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Drug-like properties of anticancer molecules elucidated from *Eichhornia crassipes*

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Abstract
Eichhornia crassipes is reported to have molecules that are active against liver, cervical, breast cancers and melanoma cells. This systematic review was conducted according to Cochrane hand book of systematic review and guidelines for systematic reviews aiming to explore the potential that the plant has in providing drug leads against cancer. The results show that only a few molecules (10) have been elucidated from leaves of the plant and shown to be active against cancers. The molecules are alkaloids and tepernoids. Some drug-like properties (Solubility, permeability, lipophilicity and melting point) of a few of the compounds are known. Drug-like properties of the compounds elucidated from the roots, flowers and stem of *Eichhornia crassipes*, as well as other compounds from the leaves are yet to be determined. It is important to further explore these molecules as well as more from this promising plant for the developing of better anticancer drugs.

Keywords: Lipophilicity, permeability, drug-leads, hit molecules, drug designing, drug development

Introduction
Cancer incidences continue to rise despite the significant progress made in recent years in therapies' development and appropriate preventive strategies. The International Agency for Research on Cancer (IARC) has projected an almost two-fold increase in new cancer cases and deaths influenced by ageing and population growth by 2030 [1]. Research indicates that the burden of cancer is not only on the patients but also on the care givers [2, 3] which significantly negatively affects socio-economic development.

Natural plant products have played a significant role in anticancer medicine for many years. By 2013, atleast 50% of drugs on the market, including cancer drugs, were made from natural products and their derivatives on the market [4]. Secondary metabolites from plants are largely responsible for bioactivities that these drugs possess. The term "dug-like" properties refers to properties that molecules from promising extracts showing bioactivity need to have in order to be considered as clinical-leads and then qualify as approved marketable drug [5].

Drug leads are compounds that have shown bioactive potential as well as sufficiently acceptable adsorption, distribution, metabolism, excretion and toxicity (ADME-Tox) properties to survive to the completion of phase I clinical trials. Many promising bioactive-proven drugs have been abandoned well within clinical trial stages and worse, some have been withdrawn from the market for reasons that include low bioavailability, poor pharmacokinetics and drug-drug interactions [5] that result from un pre-determined stability and reactivity properties. Recently, it has become imperative to integrate drug leads' properties into drug discovery and development where in-depth studies are conducted on formulation, stability, pharmacokinetics, metabolism and toxicity [6]. When developing drug, drug molecular properties should be explored, including; structural properties (lipophilicity, hydrogen bonding, molecular weight, polar surface area, shape, reactivity and pKa), physico-chemical properties (solubility, permeability and chemical stability), biochemical properties (metabolism, protein & tissue binding, transport (efflux and uptake)) and lastly pharmacokinetic and toxicity properties (clearance, half-life, bioavailability, drug-drug interaction and LD_{50}) [6]. Much as most scientists hold potency to the highest regard, it must be recognized that other factors like bioavailability of a drug matters to a high degree in drug development [7]. Studying properties of drug leads before escalating to higher drug development stages will narrow down promising drug candidates to a manageable few which will save time and financial costs. The aim of this systematic review is to summarize information on the anti-cancer proven molecules from *Eichhornia crassipes*' (Water hyacinth's) leaves, roots and stems so as to determine the gaps in drug-like property studies on the plant's molecules.

Methodology

Review design

This systematic review was conducted according to Cochrane hand book of systematic review and PRISMA guideline of systematic review [8].

Search determinations

The searches made as described below included the use of *Eichhornia crassipes* leaves, roots and stems as sources of anti-cancer pharmacological agents. The methods herein were as used in literature [9 10].

Data sources

A comprehensive search of 6 data bases was conducted; Pubmed, Chochrane library, Library of Congress, LISTA (EBSCO) and Web of science (TS), Google scholar was also explored for non-indexed data sources. Three molecular data bases, Pub Chem, Che MBL and Drug Bank were used at a later stage to check the properties of any similar molecules to those found in the plant.

