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GENUS *Pothos*: A REVIEW OF CHEMICAL CONSTITUENTS AND BIOLOGICAL ACTIVITIES

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ABSTRACT
Pothos is a genus of flowering plants that belongs to the family Araceae. It plays a vital role in developing countries as folk medicine. Numerous compounds have been reported from *Pothos*, out of which some compounds have shown prominent bioactivities. The biological studies of this genus reported various activities including antimicrobial, anticancer, antioxidant, antipyretic, anti-diabetes, bronchodilator, burn wound healing, anti-cariogenic, thrombolytic etc. This review summarizes research carried out on chemical constituents with biological activities of *Pothos* genus to date.
Keywords: *Pothos scandens*, *Pothos chinensis*, Phytochemistry, Anticancer, Antimicrobial.
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INTRODUCTION

The genus *Pothos* belongs to the family Araceae comprises 65 species of root-climbing lianes found in subtropical and tropical forests. It is distributed around the world from the Indian subcontinent to various islands of Indian Oceans and also native to China, Australia and Southeast Asia.[1-2] Linnaeus (1753, 1763) and Schott (early in the 19th century) described this genus as climbing aroids with bisexual flowers.[3] It has been used in folk medicine throughout the world for various ethno medicinal uses.[4-9] Various phytochemical studies on the genus reported that it contains both primary and secondary metabolites. The preliminary phytochemical screening reported several secondary metabolites from the different parts of this plant.[10-15] Numerous compounds have been reported from this genus. The extracts, essential oils and the compounds isolated from various species of *Pothos* exhibited several biological activities, including antimicrobial, antioxidant, antipyretic, anti-diabetes, bronchodilator, burn wound healing, anticariogenic, thrombolytic, anticancer, peritoneal mast cell stabilization, hyaluronidase inhibitory, histamine release inhibiting activities.[16-50] Despite the presence of several biological activities, only a few species from this genus were studied for the isolation of compounds. Moreover, the biological and other phytochemical studies in most of the species are still missing.

There is an increase in the trend of studying isolated compounds from a natural source in recent years due to their wide range of activities that could lead to the identification of promising lead compounds.[51-53] In this review, the phytochemistry and biological activities of various species belonging to the genus *Pothos* are described. It includes a detailed classification of phytoconstituents and a systematic analysis of the biological activities reported in the literature till 2020. A total of 89 phytoconstituents comprised of alkaloids, terpenoids, phytosterols, flavonoids, glycosides, long-chain derivatives, and miscellaneous compounds are listed in this review.

EXPERIMENTAL

The authors collected data from Science Direct, SciFinder, Google Scholar, and PubMed related to *Pothos* genus. The authors reviewed and interpreted the articles of isolated compounds with biological activities against including antimicrobial, anticancer, antioxidant, antipyretic, anti-diabetes, bronchodilator, burn wound healing, anti-cariogenic and thrombolytic.

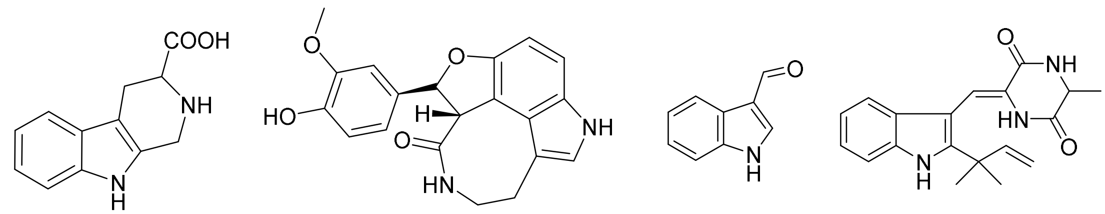
RESULTS AND DISCUSSION

Chemical constituents

The genus *Pothos* has a rich source of alkaloids, flavonoids, terpenoids, coumarin, fatty acids, glycosides and phenolic acids. A total of 89 different types of compounds isolated from *Pothos* species are depicted in Fig.-1 to 11.

Alkaloids

Pothos reported the presence of alkaloids. 1,2,3,4-tetrahydro-3-carboxy-2 carboline (**1**) is a member of the class of beta-carboline alkaloid isolated from the plants *P. scandens*.[10] Beta-carboline has a role as a plant metabolite and as a human urinary metabolite. (–)-serotobenine (**2**), indole-3-aldehyde (**3**) and Neoechinulin A (**4**) are indole alkaloid from the plants *P. scandens* and *P. chinensis*.[12-13]

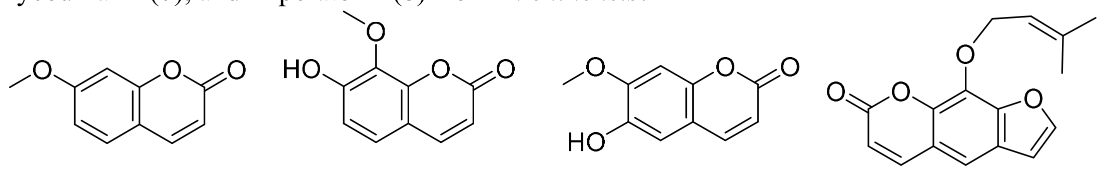


1 **2** **3** **4**

Fig.-1: Structures of Alkaloids (**1**-**4**)

