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ETHNO PHARMACOLOGICAL AND PHYTO PHARMACOLOGICAL PERCEPTION ON *KALANCHOE* (*CRASSULACEAE*) - A COMPREHENSIVE REVIEW

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ABSTRACT: Natural molecules from plants are vital sources to explore potent lead molecules in the drug discovery process. Plants as A source of medicine is an ancient practice in India. The Indian subcontinent is a wide repository of medicinal plants that are being used in the traditional system of medicines. *Kalanchoe* is one of the medicinal plants; the succulent leaf juice is prepared by grinding the leaves mechanically and is a Tyler-made medicine being prescribed by traditional practitioners to combat various diseases and disorders. Various species of *Kalanchoe* find an important place in traditional medicine across the globe. This review article is a systematic compilation of recent updates on the worldwide ethnopharmacological uses and phytomolecules as therapeutic markers, pharmacological profiles, pharmacokinetic studies and SAR of bufadienolides from varied species of *Kalanchoe*. The systematic compilation of review articles will direct the scientific community to focus their research by doing further molecular and targeted throughput screening of the lead molecules from *Kalanchoe*, results in drug discovery from the potent herbal plant *Kalanchoe*. In addition, the unveiled tylor made medicine from ethnic herb *Kalanchoe* is substantiated by the scientific studies gives the scientific validation of folklore claims of *Kalanchoe*.

INTRODUCTION: Indian subcontinent is a wide repository of medicinal plants that are used in the traditional system of medicines. Plants as a source of medicine is an ancient practice in India. About 70 percent of the rural population in India depends on native medicinal plants [1]. Exploring the potential traditional herbs is the need of the hour for modern drug discovery.

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Using the strategies in Reverse pharmacognosy to focus on molecular targets and genomic approaches could give potential leads from herbal medicines. A remarkable example of one such medicinal herb is *Taxus baccata* and its pharmaceutical phytomolecule Taxol, an antimicrotubule, an antineoplastic or cytotoxic chemotherapy drug in modern medicine.

The site of administration is into the veins as an injection or infusion. Hence exploring the potential lead molecules from the herbs would facilitate the discovery of novel leads from the asset of Indian medicinal plants. One such potential Indian medicinal plant is *Kalanchoe* belong to the family *Crassulaceae*. It is need of the hour to compile the

updated global ethnopharmacological uses, phytopharmacological studies, including the therapeutic markers, pharmacokinetic studies, and SAR of bufadienolides from *Kalanchoe*.

In addition, this review article will direct the scientific community to focus their research by doing further.

Molecular and targeted throughput screening of the lead molecules from *Kalanchoe* results in drug discovery from Indian medicinal plants against various diseases and disorders [2].

Taxonomy of *Kalanchoe*: *Crassulaceae* comprises approximately 35 genera and 1500 species, and the majority is succulents. It consists of diversified morphology, cytology, and habbit [3]. The taxonomical hierarchy of *Kalanchoe* is as follows, a kingdom: Plantae (Plants), subkingdom: Tracheobionta (Vascular Plants), super division: *Spermatophyta* (Seed plants), division: *Magnoliophyta* (flowering plants), class: *Magnoliopsida* (dicotyledonous), subclass: Roxidae, order: *Saxifragales*, family: *Crassulaceae*, genus: *Kalanchoe* [4, 5].

FIG. 1: HABITAT OF *K. GASTONNIS-BONNIERI*

FIG. 2: POTTED *K. GASTONNIS-BONNIERI*

TABLE 1: ETHNOMEDICAL USES OF *KALANCHOE GLOBALLY*

S. no.	Country	Ethnomedical uses	References
1	USA	In chickenpox, fevers and stomach aches.	6, 7
2	West Indies	In menstrual disorders, ulcers, hypotension, urinary disorders.	7
3	Brazil	In abscesses, adenoids, arthritis, athlete's foot, bronchitis, burns, calluses, conjunctivitis, coughs, dermatitis, earaches, eczema, edema, erysipelas, fever, glaucoma, headache, infections, inflammations, insect stings, intestinal problems, itch, kidney stones, lymphatic disorders, mouth sores, nervousness, rheumatism, scurvy, toothache, wart and wounds	6, 7
4	Nigeria	In coughs, earaches, eczema, inflammations	6, 7
5	Ecuador	For bruises, broken bones	6, 7
6	Guatemala	In aches, diarrhoea, skin problems	6, 7
7	India	For abdominal discomfort, boils, bruises, cholera, cuts, diabetes, diarrhoea, dysentery, flatulence, headaches, kidney stones, indigestion, insect bites, scabies, sores, urinary insufficiency and wounds	8, 9
8	Mexico	In eye infections, headaches, inflammation, menstrual disorders, pimples and wounds	6, 7
9	Peru	In bacterial infections, boils, broken bones, bronchitis, lymphomas, conjunctivitis, coughs, ear aches, eye infections, epilepsy, fever, headache, heartburn, inflammation, intestinal problems, migraine, nausea, skin problems, sores, ulcers, urethritis.	6, 7
10	Bangladesh	In cough, fever, eplilepsy, constipation and piles	10,11
11	Vietnam	Antibacterial and anti-inflammatory	12

