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A review on phytochemical constituents and pharmacological properties of *Enhydra fluctuans* Lour

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Abstract
Increased resistance and side effects of synthetic drugs has led to the exploration of bioactive compounds and drug development from plants. *Enhydra fluctuans* Lour. is an common edible plant, ethnobotanically very popular in India and parts of south- east Asia and often is used for its medicinal properties. Studies reveal that this plant has many biomedical properties like anti- microbial, anti- diarrhoeal, anti- oxidant, anti- cancer, CNS- depressant, neuro- protective, cyto- protective, thrombolytic activities. These properties can be attributed to the presence of pharmacologically active compounds like β- carotene, flavonoids, phenolic compounds, saponins, sesquiterpene lactones, phytosterols etc. The pharmacological potential infer that this plant can have potential anti- cancer properties and should be extensively investigated for pharmaceutical purposes. This review gives a comprehensive account of all the reports available about *Enhydra fluctuans* it would help to predict ways to future investigations regarding new compounds and their potential medicinal properties.

Keywords: Anti oxidant, anti cancer, flavonoids, sesquiterpene lactones, phytosterols

Introduction
Plants harbour an inexhaustible array of molecular entities. Since time immemorial bioactive natural products are being used as herbal drugs, but their application as "isolated and characterised" compounds to drug discovery and development started in the 19th century. It has been reported that nowadays plant derived products plays a critical role in modern drug development especially for antibacterial and antitumor agents [1] The plants of Asteraceae family are extensively used as medicinal plants all over the world. They are used as astringent, antipyretics, anti- inflammatories, hepatoprotective, diaphoretic, nerve tonics, laxatives etc... Some of the most common phytochemicals isolated from the plants of Asteraceae family are glycosides, flavonoids, tannins, carbohydrates, phytosterols, di- and tri- terpenoid acids and their derivatives, the oil extracts generally contains myrcene, lomonene etc. [2, 3] *Enhydra fluctuans* a member of Asteraceae Family is a marshy herb probably of Indochinese origin grows widely in tropical Asia and Africa. It is used as an edible plant in many parts of India, Bangladesh Myanmar, Sri Lanka, Malaysia, Thailand, Viet Nam. The plant is also used extensively by native peoples due to its medicinal properties. Studies reveal presence of valuable phytoconstituents like flavonoids, sesquiterpene lactones, phytosterols, β- carotene, proteins etc., which attribute to its anti- microbial, anti- oxidant, CNS depressant, thrombolytic, anti- inflammatory and analgesic properties.

Methods
The study of the literature review was carried out by searching on the electronic databases including PubMed, Science Direct, Research Gate for studies focusing on the biological and pharmacological activities of *Enhydra fluctuans* Lour. All English language articles published between 2000 and 2019 were searched. The list of references of all the relevant articles was also studied to include all reports and reviews related to the subject.

Description of the plant
A trailing marshy herb or sometimes floating on water; grows in tropical regions, in and along ditches, water courses, margins of fish ponds and rice fields in the open. It occurs from sea level upto 1,800m. It is sensitive to cold when very young. Stems are 30-60 cm long, fleshy, hollow, with a purplish tinge; internodes 7-10cm long; rooting at the lower nodes. Leaves sessile, 2.5- 7.5 cm long, opposite phylotaxy, linear to oblong in shape with acute apex and subcrenate or distinctly dented margin. Heads terminal, sessile; flowers white to greenish white; the outer pair of the involucral bracts are ovate, 1 to 1.2 cm long; the inner pair are

smaller; fruits achene, enclosed within hard receptacle scales [6]. It is able to reproduce by fragmentation and occurs so abundantly that it clogs water courses.

Geographic distribution

This species is possibly of Indochinese origin, which occurs in tropical Asia and Africa. It is common to all countries of Southeast Asia like Bangladesh, India, Indonesia, Myanmar, Malaysia, Sri Lanka, Thailand, Viet Nam etc [6].