Coumarins

Coumarins are phenolic substances that constitute fused benzene and α-pyrone rings. Ji *et al.* isolated four coumarins including 7-methoxycoumarin (**5**), 7-hydroxy-8-methoxycoumarin (**6**), 6-hydroxy-7-methoxycoumarin (**7**), and imperatorin (**8**) from *P. chinensis*.[13]



5 **6** **7** **8**

Fig.-2: Structures of Coumarins (**5**-**8**)

Fatty Acids

Fatty acids are carboxylic acids containing aliphatic long-chain carbon atoms from C-4 to C-28 in saturated or unsaturated form. Palmitic acid (**9**), Oleic acid (**10**), Linoleic acid (**11**), 9,12,15-ocatadecatrienoic acid (**12**), 13-Phenyltridecanoic acid (**13**), 13-(3',4'-Methylenedioxyphenyl)-tridecanoic acid (**14**) isolated from *P. chinensis*.[15]

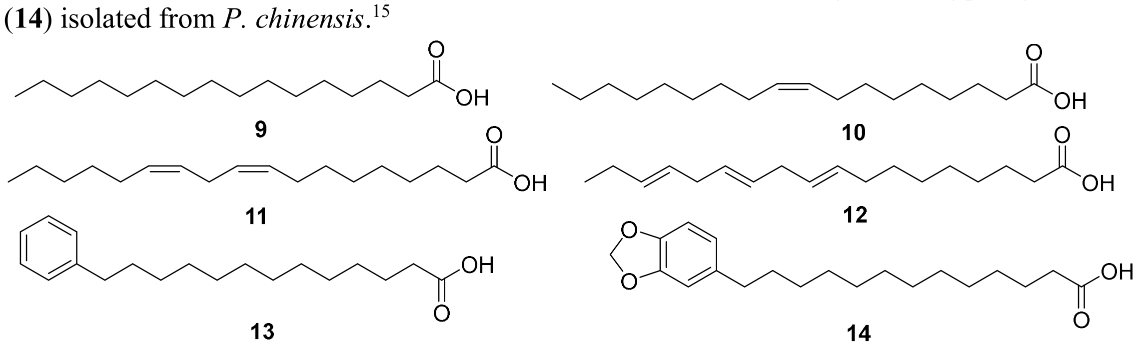


Fig.-3: Structures of Fatty acids (**9-14**)

Flavonoids

Several Flavones including Vicenin-2 (**15**), Neoschaftoside (**16**), Vitexin 2-O-xyloside (**17**), Scoparin 2-O-xyloside (**18**) and liquiritigenin (**19**) were isolated from *P. scandens*and *P. chinensis*.[4,10,14] In 2015, Muhit *et al.* have isolated flavonols including Kaempferol 3-O-gentiobioside (**20**), Quercetin 3-Ogentiobioside (**21**), Isorhamnetin 3-Ogentiobioside (**22**) from *P. scandens*.[10] An isoflavone, Daidzein (**23**), was reported from *P. chinensis*.[14] Several flavonoid glycosides including Vitexin (**24**), Vitexin 7-O-glucoside (isosaponarin, **25**), Isovitexin 7-O-glucoside (saponarin, **26**), Scoparin 7-O-glucoside (**27**), Isoscoparin 7-O-glucoside (**28**), Schaftoside (**29**), Isoschaftoside (**30**) and Chrysoeriol 7-O-rhamnosylglucoside (**31**) have been isolated from *P. chinensis*.[14]