Ethnomedical Uses of *Kalanchoe*: In the southern part of India the leaf of *Kalanchoe* gastonis-bonnieri **Fig. 1** & **2**, is being consumed in an empty stomach and after half an hour interval, one and half litres of water is to be taken for three days in early morning, results in the expulsion of kidney stone from the urinary tract. Traditional physicians are practicing this one of the potential traditional medicine to overcome renal calculi and avoid surgery or lithotripsy along with analgesics, which is the only method of choice to combat kidney stones in modern medicine. In addition, the

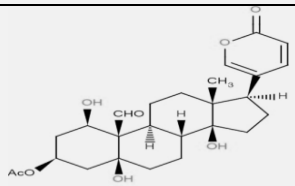
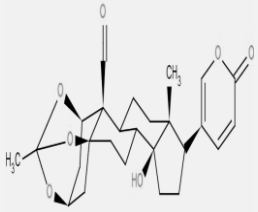
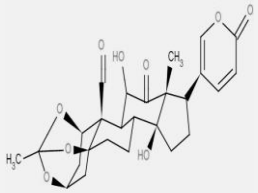
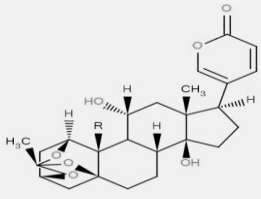
succulent leaf juice is prepared by grinding the leaves mechanically, is a Tyler-made herbal medicine being prescribed by traditional practitioners to combat urolithiasis. Various species of *Kalanchoe* find an important place in ethnic medicine across the globe [6]. The worldwide ethnomedical use of *Kalanchoe* is tabulated in **Table 1.**

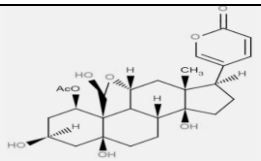
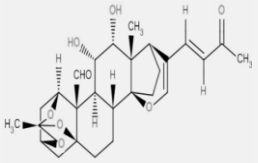
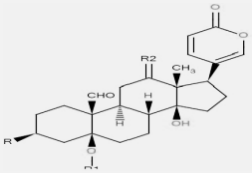
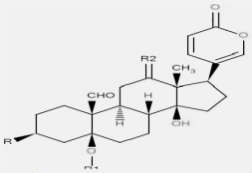
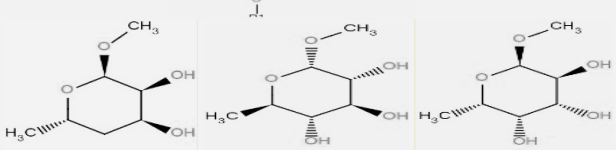
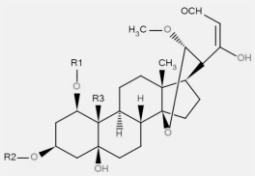
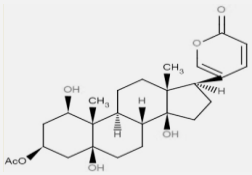
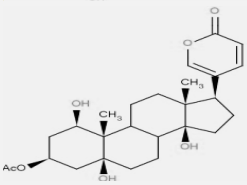
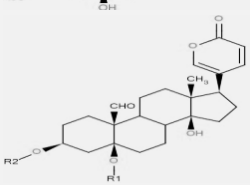
Phytomolecules AS Chemotaxonomic Markers of *Kalanchoe*: Secondary metabolites in plants are predominantly synthesized for defense mechanism. They exhibit specific pharmacological and toxicological effects on animals and humans. At a low dose they possess therapeutic action. The plants synthesizing such potential molecules as its defense mechanisms and exploring the synthesized potential molecules is the basic step of the drug discovery process. The medicinal herbs are used by native or ethnic peoples or in traditional medicine are the reservoir of lead molecules.

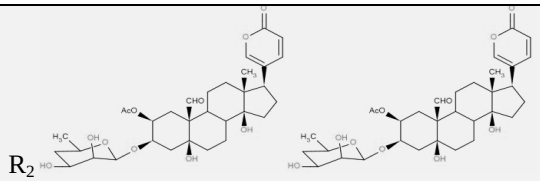
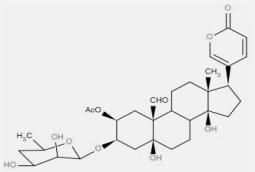
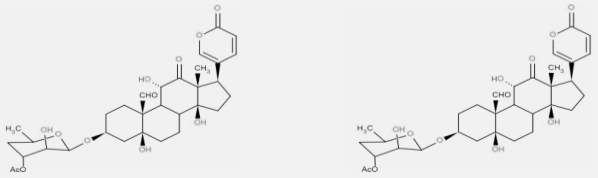
In this perspective the reservoir of leads synthesized in the *genus Kalanchoe* is been collated in this review.