Search terms

Key search terms to identify articles relevant to the plant in this study and cancer was employed, these were: "*Eichhornia crassipes* cytotoxicity", "*Eichhornia crassipes* cancer" and "Water hyacinth cancer" in any of the title, key words or abstract.

Inclusion and exclusion criteria

Articles that studied at least anticancer activities and the identification of cytotoxic compounds from *E. crassipes* regardless of the year of publication through to 14th February, 2018 were included in this study. Full texts were reviewed for those articles which were available and if not available, efforts were made to get in touch with the corresponding authors. Review articles and those which focused on other activities not considered in this review were excluded from the study.

Results and Discussion

Search results

The search of databases yielded 3428 articles from which 2104 remained after removal of the duplicates. Abstract and title screening reduced the number of articles to 9 for full text examination. Two articles [11, 12], were excluded because they were review articles. Six articles were finally included in the systematic review. Figure 1 summarizes the identification of studies for synthesis.

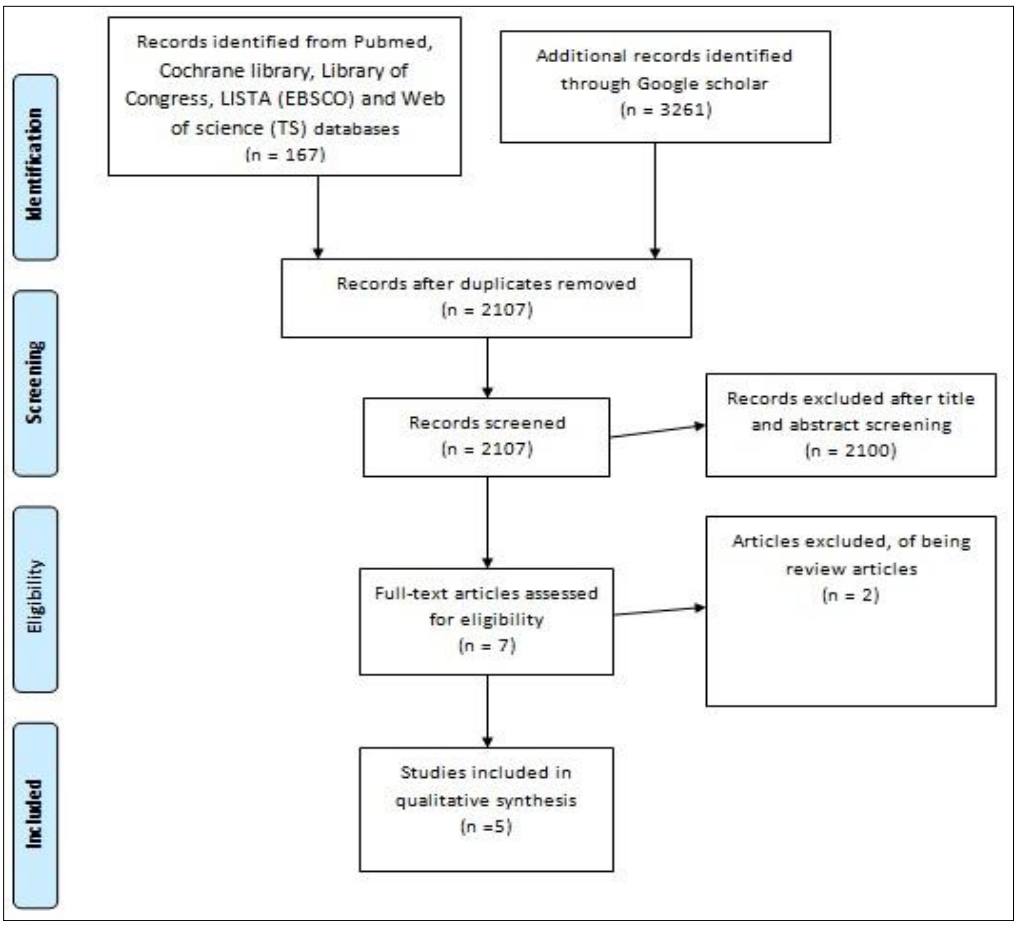

Fig 1: PRISMA flow diagram showing review criteria

Efficacy of plant extracts against cancer

Generally, crude extracts of *E. crassipes* have been found to have potential drug leads from a wide range of polarity spectrum. Anticancer activities of aqueous fractions of the plant leaves on T47D, PC3, NCI-H322 & A549 cancer cell lines [13], methanolic extracts on cervical cancer (HeLa) and methanolic extracts on mice tumors [14] indicate that polar compounds in the plant are potential drug leads. On the other hand, hexane-ethyl acetate fractions' (8.5:1.5) activities on liver cancer (HepG2), cervical cancer (HeLa), Breast cancer (MCF-7), and EACC melanoma cell lines [15] indicate that the non-polar spectrum of the plant extracts are as well potential anticancer drug leads. Tyagi & Agarwal [16], reported the general anticancer activities of phytol, a diterpene. Table 1 summarises the findings.

Table 1: Summary of findings on the efficacy *Eichhornia crassipes* extracts from the study

Author	Part of plant	Solvent used in extraction	Efficacy report	Structural elucidation of anticancer compounds
Ali *et al*[14]	Leaves	Methanolic	Tumor growth inhibition (200mg drug/kg BW) confirmed in adult male mice from 6 to 10 days observation	N/A
Kumar *et al*[13]	Leaves	Lymphorized aqueous extracts dissolved in DMSO	Growth inhibition in T47D, PC3, NCI-H322 & A549	N/A