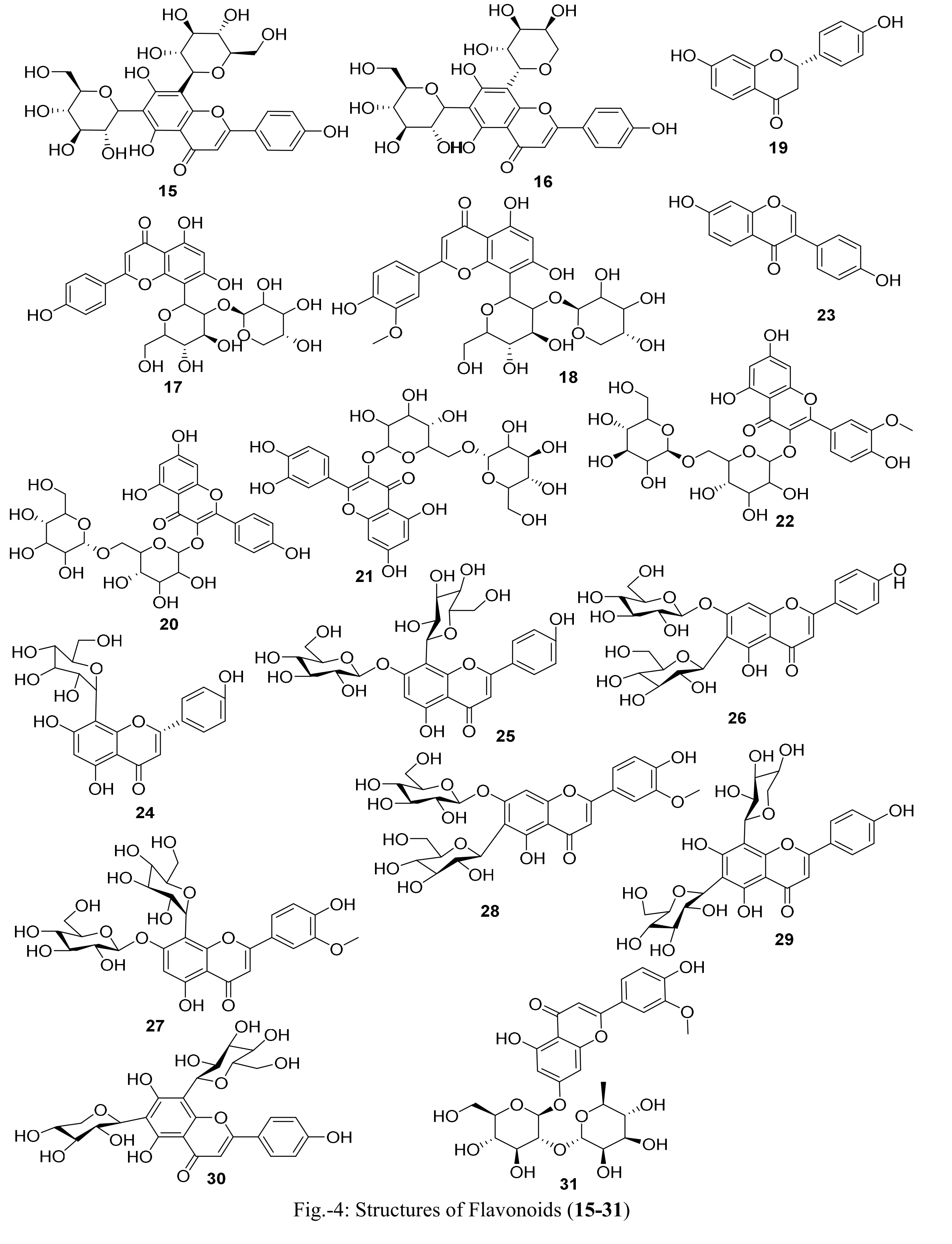


Fig.-4: Structures of Flavonoids (**15-31**)

Glycosides

In glycoside structure, a sugar molecule is bound to another functional group via a glycosidic bond. They are essential in living organisms. Some glycosides including Zizybeoside I (**32**), Canthoside A (**33**) from *P. scandens*, and Berchemolide (**34**), and Prunasin (**35**) from *P. chinensis* have been reported.[4,10] A Phenolic glycosides Markhamioside F (**36**) and a diketopiperazine, Eleutherazine B (syringin) (**37**) were reported from *P.* scandens.[10]

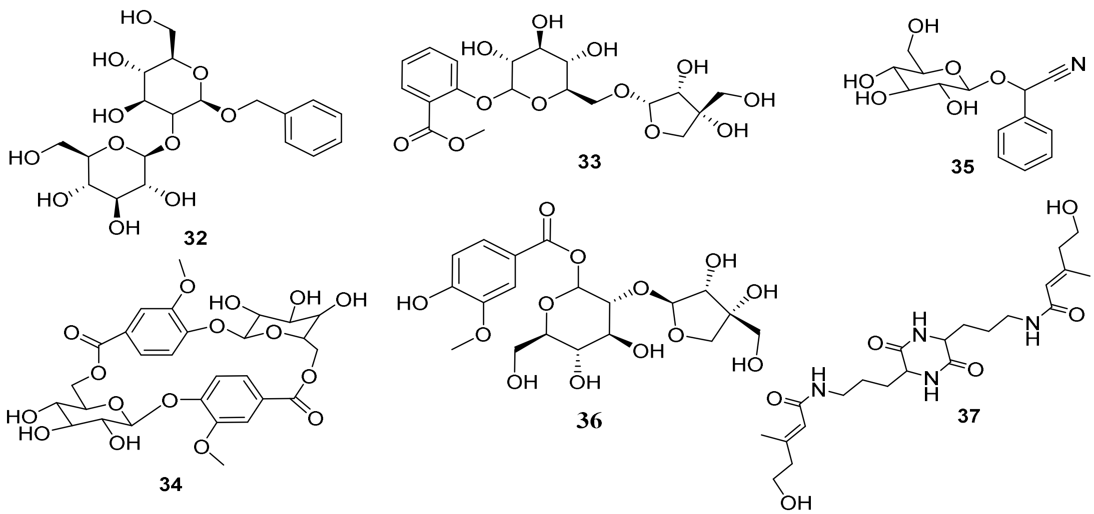


Fig.-5: Structures of Glycosides (**32-37**)