Bufadienolides - Chemotaxonomic marker of *Kalanchoe*: *Kalanchoe* reported the presence of varied, complex bufadienolides and flavonoids as the major active constituents [13]. Bufadienolides are the characteristics chemotaxonomic marker of *Kalanchoe* as well as *Crassulaceae* subfamily Kalanchooideae as a whole. Bufadienolides are reported as neurotoxins and acts in defense mechanisms against predators [14]. The varied, complex structure of bufadienolides reported in *Kalanchoe* is tabulated in **Table 2.** Bryophyllin A, B & C, Kalanchoside A, B, C, Kalanhybrin A, B, C, Bersaldeginin 1,3,5- orthoacetate, Bersaldeginin 3- orthoacetate, Bersaldeginin 1 - orthoacetate, Daigremontianin, Methyl daigremonate, Daigredorigenin 3-acetate, Hellibrigenin 3-acetate, 3-0-acetyldaigredorigenin, Lanceotoxin A & B, Kalanchoside, Bryotoxin A, B & C are reported in the species of *Kalanchoe viz*., K. *lanceolata*, K. diagremonitana, *K. tubiflora*, K. diagremonitana x tubiflora, *K. pinnata*, *K. gracilis*, K. hybrida, K. lanceolata, K. tomentosa, K. tubiflorum, and Bryophyllum *pinnata*.

TABLE 2: BUFADIENOLIDES - CHEMOTAXONOMIC MARKER FROM THE *GENUS KALANCHOE*

S. no.	Constituents	Species & Parts	Chemical Structure	References
1	Hellibrigenin-3- acetate	*k. lanceolata* - Leaves		15 & 16
2	Bersaldegenin 1,3 5-orthoacetate	*k. daigremonitana* *k. tubiflora* Leaves		15, 17, 19, 20 & 23
	Daigremontianin	*k.daigremonitana* *k. tubiflora* *k. Daigremontianax tubiflora* Leaves		
3	Bryophyllin A & C	*K. pinnata* *K. daigremontiana* Leaves		19, 23 & 15
		k. Daigremontianax tubiflora	Bryophyllin A, R= CHO Bryophyllin C, R = CH_2OH	20

4	Bryophyllin B	*Bryophyllumpinnata* Leaves		18
5	Methyl daigremonate	*K. daigremontiana x tubiflora* Leaves		19 & 15
	Bersaldegenin -3- orthoacetate Bersaldegenin -1- orthoacetate		 Bersaldegenin-3– acetate, R_1 = Ac; R_2= H Bersaldegenin-1– acetate, R_1 = H; R_2= Ac	
6	Kalanchoside A, B, C	*K. gracilis* Aerial parts	 	15 & 22
			R	**Kalanchoside A** / **Kalanchoside B** / **Kalanchoside C**
			R_1	H / H / H
			R_2	CH_2 / CH_2 / O
7	Kalanhybrin A, B, C	*K. hybrida* Whole plant		21
			Kalanhybrin A Kalanhybrin B Kalanhybrin C	**R_1**: H / Ac / H **R_2**: Ac / H / Ac **R_3**: CHO / CHO / CH_3
8	Daigredorigenin-3-acetate	*K. hybrida* Whole plant		21
9	3-O-Acetyldaigredorigenin	*K. daigremontiana*		23
10.	Lanceotoxin A Lanceotoxin B	*K. lanceolata*		23

			 R_2 Lanceotoxin Lanceotoxin B	
11	Kalanchoside	*K. tomentosa*		23
12	Bryotoxin A, B & C	*K. tubiflorum*	  Bryotoxin A R_1 R_2 Bryotoxin B CH_2OH O Bryotoxin C CHO H_2	23

Flavonoids - Chemotaxonomic Marker of *Kalanchoe*: Flavonoids are polyphenolic compounds have 15 carbon skeleton contains two phenyl ring (ring A & B) and heterocyclic ring (ring C containing oxygen). Chemically they are C6-C3-C6. Flavonoids are widely distributed in plants. They are plant pigments that attract pollinator animals. Pharmacologically they are well-known free radical scavengers. *Kalanchoe* reported for the presence of flavonols and flavone as chemotaxonomic markers in the form of flavonoid glycosides. Rhamnoside or Rhamnopyranoside is the sugar molecule as chemotaxonomic markers in the place of primary metabolites attached in the glycone part. Flavonoids glycosides reported in *Kalanchoe* species are K. spathulata, *K. gracilis*, *K. brasiliensis*, K. laciniata, *K. pinnata*, K. gastonis-bonnieri, K. streptantha, Bryophyllum pinnatum and K. marmorata. Flavonols reported in the above species are Patulein, Quercetin, Quercetin, and flavone molecules reported are Kaempferol, Eupafolin, Luteolin, Kapinnatoside (Kaempferol diglycoside), Afzelin, Rhamnoisorobin, Isorhamnetin, and Kaempferitrin **Table 3.**