Aboul-Eneine *et al*[15]	Leaves	Methanolic extract and its isolated hexane and ethyl acetate fractions	Cytotoxic to HepG-2, MCF-7, HeLa, & EACC cell lines.	9 compounds isolated and identified
Lenora *et al*[17]	Leaves	Methanolic	Cytotoxic and growth inhibition of HeLa	N/A
Tyagi & Agarwal[16]	Leaves	Methanolic	Cytotoxicity reported	1 compound elucidated

Structural identification from the extracts

Two research studies [15, 16] elucidated structural compounds active against cancers of the liver, cervix and breast and also against carcinoma. There are a few compounds that have been identified from bioactive anti-cancer fractions of *E. crassipes* leaves. The following compounds have been found through spectroscopic analyses in the plant fractions [15]: alkaloid derivatives; 18,19-secoyohimban-19-oic acid, 16,17,20,21-tetrahedro-16-(hydroxymethyl)-, methylester (15Beta, 16E), diamino-dinitro-methyl dioctylphthalate and F. 9-(2,2-dimethylpropanoilhydrazono)-2,7-bis-[2-(diethylamino)-ethoxy] fluorine and terpenoids derivatives: 1,2-benzenedicarboxylic acid, mono-(2-ethylhexyl ester); 1,2-benzenecarboxylic acid, diisooctyl ester; 1,2-benzenedicarboxylic acid, dioctylester; (3-methylphenyl)-phenylmethanol; 4-(Diethylamino)-alpha-[4-(diethylamino) Phenyl] and Isooctylphthalate. Their structures, molecular weights and bio-activities are listed in table 2. Most of the compounds isolated from *E. crassipes* were active against cervical cancer as shown in table 2. Only isooctylphthalate showed good activity (IC_{50} of 0.8 ± 0.4 ug/ml) against hepatocellular cancer. Other works [16] also reported the presence of phytol, a diterpene from *E. crassipes* leaf extracts and reported it to have anticancer activities. The molecules found above fall into alkaloidal and terpenoidal phytochemical groups. This is due to the fact that the researchers used solvent gradients that were very good at isolating these two groups. This suggests that other alkaloids and terpenoids from the plant are potential drug leads in the fight against cancer. However, these anticancer compounds from this plant cannot be limited to these two phytochemical groups. A small shift in the solvent gradient used is likely to yield more compounds from these two groups and others, also with anticancer activities. It should also be noted that molecules from roots and stems extracts of the *E. crassipes* are yet to be explored and reported as potential anti-cancer drug leads. Table 2 summarizes the structures found from the said sources.