Ethnobotanical uses

In West Bengal, North- East India, and Bangladesh it is used as a food supplement by the tribals. In North- East India people use it for the treatment of constipation. Stems are used for gastric and ulcer problems. Rural people applies finely crushed aerial parts of the plant over pimples. It also cures several skin diseases, inflamations and are used in cases of small poxes. Tribes of Meghalaya consume leaf juices orally for the treatment of liver diseases [9, 10].

Chemical constituents

Enhydra fluctuans is a good source of β-carotenes and proteins and various other components like saponins, myricil alcohol or triacontanol [Figure 1], phytosterols like cholesterol, sitosterol, stigmasterol and stigmata-5,22,25-triene-3β-ol, glucosides, a number of diterpenoid acids and their isovalerate and angelate derivatives, sesquiterpene lactones including germacranolides like enhydrin, fluctuanin, fluctuanidin, several kaurene derivatives, 4-hydroxy farnesyl acetate and gibberelines [Figure 2] [4-8]. Studies with its leaf oil reveals the presence of several components among which the major components are myrcene (37%) and limonene (28%), the other components which are reported to be less than 5% are α-pinene, €-β-ocimene, camphor, €-carophyllene, α-humulene, 1-octen-3-ol, linalool and longiverbenone. Apart from this, the two new components isolated from the oil of *Enhydra fluctuans* leaf are 1,2-dihydroperyllaldehydes (cis- and trans- 4 isopropenylcyclohexanecarboxaldehydes) [Figure 1] [11]. Components reported from methanolic extract of the plant are flavonoids, carbohydrates, reducing sugars, phenolic compounds and tannins [12]. Two flavonoids isolated from ethyl acetate fraction of the plant are baicalein 7- O- glucoside and baicalein 7- O- diglucoside [Figure 2] which are reported to have cytotoxic activity as well as analgesic and anti-inflammatory activity, which can be attributed to its high free radicle scavenging and anti- oxidant potentiality [13-14]. An isoflavone glycoside 4',5,6,7-tetrahydroxy-8-methoxyisoflavone-7-O-beta-D-galactopyranosyl-(1→3)-O-beta-D-xylopyranosyl-(1→4)-O-alpha-l-rhamnopyranoside considered as a novel bioactive constituent was reported from the methanolic extract of *Enhydra fluctuans* Lour.. This constituent has antimicrobial and anti-fungal properties [15]. A 24 kDa arabinogalactan reported from water extract of *Enhydra fluctuans* leaves have a (1, 3)- linked β- d – Galp main chain, substituted at O- 6 by (1, 6)- linked β- d- Galp side chains. The latter residues are substituted at O- 3 by (1, 3)-, (1, 5)-, and (1, 3, 5)- linked α- I- Araf chains and nonreducing end units of a α-l-Araf and β-d-Galp. Studies reveals that this carbohydrate polymer contains esterified phenolic acids and exhibits anti- oxidant properties [16]. Pharmacological activities of some of the pure compounds reported from *Enhydra fluctuans* Lour. has been studied in different systems and significant results has been obtained which infers various biomedical properties of the plant. [Table 1]

Antioxidant potentials

Total anti oxidant activity: Anti- oxntioxidant activity of cold lyophilised leaf extract of *Enhydra fluctuans* is mainly attributed to its Flavonoid content and the total antioxidant experimentally found to be 0.138 mg equivalent to ascorbic acid per mg of the plant material [17].

DPPH radicle scavenging activity: DPPH scavenging activity is due the presence of high concentrations of polyphenolic compounds and flavonoids. Ethanol, petroleum ether, methanol, chloroform, ethyl acetate and butanol extracts as well as crude extract shows DPPH scavenging activity. As reported ethanol extract of the plant can scavenge 61.67% DPPH at 500 µg/ml concentration [18]. DPPH activity of the Ethyl acetate fraction of the plant gives lowest IC_{50} value as compared to other extracts [19].