TABLE 3: FLAVONOIDAL MARKER COMPOUNDS FROM THE *GENUS KALANCHOE*

S. no.	Phyto-constituents	Species & Part	Chemical structure								Ref.
1	Patuletin-3,7-di-rhamnoside	*K. spathulata* Leaves& flowers	R_1 o-rhamnoside	R_2 OH	R_3 OCH_3	R_4 o-rhamnoside	R_5 H	R_6 OH	R_7 OH	R_8 H	24, 25, 26, 27 & 28
2	Patuletin	*K. spathulata* Leaves & flowers	R_1 OH	R_2 OH	R_3 OCH_3	R_4 OH	R_5 H	R_6 OH	R_7 OH	R_8 H	24, 25, 26, 27 & 28
3	Quercetin	*K. spathulata* Leaves & flowers *K. gracilis* Aerial parts	R_1 OH	R_2 OH	R_3 H	R_4 OH	R_5 H	R_6 OH	R_7 OH	R_8 H	25, 26, 27, 28, 29 & 30
4	Quercetin-3-O-glucoside-7-O-rhamnoside	*K. spathulata* Leaves & flowers	R_1 O-glucoside	R_2 OH	R_3 H	R_4 O-rhamnoside	R_5 H	R_6 OH	R_7 OH	R_8 H	24, 25, 26, 27 & 28
5	Kaempferol	*K. spathulata* Leaves & flowers *K. gracilis* Aerial parts	R_1 OH	R_2 OH	R_3 H	R_4 OH	R_5 H	R_6 H	R_7 OH	R_8 H	24, 26, 27, 28, 29 & 30

6	Kaempferol-3-O-rhamnoside	*K. spathulata* Leaves & flowers	R_1 O-rhamnoside	R_2 OH	R_3 H	R_4 OH	R_5 H	R_6 H	R_7 OH	R_8 H	25, 26, 27
7	Eupafolin-4'-O-rhamnoside	*K. gracilis* Aerial parts	R_1 OH	R_2 OH	R_3 OCH_3	R_4 OH	R_5 OH	R_6 H	R_7 O-rhamnoside	R_8 H	29 & 30
8	Eupafolin-3-7 di-O-rhamnoside	*K. gracilis* Aerial parts	R_1 O-rhamnoside	R_2 OH	R_3 OCH_3	R_4 O-rhamnoside	R_5 H	R_6 H	R_7 OH	R_8 H	29 & 30
9	Eupafolin-3-O-rhamnosyl-7-O-(4-O-acetylrhamnoside)	*K. gracilis* Aerial parts	R_1 O-rhamnoside	R_2 OH	R_3 OCH_3	R_4 4-O-acetyl rhamnoside	R_5 H	R_6 H	R_7 OH	R_8 H	29 & 30
10	Eupafolin-3-O-(3-O-acetylrhamnosyl)-7-O-(3-O-acetylrhamnoside)	*K. gracilis* Aerial parts	R_1 3-O-acetyl rhamnoside	R_2 OH	R_3 OCH_3	R_4 3-O-acetyl rhamnoside	R_5 H	R_6 H	R_7 OH	R_8 H	29 & 30
11	Luteolin	*K. gracilis* Aerial parts	R_1 H	R_2 OH	R_3 H	R_4 OH	R_5 H	R_6 OH	R_7 OH	R_8 H	29 & 30
12	Quercitrin	*K. gracilis* Aerial parts	R_1 O-rhmanoside	R_2 OH	R_3 H	R_4 OH	R_5 H	R_6 OH	R_7 OH	R_8 H	29 & 30
13	Eupafolin	*K. gracilis* Aerial parts	R_1 OH	R_2 OH	R_3 OCH_3	R_4 OH	R_5 H	R_6 H	R_7 OH	R_8 H	29 & 30
14	Patuletin-3-O-(4"-O-acetyl- α-L-rhamnopyranosyl)-7-O-(2"'-O-acetyl-α- L-rhamnopyranosid)	*K. brasiliensis* *K. laciniata* *K. spathulata* Juice of fresh stems & leaves	R_1 4" – o-acetyl rhamnoside	R_2 OH	R_3 OCH_3	R_4 2"'- o-acetyl rhamnoside	R_5 H	R_6 OH	R_7 OH	R_8 H	31, 24, 15, & 32
15	Patuletin-3-O-α-L-rhamnopyranosyl-7 O-(2"'- O-acetyl-α-L-rhamnopyranosid)	*K. brasiliensis* *K. laciniata* *K. spathulata* Juice of fresh stems & leaves	R_1 O-rhamanoside	R_2 OH	R_3 OCH_3	R_4 2"'- o-acetyl rhamnoside	R_5 H	R_6 OH	R_7 OH	R_8 H	31, 24, 15, & 32
16	Patuletin-3-O-(4"-O-acetyl- α-L-rhamnopyranosyl)-7-O-rhamnopyranoside	*K. brasiliensis* *K. laciniata* *K. spathulata* Juice of fresh stems & leaves	R_1 4"–O-acetyl rhamnoside	R_2 OH	R_3 OCH_3	R_4 O-rhamanoside	R_5 H	R_6 OH	R_7 OH	R_8 H	31, 24, 15, 32 & 33
18	8-methoxy quercetin 3,7-Di-O-rhamnopyra	*K. brasiliensis* *K. laciniata* *K. spathulata* Extracts	R_1 O-rhamnoside	R_2 OH	R_3 H	R_4 O-rhamnoside	R_5 OCH_3	R_6 OH	R_7 OH	R_8 H	31, 24, 15, 33 & 34