Table 2: Anti-cancer bioactive compounds identified in *E. crassipes'* leaves

Molecular name	Bioactivity expressed as cytotoxicity (IC_{50} in µg/mL) on various targets			
	EACC	HeLa	MCF7	HepG2
18,19-Secoyohimban-19-oic acid, 16,17,20,21-tetrahedro-16-(hydroxymethyl)-,Methylester(15Beta,16E)	6.04 ± 0.5	7.7 ± 4.0	13.60 ± 5.3	40.2 ± 10.1
1,2-Benzenedicarboxylic acid, mono-(2-ethylhexyl ester)	17.3 ± 3.5	10.7 ± 1.3	13.4 ± 1.9	28.3 ± 3.7
1,2-Benzenecarboxylic acid, diisooctyl ester	7.29 ± 1.6	12.8 ± 5.1	19.4 ± 9.2	74.2 ± 12.5
Diamino-dinitro-methyl dioctylphthalate	6.42 ± 0.8	4.3 ± 2.3	27.2 ± 2.5	23.6 ± 7.0
1,2-Benzenedicarboxylic acid, dioctylester	8.19 ± 1.2	9.90 ± 3.4	31.40 ± 9.6	56.1 ± 12.3
9-(2,2-Dimethylpropanoilhydrazono)-2,7-bis-[2-(diethylamino)-ethoxy]fluorine	9.90 ± 2.6	6.9 ± 3.1	41.3 ± 6.4	14.9 ± 8.1
(3-methylphenyl)-phenyl methanol	12.7 ± 4.2	9.0 ± 3.7	17.5 ± 4.7	23.8 ± 5.4
4-(Diethyl amino)-alpha-[4-(diethyl amino)Phenyl]	12.3 ± 2.7	14.1 ± 7.0	11.1 ± 6.1	15.4 ± 3.6
Isooctylphthalate	22.8 ± 6.9	11.8 ± 7.0	69.1 ± 4.9	0.8 ± 0.4
Phytol	N/A	N/A	N/A	Activity reported with no specificity

Drug-like properties

No work was found on the plant where drug-like properties were studied on its molecules. Some few drug-like properties of the compounds similar to the ones found in this plant leaves were found on chemical databases, not from this plant, but from other sources as shown in table 3.

Table 3: Drug like properties of similar compounds from chemical databases

Molecule	Log P	pKa	Solubility	MP	HBD	HBA	Color	Odor
Isooctylphthalate	**8.38, 3-4**		**Insoluble, 9.0X10^{-2} mg/L (25◦C)**	**-4◦C, -45◦C.**	**0**	**4**	**Nearly colorless, Oily liquid**	**Mild odor,**
(3-methylphenyl)-phenyl methanol or say Phenyl-m-tolyl-methanol	N/A		N/A	53◦C	1	1	N/A	N/A
1,2-Benzenedicarboxylic acid, dioctylester or dioctylphtalate	8.1		0.022 mg/L at 25 ◦C, <1mg/ml (66◦F)	25◦C	0	4	Clear, oily	N/A
1,2-Benzenecarboxylic acid, diisooctyl ester	N/A		Insoluble in water	-4◦C	N/A	N/A	N/A	N/A
1,2-Benzenedicarboxylic acid, mono-(2-ethylhexyl ester)	N/A		<1 mg/ml (70◦F)	N/A	1	4	N/A	N/A
Phytol			N/A	< 25 °C	1	1	N/A	N/A

N/A in this table means the data is not available on open sources and databases used in this systematic review

However, two molecules similar to those found in the plant leaves (Isooctylphthalate and 1,2-benzenedicarboxylic acid, dioctylester) were found in the chemical data bases to have their lipophilicity, solubility (aq, 25◦C), HBDs, HBAs, color and melting point known from other studies. Ionization of the all the compounds is yet to be reported. Despite that, isooctylphthalate is shown to have different values of lipophilicity and melting point in the data bases due to different test conditions. It is imperative to study drug-like properties exhaustively of molecules from *E. crassipes* because it already shows potential to be a good source of anticancer drug candidates for future drug development.