Presence of Phenolics: Phenolic compounds are reported to be powerful antioxidants. The presence of hydroxyl groups are responsible for its antioxidant properties and plays an important role in preventing lipid oxidation. Many studies have revealed that ethyl acetate extract shows highest phenolic content as pyrocatechol equivalents [19]. Many reports indicate that *Enhydra fluctuans* contains a good amount of phenolic compounds [18]. Ethanol extract has greater amount of total phenolics as compared to chloroform extract and petroleum ether extract. The total phenol content is estimated to be 153 ± 0.38 mg/mL in methanolic extract of *Enhydra fluctuans* [12].

Presence of Flavonoids: Significant amount of flavonoid has been reported from *Enhydra fluctuans.* Total flavonoid content is estimated to be (172.04 ± 0.56) mg/mL [12].

Nitric oxide scavenging activity: Experimental estimations reveals that ethanol extract of the aerial parts of the plant possesses good NO- scavenging activity and can produce maximum inhibition. Ethanol extract of *Enhydra fluctuans* is reported to have lower IC_{50} than chloroform and petroleum ether extract [18]. Some other studies showed ethyl acetate extract of the plant have the most NO- scavenging activity followed by methanolic extract and chloroform extract [19].

Superoxide scavenging activity: Ethanol, chloroform and pet ether extracts of the plant shows superoxide scavenging activity. According to some scientists ethanol extracts has better ability to scavenge superoxides [20], while some others says ethyl acetate extract of the plant have maximum superoxide scavenging activity [19].

Reducing power: The reducing power of Pet- ether, chloroform, and ethanol extract of *Enhydra fluctuans* has been studied and concluded that the activity increase with increase in concentrations. The reducing power of ethanol is more than the other two extracts [18].

Free iron chelating activity: The IC_{50} value for iron chelating activity with the lyophilised leaf extract of *Enhydra* fluctuans is 6.38 mg/mL. Iron plays an important role in formation of oxygen derived free radicals, therefore chelation of iron prevents formation of free radicles [17].

Pharmacological properties

Analgesic and anti-inflammatory activity

The flavonoids isolated from the leaves of *Enhydra* shows anti inflammatory activity by inhibiting COX- 2 and 5- LOX

with an IC^{50} value of 80 µg/mL and 92 µg/mL respectively. It shows potent anti- inflammatory activity against carrageenan and histamine induced acute inflammation. The flavonoid extracted from *Enhydra* shows significant *in vivo* anti inflammatory activity in carrageenan indused rat paw oedema and cotton pallet induced granuloma in rats [21]. Some researchers also reported that methanolic extract of *Enhydra* fluctuans shows promising analgesic activity against acetic acid induced writhing and tail- flick method [22]. The total flavonoids are responsible for 27.05% and 55.49% protection against acetic acid induced writhing response in Swiss Albino mice when administered orally at doses 200mg/kg and 400mg/kg [14] [Table 2]

Anti- cancer activity
Flavonoids of *Enhydra fluctuans* are reported to have anticancer activity against Ehrlich's ascites carcinoma (EAC) bearing Swiss Albino Mice, it significantly reduces volume of tumor cells and increases the life span. Treatment with flavonoids of *Enhydra fluctuans* restored the hematological parameters like malonaldehyde content and anti- oxidant enzyme activity [13]. [Table 2]

Anti- diarrhoeal activity: It has been reported that both methanolic and aqueous extract of *Enhydra fluctuans* shows significant results against castor oil induced diarrhoea in mice. The rate of inhibition is 41.18% and 67.07% in aqueous and methanolic extract respectively as compared to 84.70% inhibition produced by standard drug loperamide. The methanolic extract is capable of moderately inhibiting the growth of *Shigella dysenterica*, *Shigella boydii* and *Shigella flexneri* while aqueous extract inhibits the growth of *Staphylococcus aureus* as well as *Shigella flexneri* and *Shigella boydii* [23]. [Table 2]

Antihelmintic activity
The antihelmintic activity of methanolic extract of the plant was studied on *Pheretina posthuma* with different concentrations from 10mg/mL to 80mg/mL and the paralysis time calculated was 33.66- 21.33 mins while that of death time calculated was 70.33- 33.33 mins as compared to 35.33 mins and 71.33 mins respectively when treated with standard albendazole [12].