	noside										
20	8-methoxykaempferol-3,7-di-O-rhamnopyranoside	*K. brasiliensis, K. pinnata& K. gastonis bornieri*	R_1 O-rhamnoside	R_2 OH	R_3 H	R_4 O-rhamnoside	R_5 OCH_3	R_6 H	R_7 OH	R_8 H	32
19	3-*O*- _-L-rhamnopyranosyl-3,3_,4_,5,7-pentahidroxi-8-methoxyflavone	*K. brasiliensis K. laciniata K. spathulata* Juice of fresh stems & leaves	R_1 4’’-O-acetyl rhamnoside	R_2 OH	R_3 OCH_3	R_4 O-rhamnoside	R_5 OCH_3	R_6 OH	R_7 OH	R_8 H	31, 24, 15, 32 & 33
20	4""-Acetylsagittatin A	*K. streptantha* Leaves	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	34 & 24
21	Kapinnatoside	*K. pinnata* Leaves	R_1 O-arabinose(1 2) rhamnoside	R_2 OH	R_3 H	R_4 O-acetyl rhamnoside	R_5 H	R_6 H	R_7 OH	R_8 H	35
22	Quercetin-3-O-α-L-arabinopyranosyl (1 →2) α—L-rhamnopyranoside	*K. pinnata* leaves	R_1 O-xylose(1 2) rhamnoside	R_2 OH	R_3 H	R_4 O-acetyl rhamnoside	R_5 H	R_6 H	R_7 OH	R_8 H	35
23	Afzelin	*Bryophyllumpinnatum* leaves	R_1 O-arabinose(1 2) rhamnoside	R_2 OH	R_3 H	R_4 OH	R_5 H	R_6 OH	R_7 OH	R_8 H	36 & 37
24	α-rhamnoisorobin	*Bryophyllumpinnatum* leaves	R_1 O-rhamnoside	R_2 OH	R_3 H	R_4 OH	R_5 H	R_6 H	R_7 OH	R_8 OH	36 & 37
25	Isorhamnetin-3-O-α-L-1C4-rhamnopyranoside	*K. marmorata* leaves	R_1 O-rhamnoside	R_2 OH	R_3 H	R_4 OH	R_5 H	R_6 OCH_3	R_7 H	R_8 OH	38
26	Quercitin -3-O-β-D-4C1-glucopyranoside	*K. marmorata* leaves	R_1 O-glucoside	R_2 OH	R_3 H	R_4 OH	R_5 H	R_6 OH	R_7 OH	R_8 H	38
27	Kaempferitrin	*Bryophyllum pinnatum* leaves	R_1 O-rhamnoside	R_2 OH	R_3 H	R_4 O-rhamnoside	R_5 H	R_6 H	R_7 OH	R_8 OH	38
28	Kaempferol 3-O-α-L-(2-acetyl)rhamnopyranoside-7-O-α-L-rhamnopyra	*Bryophyllum pinnatum* leaves	R_1 O- 2 acetyl rhamnoside	R_2 OH	R_3 H	R_4 O-rhamnoside	R_5 H	R_6 H	R_7 OH	R_8 H	38

	noside										
29	Kaempferol 3-O-α-L-(3-acetyl)rhamnopyranoside-7-O-α-L-rhamnopyranoside	*Bryophyllum pinnatum* leaves	R_1 O- 3acteyl rhamnoside	R_2 OH	R_3 H	R_4 O-rhamnoside	R_5 H	R_6 H	R_7 OH	R_8 H	38
30	Kaempferol 3-O-α-L-(4-acetyl)rhamnopyranoside-7-O-α-L-rhamnopyranoside	*Bryophyllum pinnatum*	R_1 O- 4acteyl rhamnoside	R_2 OH	R_3 H	R_4 O-rhamnoside	R_5 H	R_6 H	R_7 OH	R_8 H	38
31	3',4'-dimethoxy quercetin	*K. pinnata* leaves	R_1 OH	R_2 OH	R_3 H	R_4 OH	R_5 H	R_6 OCH_3	R_7 OCH_3	R_8 H	39