Lignans

Some lignans including (+)-syringaresinol (**38**), (-)-medioresinol (**39**), honokiol (**40**), hinokinin (**41**) were reported from *P. scandens* and *P. chinensis*.[12,13,15]

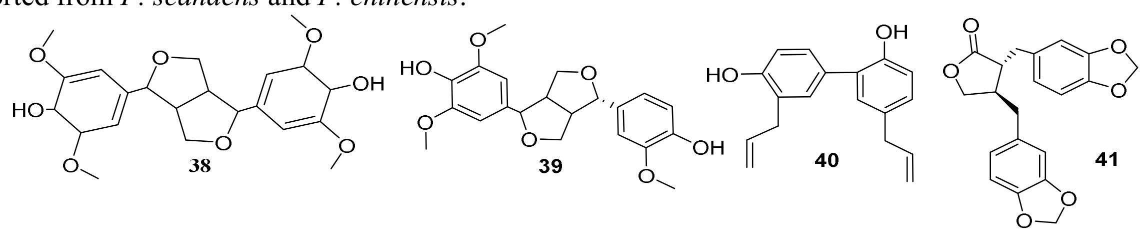


Fig.-6: Structures of Lignans (**38-41**)

Phenylamides

Phenylamides are the conjugated form of amines and phenolic acids. They are extensively distributed throughout the plant kingdom as a function of growth and development. In this class of compounds, N-trans-cinnamoyltyramine (**42**), N-trans-feruloyltyramine (**43**) and N-trans-p-cumaroyltyramine (**44**) were reported from both the species *P. scandens* and *P. chinensis*.[12-13] However, N-cis-p-coumaroyltyramine (**45**) and N-cis-feruloyltyramine (**46**) were reported from *P. chinensis*.[13]

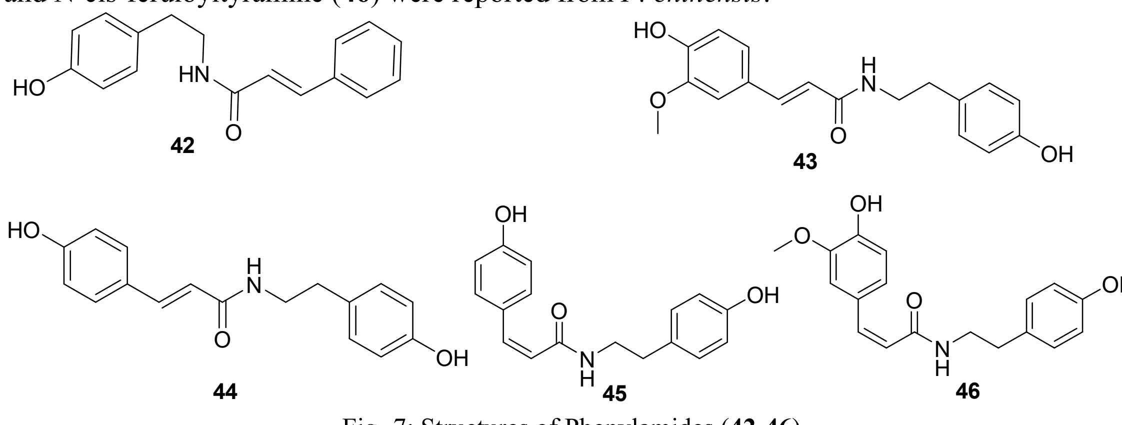


Fig.-7: Structures of Phenylamides (**42-46**)

Phenolic Acids

Phenolic acids are aromatic acids composed of a phenolic ring and an organic carboxylic acid function (C_6-C_1 skeleton). Several compounds belong to this class including Benzoic acid (**47**), p-anisic acid (**48**), p-toluic acid (**49**), p-hydroxybenzoic acid (**50**), vanillic acid (**51**), syringic acid (**52**), 3,4,5-trimethoxycinnamic acid (**53**), 3, 4-dimethoxycinnamic acid (**54**), ferulic acid (**55**), p-hydroxycinnamic acid (**56**), p-hydroxybenzaldehyde (**57**), vanillin (**58**), syringaldehyde (**59**), p-methoxyphenyl-propionic acid (**60**), p-hydroxyphenyl-propionic acid (**61**), (R)-2-hydroxy-1(4-hydroxy-3-methoxypheny) propan-1-one (**62**), p-hydroxyphenylethanol (**63**), and diisobutyl phthalate (**64**) were reported from *P. chinensis*.[13]