Antimicrobial activity: Investigations regarding antibacterial activity reveals that methanolic extract of *Enhydra fluctuans* have moderate antibacterial activity against several Gram negative bacteria like *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, Salmonella *paratyphi* and few Gram positive bacteria like *Bacillus megaterium*, *Staphylococcus aureus* [24]. According to a report methanolic extract of *Enhydra fluctuans* possess maximum antibacterial activity against *Staphylococcus aureus* followed by *Escherichia coli* and *Pseudomonas aeruginosa* [25]. Methanolic extract of the leaf of *Enhydra* fluctuans has low to moderate anti- fungal activity against *Aspergillus niger* and *Fusarium* sp. Acetone fraction of the leaf of the plant shows inhibition of *Aspergillus fumigates* as well as *Aspergillus niger* and *Fusarium* sp [26]

CNS depressant activity
Benzene, chloroform and ethyl acetate extract of *Enhydra fluctuans* produces Central Nervous System depressant activity. Studies reveal that extracts of *Enhydra fluctuans* significantly possesses spontaneous motility depressant, sedative, anticonvulsant and anti- stress activities in Swiss Albino mice [27] [Table 2].

Cytoprotective activity
Studies reveal that the aqueous extracts of *Enhydra fluctuans* exhibits cytoprotective activity and defensive role against heavy metal toxicity. The aqueous extract restores lead acetate induced decrease in cell viability in hepatocyte [20]. Aqueous extract of the plant also provides significant protection against $NaAsO_2$ induced cytotoxic effects like lipid peroxidation, protein carboxylation, alterations in the levels of extrinsic and intrinsic transcription proteins and reduction in glutathione levels in hepatocytes. Furthermore *in vivo* assays confirmed the cytoprotective activity against bioaccumulation of arsenic as well as arsenic induced abnormal hematological parameters and redox imbalance in liver of mice [28]. Reports suggests that $CdCl_2$ induced reduction in cell viability can also be significantly altered by treatment with Aqueous extract of the plant. *In vivo* assays has also proved aqueous extract of *Enhydra fluctuans* to have remarkable counter reactions against Cadmium bioaccumulation and oxidative stress in liver, kidney, heart, brain, and testes of mice [29]. [Table 3]

Hepatoprotective Activity
Petroleum ether, chloroform, ethyl acetate and ethanol exract of aerial parts *Enhydra* fluctuans significantly decreases CCl_4 induced elevation of SGOT, SGPT, alkaline phosphatase and total billurubin levels in rats. Histopathological profiling also confirmed protective effects of pet ether, chloroform, ethyl acetate and ethanol extract of the plant against CCl_4 induced extensive necrosis and steatosis [30-31].

Thrombolytic activity
It has been shown by a group of scientist that 10mg/mL of methanolic extract of *Enhydra fluctuans* exhibits 31% thrombolytic activity as compared to 41% activity of standard streptokinase and the thrombolytic activity of the methanolic extract increases with the increase in the concentration [12].

Discussion
From the above mentioned biomedical characterestics of *Enhydra fluctuans* it is clear that the plant has free radical scavenging properties. Several researches suggested that oxidative stress is the cause of several diseases with special mention to cancer. Thus *Enhydra fluctuans* should have potential anti- cancer activity, but has been reported only against Ehrlich's Ascites Carcinoma (EAC) bearing Swiss Albino Mice. Thus further investigations are required to establish its anti- cancer activity of the plant extracts. Apart from anti- oxidant properties it has anti- microbial, cyto-protective, anti- infalamatory and analgesic, CNS depressant, thrombolytic activities. The rich repository of biomolecules indicate that further researches would lead to contributions in the field of pharmaceuticals.