Pharmacological Studies on *Kalanchoe*: Various species of *Kalanchoe* is referenced in folklore and traditional medicine worldwide. Updated pharmacological studies of *Kalanchoe* using *In-vitro* & *In-vivo* screening methods with species names is tabulated in **Table 4.** *Kalanchoe* exhibits diversified pharmacological action due to the presence of multifaceted, complex phytomolecules. *Kalanchoe* exerts action on various non-communicable diseases as well as communicable diseases, based on the scientific studies so far and showed neuropharmacological activity, CNS depressant activity, sedative activity, anticonvulsant activity, cardiovascular activity, cytotoxic and antitumor activity, anti-inflammatory activity, analgesic, wound healing, hepatoprotective activity, immunomodulatory activity, diuretic & urolithiatic activity, antihypertensive activity, antidiabetic activity, muscle relaxant, and uterine relaxant activity, antiallergic activity, acetylcholine esterase inhibitory activity, thyroid peroxidise. Inhibition activity, inhibition of lymphocyte proliferation activity as a pharmacological action on non-communicable diseases and antiviral, antifungal, antibacterial, antileishmanial activity as pharmacological action on communicable diseases including insecticidal activity.

TABLE 4: PHARMACOLOGICAL ACTIVITY OF *KALANCHOE*

S. no.	Plant	Pharmacological Studies Reported		References
1	*Bryophyllum pinnatum*	Antiulcer activity – *In-vivo* studies	Methanol fraction from the leaf extract	36, 40 & 41
		CNS depressant activity – *In-vivo* studies	Methanol Fraction of leaf extract.	36, 40 & 41
		Neuropharmacological activity – *In-vivo* studies	Ethanolic leaf extract - Cardiac glycosides - Bufadienolides & flavonoids	
		Neurosedative and muscle relaxant activity – *Invivo* studies	Saline leaf extract	
		Cytotoxic activity – *In-vitro* cell line studies	Bryophyllin B	18
		Anti-Inflammatory Activity – *In-vivo* studies	Methanol Fraction of leaves	41
		Uterine relaxant activity– *In-vivo* studies	Leaf press juice and its chemical fractions	15 37
		Effect on hematological parameters – *In-vivo* studies	Methanolic leaf extract	37
		Wound healing activity – *In-vivo* studies	Plant extracts- Saponins (aggregating erythrocytes), Tannins (astringent effect)	37
2	*K. pinnnata*	Immunomodulatory activity – *Invivo* studies	Aqueous leaf extract	42 & 41
		Immunosuppressive effect – *Invivo* studies		

		Antiviral activity- *Invitro* studies	Juice of the plant	43
		Antileishmanial activity – *Invitro* studies	Flavonoid extract and Aqueous leaf extract -	35
		Hepatoprotective activity – *Invitro* and *Invivo* studies	Juice of the leaf & ethanolic extract of the marc left after expressing the juice	44 & 41
		Antioxidant activity – *Invivo* studies	Aqueous leaf extract	45
		Anthelmentic Activity – *Invitro* studies	Chloroform, methanolic & aqueous root extract	41
		Wound healing activity –*Invivo* studies	Ethanolic leaf extract	41
		Anti-Hypertensive Activity –*Invivo* studies	Aqueous leaf extract	41
		Antinociceptive, anti-inflammatory and anti- diabetic activity - *Invitro* and *Invivo* studies	Aqueous leaf extract - Flavanoids, polyphenols, triterpenoids	41
		Analgesic and anti-convulsant effects - *Invivo* studies	Hexane, methylene chloride, ethyl acetate, n-butanol fraction and aqueous residue of Methylene chloride / methanol (1:1) extract	41
		Diuretic and anti- urolithiatic activity - *Invitro* studies	Hydro- alcoholic leaf extract	41
		Anti-tumour activity – *Invitro* studies	Bufadienolides e	20
		Anti- allergic activity – *Invivo* studies	Aqueous extract	41
		Acetylcholinesterase inhibition activity - *Invitro* studies	Extract of the leaves	41
		Anti- fungal activity - *Invitro* studies	Ethanolic extracts	13
		Anti-microbial activity - *Invitro* studies	60% methanolic leaf extract	
3	*K.brasiliensis*	Inhibiton of Lymphocytes proliferation activity – *Invitro* studies	Fractionations of the juice of fresh stems & leaves	46
		Anti-inflammatory activity – *Invivo* studies	Amino acid salt	46
		Thyroid Peroxidase inhibitor – Invitro studies	Aqueous extract	47
4	*K. crenata*	Analgesic activity – *Invivo* studies	Aqueous & ethanol leaf extracts Methylene chloride/methanol(1:1) Fractions - hexane, methylene chloride, ethyl acetate, n-butanol	48
5	*K. blossfeldiana*			
6	*K. beharensis*	Antiviral activity- *Invitro* studies	Juice of the plants	13
7	*K.waldheimii*			
8	*K.daigremontiana x K.tubiflora*	Sedative activity – *Invivo* studies	Bufadienolide compounds	49
		Cytotoxic activity – *Invitro* studies	Bufadienolide compounds	49
		Insecticidal activity – Invitro studies	Bufadienolide compounds	49
9	*K. mortagei*	Cytotoxic and Apoptotic Activity - Invitro studies	Bufadienolide compounds	50
10	*K.gracilis*		Aerial parts	13
11	*K.hybrida*		Methanolic extract	13
	K.thrysiflora	Cytotoxic activity - *Invitro* studies	Dichloro methane fraction	51
12	*k.bragilliensis*	Acetylcholinesterase inhibition activity - *Invitro* studies	Extract of leaves	13
13	*k.gastonisbonnieri*			

