drug [117].

2.2.23. Immunostimulant effects

The ethanolic and aqueous extracts of leaves of *A. indicum* were screened for their immunomodulatory activity on specific and non-specific immunity using hemagglutination antibody (HA) titer, delayed type hypersensitivity (DTH), neutrophil adhesion test and carbon clearance tests. The oral administration of the ethanolic extract at dose of (200 mg/kg, p.o.) and aqueous extract at (400 mg/kg, p.o.) showed a significant increase in the production of circulating antibody titre as well as it significantly potentiated the DTH reaction. It exhibited a significant increase in percentage neutrophil adhesion fibers and phagocytic activity. The immunostimulant effect of this plant could be attributed to the flavonoids content [118].

2.2.24. Anti-venom effect

In vitro anti-venom activity of the hexane and methanolic extracts of *A. indicum* leaves were evaluated against *Echis carinatus* venom. Both extracts were able to inhibit acetylcholinesterase, phospholipase, hyaluronidase, protease and phosphomonoesterase toxic enzymes present in snake venom. The methanolic exhibited greater activity more than the *n*-hexane extract. It showed the maximum inhibition in case of phosphomonoesterase and phosphodiesterase (100%) and minimum inhibition in phosphomonoesterase (14%) at a concentration of 250 µg/ml [119].

2.2.25. Wound healing activity

The wound healing effects of ethanolic extract of *A. indicum* leaves was studied using excision wound model in albino rats. The extract showed significantly wound contracting and increase in wound closure rate greater than that the reference standard nitrofurazone [120].

2.2.26. Anti-hyperlipidemic activity

Lipid lowering effect of the ethanolic and aqueous extracts *A. indicum* leaf was evaluated using triton and diet induced hyperlipidemic models in wistar strain albino rats. Both extracts at dose of 400 mg/kg inhibited the elevation in serum cholesterol and triglyceride levels with increase in high-density lipoprotein cholesterol in high-fat diet-induced hyperlipidemic rats [121]. The 50% hydro ethanolic extract of *A. indicum* leaves showed significantly reduction in both triglycerides and total cholesterol levels after 12 days of pretreatment with the extract at doses of 200 and 400 mg/kg in poloxamer induced hyperlipidemia in rats. The plant significantly reduced TG levels by 16.85 and 20.64%, respectively and decreased TC level by 37.39% and 43.8%, respectively. In addition to, LDL and VLDL levels were found to be significantly decreased. While, the extract didn't show any changes on HDL cholesterol [122].

2.2.27. Cardioprotective activity

The ethanolic extract of *A. indicum* roots was evaluated for protection against isoproterenol induced myocardial infarction in male wistar rats. The extract was orally administrated at doses of 100 and 500 mg/kg. The ethanolic extract of *A. indicum* (100 mg/kg) was safe and highly effective in preventing cardiovascular dysfunction in rats, possibly due to antioxidant property. However, extract of *A. indicum* (500 mg/kg) was found to produce myocardial injury on its own and failed to reverse the isoproterenol induced myocardial injury [123].

2.2.28. Anti-hypertensive Activity

The water, acetone and ethanol extracts of *A. indicum* root inhibited angiotensin converting enzyme by 18, 9 and 1.0%, respectively that confirmed the folk use of this plant as a diuretic and antihypertensive agent [124].

2.2.29. Effect on libido

The methanolic extract of *A. indicum* aerial parts was investigated for the libido enhancement activity at doses 100, 200 and 400 mg/kg for 21 days using automated runway methodology and coupulatory behavior models. The pretreatment with 400 mg/kg of the extract significantly lowered runtime for female and male rat target at the 11th and 21st day. The dose at 200 mg/kg reduced the runtime for male target only after 11 days, while the extract at dose of 100 mg didn't show any significant activity. The extract significantly improved the runway parameters and coupulatory behavior exhibiting its effectiveness in enhancing the female libido [125].