Conclusions
This review is intended to offer an overview of the literature available regarding ethnotanical uses, phytochemicals and bioactivities of the plant *Enhydra fluctuans*. From this overview it is evident that the plant has several biomedical activity [Figure 3] which makes it a potential therapeutic for many diseases. The pharmacological activities of this plant are due to the presence of various bioactive compounds. Isolation, identification and characterization of these compounds would open new fields of research in therapeutics of several diseases.

Table 1: Biomolecules Isolated From the Plant and Their Pharmacological Activities [32-42]

Biomolecules from *Enhydra fluctuans*	Pharmacological Activities	References
β- Carotene	Provitamin A activity. Lipid oxide and lipid peroxide radicle scavenging activity. Singlet oxygen quencher.	[21]
Saponins	Inhibition of tumor angiogenesis its inducer and adhering, invasion and metastasis of tumor cells.	[22]
Sesquiterpene lactones- Germacranolides like enhydrin, fluctuanin and fluctuanidin.	Executes anticancer activity by inhibiting inflammatory response, prevention of metastasis and induction of apoptosis. Apart from this they have potentiality to cure cardiovascular diseases, have antimalarial, antimigraine, analgesic activity, prevention of neurodegeneration. Treatment of common human ailments like diarrhoea, flu etc.	[23, 24]
Flavonoides like baicalein 7- O-glucoside and baicalein 7- O-diglucoside	Inhibits cell proliferation, triggers mitochondria mediated apoptosis, exhibits cytotoxic effect on leukemia cells.	[25]
Sitosterol	Induces apoptosis when added to cultured human prostate, breast, colon cancer cells, hence plays significant role in management and prevention of human cancer.	[26]
Stigmasterol	Has cytotoxic activity, inhibits tumor promotion, enhances activities of catalase, superoxide dismutase, glutathione etc.. It also shows anti- mutagenic effects.	[27]
Myrcene	Decreases the production of reactive Oxygen Species, Matrix metalloproteinase-1 and 3, and increased transforming growth factor-6 and type I procollagen secreation in UVB irradiated human dermal fibroblast. Myrcene enhances antigen specific total IgG immune response to Ovalbuin, suggesting Th1 immune response.	[28, 29]
Limonene	It shows 75- 95% antibiofilm activity against pathogens like *Streptococcus pyogenes, Streptococcus mutans, and Streptococcus mitis* in concentration dependent manner. Metabolite profiling of plasma samples from early stages of breast cancer patients receiving limonene shows significant decrease in cyclin D1 expression and several other changes in metabolic pathways.	[30, 31]

Table 2: Clinical Trials of Biomedical Activities with Crude Extracts

Crude extracts / pure compounds	Biomedical Activity Tested	Clinical Trials	References
Methanolic and aqueous extract	Anti- diarrhoeal activity	Castor oil induced diarrhoea in Swiss Albino Mice	[23]
Methanolic Extract	Analgesic	Acetic acid induced writhing and tail flick in Swiss Albino Mice	[22]
Benzene, Chloroform, Ethyl acetate extract	CNS depressant activity	Spontaneous motility depressant, sedative, anticonvulsant and anti- stress activities in Swiss Albino Mice	[27]
Total flavonoids content	Anti- cancer activity	Ehrlich's ascites carcinoma bearing Swiss Albino Mice	[13]
Total flavonoids content	Anti- Inflamatory	Carrageenan induced rat paw oedema and cotton pallet induced granuloma in rats	[21]
Methanolic extract	Anti-helminthic activity	Paralysis and death time of *Pheretima possthuma*	

Table 3: Evidences of Biomedical Activities In Cell Lines With Aqueous Extracts

Fraction of the Plant	Biomedical Activity	Cell Lines	References
Aqueous extract	Defensive role against Lead acetate toxicity	Liver cells of mice.	[20]
Aqueous extract	Defensive role against Sodium arsenite toxicity	Liver cell of mice	[28]
Aqueous extract	Defensive role against Cadmium chloride toxicity	Liver, kidney, heart, brain, testes cells of mice.	[29]

Summary

- *Enhydra fluctuans* is an ethnobotanically important plant belonging to the family Asteraceae.
- It contains many biologically active molecules like β-carotene, myricil alcohol, flavonoids, polyphenols, tannins, sesquiterpene lactones etc.
- It shows a number of bioactivities like anti- microbial, antioxidant, anti- cancer, anti- inflammatory and analgesic, thrombolytic, cytotoxic, CNS depressant properties.
- Isolation and characterization of new compounds along with clinical trials will open new fields of research in therapeutics of several diseases.