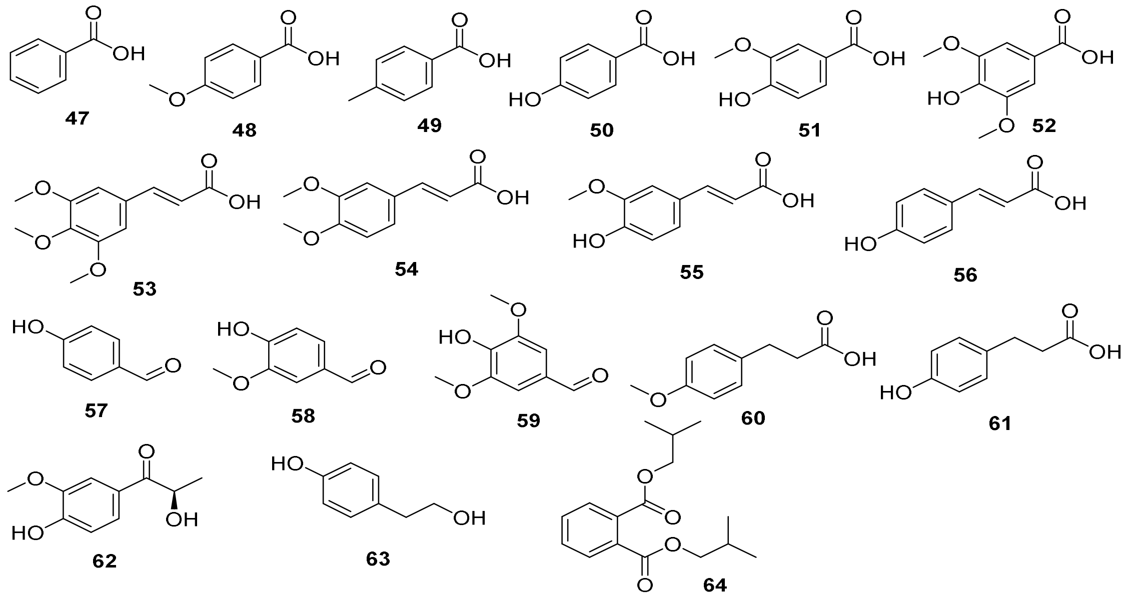


Fig.-8: Structures of Phenolic acids (**47-64**)

Steroids

Steroids are organic compounds composed of four fused rings including three six-member cyclohexane rings and one five-member cyclopentane ring. Some steroids including β-sitosterol (**65**), β-daucosterol (**66**), and 24-propylcholest-7-en-3-ol (**67**) were reported from *P. chinensis*.[15] Muhit *et al.* isolated three stigmastane type steroid stigmast-4-en-3-one (**68**), stigmast-4,22-diene-3-one (**69**) and β-sitosterol glucoside (**70**) from *P. scandens*.[11]

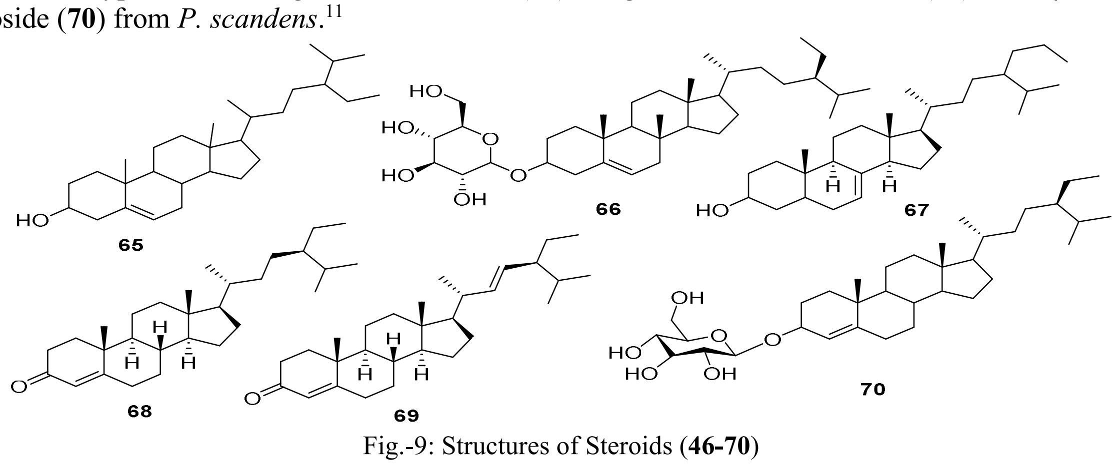


Fig.-9: Structures of Steroids (**46-70**)