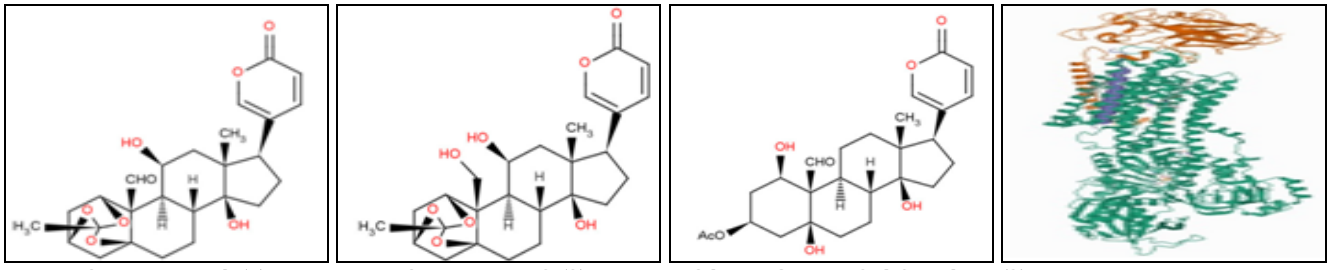
Phytomarkers as Therapeutic Potential of *Kalanchoe*: Natural bioactive phytomolecules is the important source of drug discovery. Exploring the phytoleads will hit the therapeutic targets against various human diseases and disorders. The pharmacological action is scientifically validated by various *in-vitro* and *in-vivo* screening for the lead molecules from *Kalanchoe*. The phytoleads, along with pharmacological studies, is tabulated in **Table 5.**

Bufadienolides: Daigremontianin, Bersaldegenin-1,3,5- orthoacetate (K. *daigremontiana* x *K. tubiflora*) exerts sedative and cytotoxic action,

Bryophyllin A (IC^{50} = 0.4 mM) more potent, Bryophyllin C, Bersaldegenin-3 acetate (K. *pinnata*) showed antitumor activity, 3β-Acetate Hellebrigenin, Bufotalinin, 19-Oxo-bufalin, Hellebrigenin, Monohydroxy-bufotalin, 19-oxo-desacetylcinobufagin, 1βHidroxybufalin, Bufalin, and 3-Dehydroxy cinobufagin (K. mortagei) showed cytotoxic and apoptotic activity. Bryophyllin B (*K. brasiliensis*) showed Cytotoxic activity.

TABLE 5: PHYTOMARKERS OF *KALANCHOE* AND ITS THERAPEUTIC POTENTIAL

S. no.	Marker compound		Plant	Pharmacological action	References
1	Daigremontianin Bersaldegenin- 1,3,5- orthoacetate	Bufadienolides		Sedative activity – *Invivo* studies Cytotoxic activity	49
2	Methyl daigremonate Bersaldegenin- 1,3,5-orthoacetate, Daigremontianin, Methyl daigremonate, Bersaldegenin-1-acetate	Bufadienolides	*K.daigremontiana* x *K.tubiflora*	*Insecticidal activity* – *Invitro* studies	18
3	Patuletin acetyl rhamnoside	Flavonoid	*K. brasiliensis*	Inhibiton of Lymphocytes proliferation activity – *Invitro* studies	29
4	*Kalanchosine* dimaleate	Amino acid salt		Anti-inflammatory activity – *Invivo* studies	52
5	Quercetin Quercitrin (Potent compound with low toxicity profiles) Afzelin	Flavonoid	*K. pinnata*	Antileishmanial activity - *Invitro* studies	33
6	Bryophyllin A (IC50=0.4mM) more potent Bryophyllin C, Bersaldegenin-3 acetate	Bufadienolide		Anti-tumour activity- *Invitro* studies	49
7	Quercetin 3-0-α-L- rabinopyranosyl, α-l-rhamnaopyranoside, Quercetin-3-o-α-L-rhamnopyranoside	Flavonoid		Antileishmanial activity – *Invitro* studies	53
8	Quercitrin	Flavonoid		Anti- allergic activity	31
9	3β-Acetate Hellebrigenin, Bufotalinin, 19-Oxo-bufalin, Hellebrigenin, Monohydroxy-bufotalin, 19-oxo-desacetylcinobufagin, 1βHidroxybufalin, Bufalin, and 3-Dehydroxy cinobufagin.	Bufadienolides	*K. mortagei*	Cytotoxic and Apoptotic Activity - *In-vitro* studies	50
10	1 (3-oxo-olean-12-ene) & β-sitosterol	Alkene compound & Steroid	*K.thrysiflora*	Cytotoxic activity - *In-vitro* studies	51
11	Bryophyllin B	Bufadienolide	*Bryophyllum pinnatum*	Cytotoxic activity – *In-vitro* cell line studies	16