Conflict of interest

The authors declare the have no conflict of interest.

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Abbreviations used

CNS- Central Nervous System, DPPH- 2,2- diphenyl- 1-picrylhydrazyl, NO- nitric oxide, $NaAsO_2$- Sodium arsenite, $CdCl_2$- Cadmium chloride, EAC- Ehrlich's ascites carcinoma.

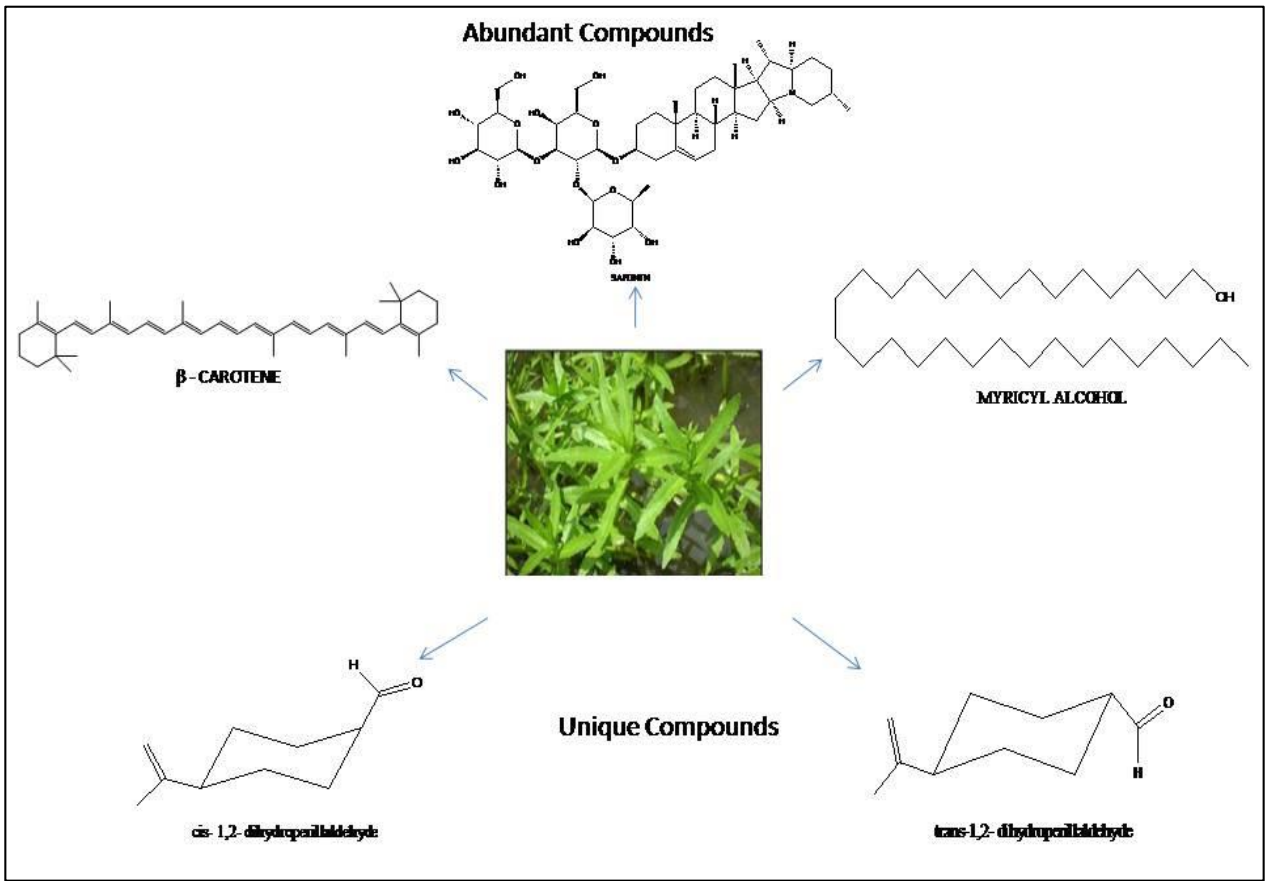

Fig 1: Some of the phytochemicals obtained from *Enhydra fluctuans* Lour.