2.2.30. Aphrodisiac activity

The aqueous extract of *A. indicum* roots possessed marked an aphrodisiac activity, when administrated orally at various doses (100, 200 and 400 mg/kg) in male rats and mice. The extract at 200 and 400 mg/kg exhibited a significant increase in the frequency of penile erection episodes with penile erection index 229 and 332, respectively compared to 350 penile erection index of sildenafil. All the extract doses showed a significant increase in the number of female licking behavior and the mating performance of males in addition to significant increase in the sperm count [126].

2.2.31. Abortifacient effects

The aqueous extract of *A. panosum* was orally administrated at an early stage of pregnancy in female albino rats at doses of 50,100 and 150 mg/kg for five days. All doses of the extract were found to be abortifacient particularly the dose of 150 mg/kg exhibited 100% abortifacient activity [127]. The effect of the alcoholic, hot aqueous extracts and crude powder of *A. indicum* seeds on genital organs and fertility of pregnant female albino rats was studied at dose of 25, 50 and 75 mg/kg/day for 15 and 30 days. All plant extracts increased the body weight and

reduced genital organs in addition to the inhibition of the ovarian function, change the uterine structure leading to prevention of the implantation [128]. The 50% methanolic extract of *A. indicum* fruits showed a potent significant suppression of uterine peroxidase enzyme activity and uterus weight induced by estradiol in ovariectomized rats at different concentrations (100, 200 and 500 mg/kg). The extract was found to be a highly potent estrogen antagonist [129].

2.2.32. Toxicological studies

The oral administration of the aqueous extract of *A. indicum* and the fresh juice of leaves at doses of 2, 4, 6, 8 and 10 g/kg body weight in mice for 14 days showed that the plant was found to be safe at doses of 10 g/kg as well as 10 ml/Kg as no significant changes in the body weight or adverse effects were shown. Concomitantly, there was no mortality at any dose up to 10 g/kg [130]. The ethanolic and aqueous extract of leaves of *A. indicum* were orally administered at doses of 2 and 4 g/kg in mice for 14 days and both extracts were found to be safe at these previously mentioned doses with no mortality observed [118]. The LD_{50} of the aqueous extract of *A. indicum* (whole plant) was found to be greater than 5g/kg in rats [62]. A starting dose of 2 g/kg of the 75% methanolic extract of *A. indicum* leaves was orally administrated to three female rats for 14 days, where it didn't show any signs of toxicity. The extract possessed LD_{50} value more than 2 g/kg [46]. The oral administration of the ethanolic extract of A. mauritianum roots at doses of 0.5, 1.0 and 1.5 g/kg in albino rats showed no mortality or signs of toxicity like; change in skin, eyes or mucous membrane or in respiratory, circulatory, behavior patterns. Convulsions and salvation were also not affected [44]. The aqueous methanolic extract of *A. bidentatum* (aerial parts) didn't show any signs or symptoms of toxicity or mortality up to 2 g/kg dose in rabbits indicating that the LD50 of the plant is higher than 2 g/kg [60]. Oral administration of the ethanolic and aqueous extracts of A. glacum seeds at doses of 75 and 300 mg/kg for two weeks in rats showed that both extracts were toxic but not fatal and produced damage and necrosis in the liver attributed to the decreased activity of ALT and increased activity of AST, in addition to kidney damage [131].

Conclusion

This review provides valuable information about the various phytoconstituents and biological activities of genus Abutilon for the first time. It is reported that Abutilon plants contain different classes of chemical constituents including flavonoids, alkaloids, fatty acids, steroids, triterpenes, coumarins and iridoid glycosides together with a several medicinal benefits such as such as antioxidant, anti-inflammatory, antipyretic, hepatoprotective, analgesic and anti-hyperglycemic. According to the present review, genus abutilon is considered a good point of interest and some species such as *A. pannosum, A. mauritianum, A. crispum, A. grandiflorum, A. bidentatum, A. figarianum A. ochsenii* and *A. vitifoliumneed* further studies to explain the mechanisms of action of its biological actions that assists to develop and explore new drugs from natural source.

Declarations of interest

The authors declare that they have no conflict of interest.

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