Terpenoids

The genus *Pothos* is rich in terpenoids. Different classes of terpenoids like, hemiterpenene, diterpene, triterpene were reported from this genus. Hemiterpene glucosides including Pothobanoside A (**71**), Pothobanoside B (**72**), Pothobanoside C (**73**), and Canthoside B (**74**) were reported from *P. scandens*.[10] Two Diterpenoids including Methyl Pothoscandensate (**75**) and (3β)-ent-kaurane-3,16,17-triol (**76**) were reported from the whole plant of *P. scandens*.[12] Muhit *et al.* isolated four cycloartane type triterpenoids

triterpenoids including 24-methylenecycloartanol (**77**), 24-methylenecycloartenone (**78**), 24-en-cycloartenone (**79**), 24-methylenecycloartanylferulate (**80**) from *P. scandens*.[11] A Norisoprenoid type triterpenoids, Dehydrovomifoliol (**81**) was also reported from *P. chinensis*.[13] Two Carotenoids, also called tetraterpenoid, including Loliolide (**82**) and (+)-epiloliolide (**83**) were isolated from *P. chinensis*.[13]

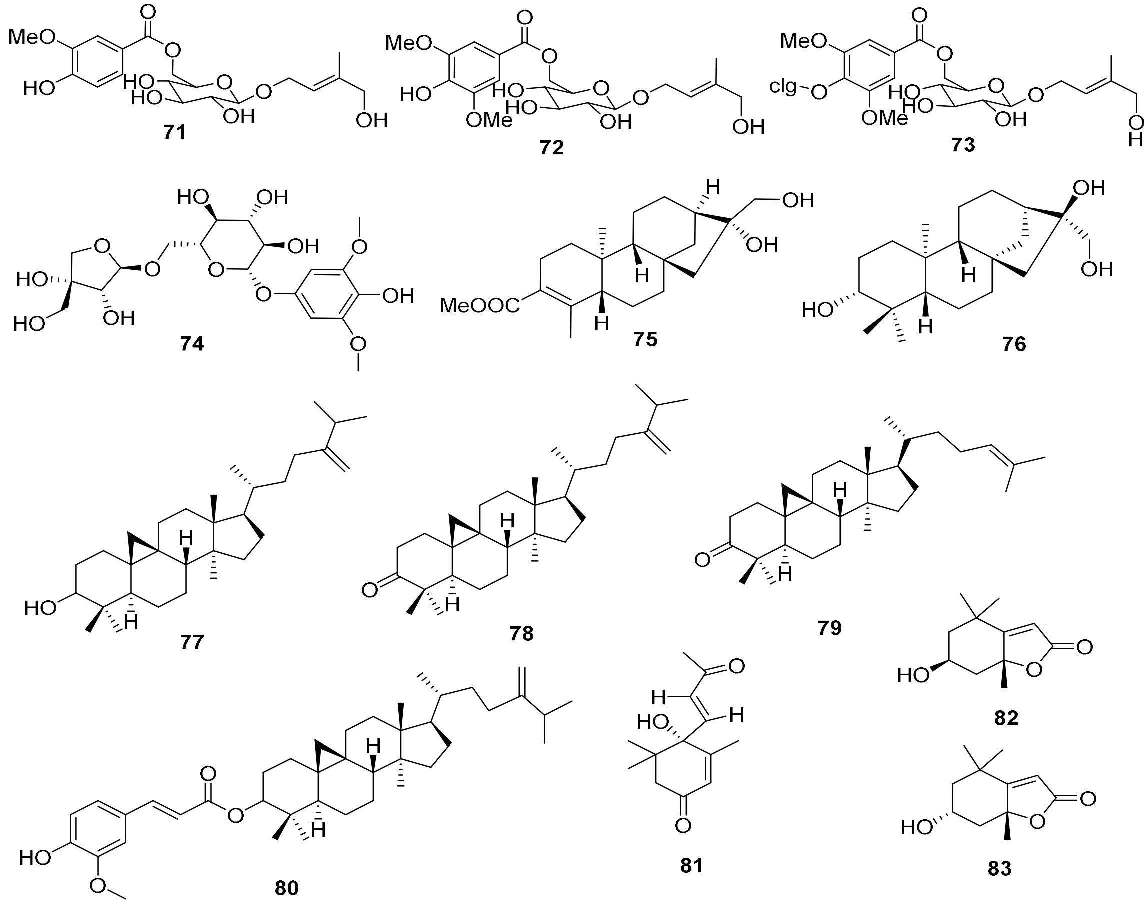


Fig.-10: Structures of Terpenoids (**71-83**)

Miscellaneous

Three long-chain molecules including Hentriacontane (**84**), 1-monostearin (**85**), 1-monopalmitin (**86**) were isolated from *P. chinensis*.[15] Parygul *et al.* isolated an aldehyde, 4-hydroxy-3,5-dimethoxybenzaldehyde (**87**) from *P. chinensis*.[4] A Phenyl isobutanol named Pothobanol (**88**) was reported from *P. scandens*.[10] A tetracyclic phenol, Racemosol (**89**) was reported from *P. chinensis*.