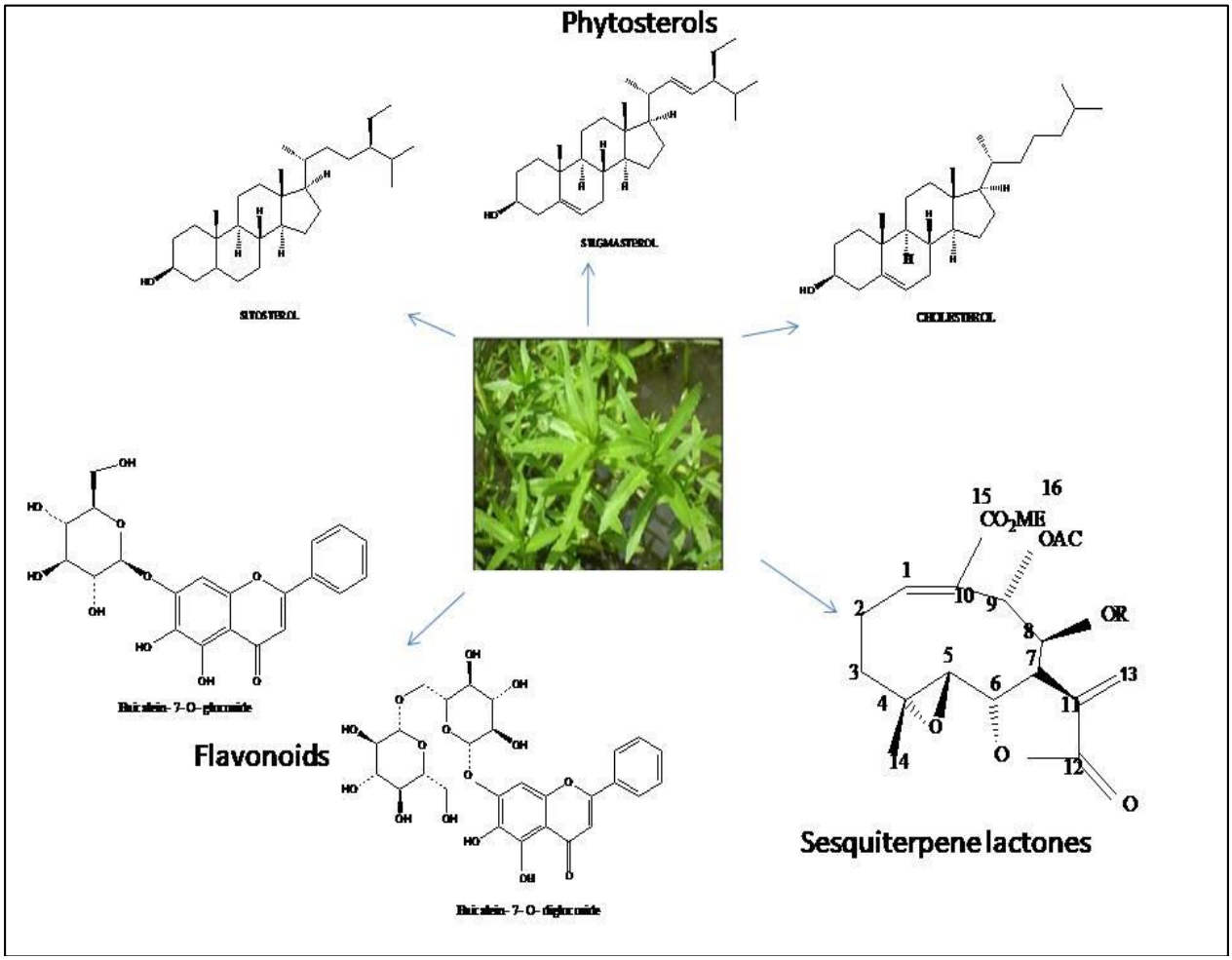

Fig 2: Sesquiterpene lactones, Phytosterols and Flavonoids isolated from *Enhydra fluctuans* Lour.

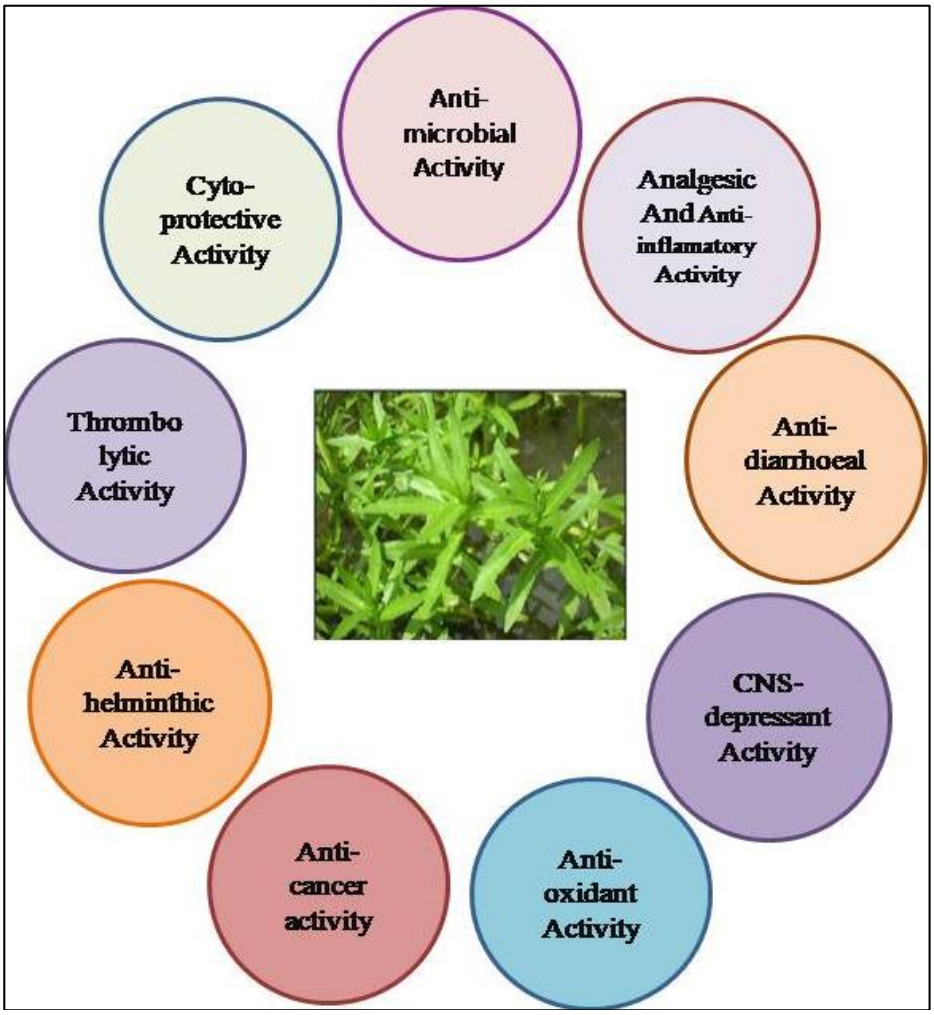

Fig 3: Various Pharmacological activities of crude extracts from *Enhydra fluctuans* Lour.

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