BRYOPHYLLIN A (1) **BRYOPHYLLIN C (2)** **BERSALDEGENIN-3-ACETATE (3)**

FIG. 3: PDB ID 4RES- STRUCTURE OF NA+/K+-ATPASE

Flavonoids [54]: Patuletin acetyl rhamnoside (*K. brasiliensis*) showed inhibiton of lymphocytes proliferation activity, Quercetin, Quercitrin (Potent compound with low toxicity profiles), Afzelin, Quercetin 3-0-α-L- rabinopyranosyl, α-l-rhamnaopyranoside, Quercetin-3-o-α-L-rhamnopyranoside (*K. pinnata*) showed antileishmanial activity, Quercitrin(*K. pinnata*) showed antiallergic activity.

Amino Acid Salt: *Kalanchosine* dimaleate (*K. brasiliensis*) showed anti-inflammatory activity.

Alkene Compound & Steroid Compound: 1-(3-oxo-olean-12-ene) & β-sitosterol (*K. thrysiflora*) showed Cytotoxic activity.

Pharmacokinetic and Efficacy Studies:

Metabolism of Quercetin Glycosides From *K. Pinnata* Against Cutaneous Leishmaniasis: Three flavonoid glycosides present in the aqueous extract (320 mg/kg b/w) of *K. pinnata* Quercetin 3-O- α-L-arabinopyranosyl (1→2)- α-L-rhamnopyranoside, Quercetin 3-O-α-L-rhamnopyranoside and Quercetin (16 mg/kg body weight/oral daily) significantly reduces the parasite load and controls lesion growth caused by *Leishmania amazonensis*. The plasma of the treated mice showed quercetin and quercetin glucuronides are the metabolites of flavonoid glycosides from *K. pinnata*. The pharmacological activity is due to the presence of quercetin glycosides [53].

SAR of Bufadienolides AS Na+/K+-Atpase Inhibitor as an Anticancer Agent – *In-silico* Studies [55]: The protein target used for the study is Na+/K+-ATPase originated from Sus scrofa (PDB 1D 4RES).

The binding pose of bufadienolides- Bryophyllin A (1), Bryophyllin C (2), Bersaldegenin-3-acetate (3) from *Kalanchoe pinnata* on the protein target, is virtually screened and the functional group of the compounds 1-3 responsible for better binding is investigated computationally using Auto Dock 4.2. The steric hindrance of Glu117 to the 1, 3, 5-orthoacetate moiety is removed.

TABLE 6: COMPUTIONAL STUDY OF BUFADIENOLIDES WITH NA+/K+-ATPASE

Compound	Binding energy	PSA	Log p	H-Bond	Hydrophobic interaction	Pi-interaction
1	-10.7	111.5	0.9	4	4	7
2	-9.5	114.7	0.7	4	3	7
3	-3.0	130.4	0.4	3	3	5

Hydrogen bond energy, electrostatic interaction, and ligand efficiency is also investigated.

The docking studies showed that 1,3,5-orthoacetate moiety, 10-CHO, 11-OH, and 14-OH is responsible for the increased activity of compound 1 Bryophyllin A other than compound 2 & 3. 11-OH group appeared to decrease the toxicity of *bufadienolide* [55].

CONCLUSION: The species of *Kalanchoe* (*Crassulaceae*) has diversified morphology, cytology and habit. The current updates on ethnopharmacological, phytochemical and pharmacological studies on *Kalanchoe* are collated in this review article. *Bufadienolides* and flavonoids are the chemotaxonomic markers of *Kalanchoe*. *Bufadienolides* are investigated as a toxic substance; research work has to be focused on identifying the therapeutic dose; hence it may have a narrow therapeutic window similar to cardiac glycosides, digoxin. In addition, due to the diversified chemical structure of phytometabolites, *Kalanchoe* exerts varied pharmacological action. The metabolic study of quercetin glycoside and SAR of bufadienolides are scientifically noticeable; hence pharmacokinetic studies and SAR of the phytomolecules is the need of the hour to identify lead molecules in the drug discovery process. The unveiled tylor made medicine from ethnic herb *Kalanchoe* is substantiated by the scientific studies gives the scientific validation of folklore claims of *Kalanchoe*.

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