Biological Activities

The biological studies revealed that isolated compounds and crude extracts of *Pothos* possess wide activities, such as antimicrobial, anticancer, antioxidant, antipyretic, anti-diabetes, bronchodilator, burn wound healing, anti-cariogenic, thrombolytic etc. *in vitro* and *in vivo* models.

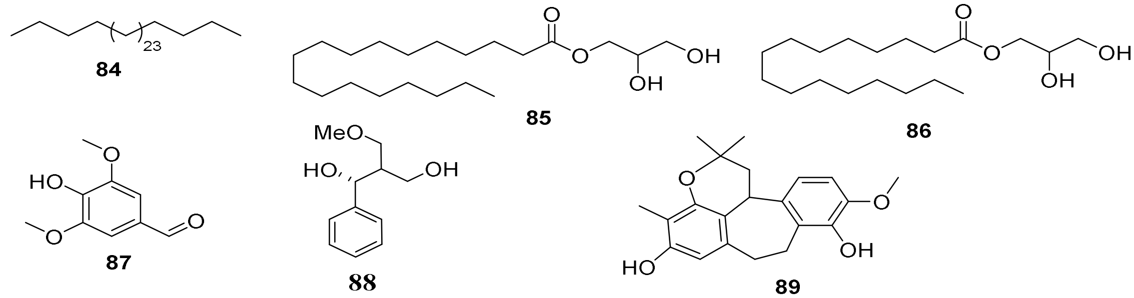


Fig.-11 Structures of Miscellaneous compounds (**84-89**)

Anticancer Activity

The 50% ethanol extract of *P. scandens* aerial parts exhibited cytotoxicity against MCF-7, a breast cancer cell line with IC_{50} value 90.18 ± 5.20 μg/ml and also cell death of MCF-7 treated with the extract was due to the induction of apoptosis.[20, 36] According to Muhit *et al.*, all the isolated compounds from *P. scandens* including compounds (**68-70**, **77-80**) exhibited mild to strong antiestrogenic activity against MCF-7 and T47D cancer cell lines which were compared with tamoxifen.[11] Among these compounds, Compound **77** inhibited 90% of estradiol (E2)-induced cell proliferation at 0.01 μM concentration in MCF-7 and T47D cell lines. Compound **80** exhibited 90% of estradiol (E2)-induced cell proliferation in MCF-7 cells at a concentration of 10.0 μM whereas only 0.01 μM was required for compound **69** for the same activity in T47D cell. In another study by Muhit *et al.* evaluated the anti-estrogenic activity of *P. scandens* towards MCF-7 and T47D cancer cell lines.[10] The syringoyl derivatives exhibited anti-estrogenic activity than less oxygenated derivatives against cancer cell lines. Among the isolates, Pothobanoside B (**72**), pothobanoside C (**73**) and canthoside B (**74**) exhibited anti-estrogenic activities against cell lines MCF-7 and T47D. According to Yusuf *et al.* the methanolic extract of *P. scandens* leaf has strong cytotoxic activity with LC_{50} value of 14.195 μg/ml whereas standard vincristine sulphate showed LC_{50} value of 0.305 μg/ml.[36] In a study by Jethinlalkhosh *et al.* reported the therapeutic effect of *P. scandens* on carbohydrate metabolizing enzymes, suggesting the species *P. scandens* as potential anticancer activity.[21]

Antimicrobial Activity

The *in-vitro* antimicrobial activity of *P. scandens* extracts against four microbial strains showed that the hexane and the ethyl acetate extracts were active against MRSA bacteria and *Candida albicans* with a zone of inhibition 6.59 mm and 8.30 mm respectively.[23] The methanol extract of *P. scandens* showed that gram positive bacteria were inhibited at low concentrations (250μg/ml and 200μg/ml) than Gram negative bacteria (400μg/ml to 500g/ml).[34] However, methanol extracts of *P. scandens* were reported antifungal activity against *Aspergillus niger*, *Candida albicans*, *Microsporium gypsium*, *Chrysosporium keratinophilum*, *Trichophytum rubrum* and *Chrysosporium indicum*.[35]

Antioxidative Activity

In a study by Jethinlalkhosh *et al.*, *P. scandens* showed potent antioxidant activity with IC_{50} value (240.44±4.62 μg/mL) for inhibiting hydroxyl radical.[19] Sajeesh *et al.* reported *in vitro* antioxidant activity of ethanol and methanol extract of *P. scandens* root.[33] Huang *et al.* studied antioxidant capacities of total flavonoids of *P. chinensis* by using the DPPH assays and reported that the DPPH scavenging rate of the flavonoids increases with concentration and time.[37] In another study by Hemalatha *et al.* observed the higher antioxidant potential of the petroleum ether, ethyl acetate and chloroform extracts of the aerial roots of *P. aurea* in both DPPH scavenging assay and reducing capacity assay.[16]

Antipyretic Activity

In India, According to Lalitharani *et al.*, *P. scandens* leaves have been employed to lower body heat and induce conception.[25-26] Sajeesh *et al.* studied antipyretic activity of the methanolic extract of *P. scandens* L. root and reported a considerable decrease of temperature in pyrexia induced Wistar albino rats at a concentration of 200 and 400 mg/Kg doses compared with standard drug paracetamol.[33]

Hyaluronidase Inhibitory Activity

A strong hyaluronidase inhibitory activity was shown by flavonoids, luteolin, apigenin, and kaempferol, whereas moderate activity was shown by quercetin. Muhit *et al.* studied the hyaluronidase inhibitory activity of chemical constituents of *P. scandens*L.[10] comparing positive control, mammalian hyaluronidase and rosmarinic acid. Among these compounds, nine compounds showed significant inhibition at 200 μM. Pothobanoside A (**71**) could be potential as an anti-tumor compound that showed significant activity with an inhibition rate of 46.7%, whereas rosmarinic acid had an inhibition rate of 64.7%. Moreover, Pothobanoside A (**71**), Pothobanoside B (**72**), Pothobanoside C (**73**), Pothobanol (**88**), Isoschaftoside (**30**), Vicenin-2 (**15**), Neoschaftoside (**16**) and Vitexin 2′′-O-xyloside (**17**) isolated from *P. scandens* have shown hyaluronidase inhibitory activity.

Other Activities

Hossain *et al.* showed *in vitro* anti-diabetic activity of the methanol extract of *P. scandens* leave using α-amylase enzyme inhibition technique with IC_{50} value of 1.49±0.190 mg/mL whereas standard drug acarbose showed IC_{50} value of 1.30±0.015 mg/mL.[17] In addition, the *in vivo* study of *P. scandens* by OGTT method using male Swiss albino mice in varying concentrations of the sample indicated the dose-dependent anti- diabetic activity.[17]

The species *P. scandens* was found anti-cariogenic activity. Junaid *et al.* studied anticariogenic activity of the methanol extract of *P. scandens* leaf against some clinical isolates of *Streptococcus mutans* recovered from dental caries patients.[18] They showed the inhibition of the growth with a zone of inhibition 1.1 to 1.9 by testing for their sensitivity to the extract by Agar well diffusion method.

Kim *et al.*, evaluated the anti-inflammatory activity of ethanol extract of *P. scandens*in lipopolysaccharide-stimulated murine RAW 264.7 cells.[24] The species *P. scandens* has been used traditionally in asthma. Hossain *et al.* revealed the bronchodilator activity of extract of *P. scandens* leaves, applied on Wister rat by counting the pre convulsive time showed 41.56% protection at 100mg/kg dose with a comparison of standard drug Salbutamol.[17]

Blood clot formation leads to severe problems like anoxia, hypertension, stroke to the heart etc.[28] According to Yusuf *et al.*, the methanolic extract of *P. scandens* leaf showed thrombolytic activity of 19.451±1.711% lysis of clot whereas standard drug streptokinase (positive control) showed 69.480± 2.651% and water showed (negative control) 3.0695± 0.497%.[36]

Mohammed *et al.* prepared gel formulations of ethanolic extract of *P. scandens* (4% w/v) which showed a significant wound healing effect treated in animals.[27] Sainuddin *et al.* prepared four different gel formulations A1, A2, A3 and A4 of ethanolic extract of *P. scandens* using Carbopol 940 in of 0.5, 1.0, 1.5 and 2.0%. They found the second formulation (A2) to be transparent, non-greasy and stable but the third (A3) and fourth (A4) formulations to be translucent, tested for primary skin irritation and showed no signs of irritation.[38]

Pothobanoside C (**73**) and pothobanol (**88**) isolated from *P. scandens* have shown significant histamine release inhibition compared with positive control EGCgG3Me.[10] Pothobanoside B (**72**) isolated from *P. scandens* have shown significant histamine release inhibitory from basophilic cells.

Future Directions

Although the genus *Pothos* has significant medicinal value, only a few species have been explored exhaustively for their chemical constituents and pharmacological activities till now. Further research with different species that have not been explored will provide new intuition in phytochemistry and its pharmacological properties. As illustrated in this review, *Pothos* is an abundant source of novel compounds which have shown promising bioactivities. The study of different biological properties to those isolated compounds with a wide range of activities could lead to the identification of promising lead compounds. Knowing the significance of the genus, in recent years, the scientific interest has increased greatly for further scientific exploration of this genus, to ascertain their therapeutic efficacy and commercial exploitation.

CONCLUSION

The genus *Pothos* have been utilized around the world in traditional remedy for decades. The genus provides an attractive bio resource for drug discovery research. The chemical constituents of this genus have shown promising several biological activities and would be potential for further research. Although the genus has great traditional value and also several biological activities but the detailed phytochemical study so far has not been explored. However, only two species *P. scandens* and *P. chinensis* were studied for isolation of bioactive compounds.

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