Hansch[18] stated that drug-like properties are intrinsic molecular properties and recommended that a medicinal chemist needs to optimize them apart from pharmacological properties in drug discovery and development. Lipophilicity (Log P and log D*x*) is an inclination of a compound to partition into an aqueous matrix versus a non-polar lipid matrix [19]. Generally, lipophilicity is calculated from the log of the ratio of the concentration of the compound in organic phase to the concentration of the compound in aqueous phase [20]. There is a high correlation between lipophilicity and other drug property models affecting ADME-Tox. These include absorption, permeability, distribution, plasma protein binding, metabolism, elimination and toxicity [21]. For example, Kerns and Di [6] reported that oral dosing optimal gastrointestinal absorption by passive diffusion permeability generally falls in the range 0 ≤Log P ≤3, giving a good solubility-permeability balance. Drug molecules with lower LogP have poorer lipid permeability due to their higher polarity, above the range, molecules are more non-polar, with poorer aqueous solubility. $LogD_{7.4}$ in the range of 1 -3 is ideal for balanced properties [6]. PKa is the negative log of the ionization constant, K_a. Drug pK_a influences solubility, permeability, lipophilicity and protein binding abilities a drug will have, which consequently have a direct effect on pharmacokinetic characteristics (PK) [19]. Molecules that are ionized are more soluble in aqueous media than are neutral molecules due to their higher polarity. On the other hand, neutral molecules are more permeable than ionic molecules. This is because neutral molecules have a much higher lipophilicity and they are considered the dominant form to permeate by passive diffusion [19]. pK_a has a major effect on solubility as it is a determining factor of the degree of ionization. After oral dosing, intestinal absorption of the drug is determined by these same factors. It should be noted that lowly permeable compounds often have higher solubility and vice versa [6].

According to Lipinski's 'rules of 5', the number of hydrogen bond acceptors (HBAs) and donors (HBDs) that a drug structure has influences pKa of drug properties [19]. Drug structures are likely to have poor permeation and solubility when they have more than 5 HBDs (summation of all NHs and OHs) and 10 HBAs (summation of all Ns and Os) [22]. HBDs and HBAs can manually be determined by structural inspection.

Melting point is a widely applied physical property in biochemistry and pharmaceutical sciences that fundamentally specifies the temperature at which matter transits from the solid to liquid phases [23]. It is a measure of the crystal lattice energy of a compound. It is used to characterize compounds, evaluate purity and predict solubility of drug molecules[24]. It can be determined directly using a melting point determination machine or from the relationship:

$$\text{Log } S = 0.8 - \text{LogP}_{(ow)} - 0.01(MP-25) \quad \text{..... (Eq.1)}$$

Where S is aqueous solubility, LogP is lipophilicity, ow is for octanol-water phases and MP is melting point in degree Celsius [25].

Solubility is the maximum possible concentration reached by a compound in solvent matrices at equilibrium with solid compounds. Low solubility compounds can lead to poor oral and intravenous (IV) dose absorption and bioavailability of a drug and the patient is forced to bear the burden of taking frequent and high doses to compensate for poor bioavailability. Biological and property assays are erratic [6]. This also brings challenges to drug development as it ends up with expensive formulations and increases time of development. It is necessary to specify study conditions in the determination of solubility as it differs depending on environmental factors. Solubility is affected by lipophilicity which is determined by H-bonding, ionic interactions, Vander Waals and dipoles. Molecular shape and weight have also a bearing on solubility as is pKa, which reflects the ionizability of functional groups. Crystal lattice energy, measured by melting point, also influences solubility [24]. This depends on how crystals are stacked and the melting point of the molecules. As seen from equation 1, crystal energy lattice measure can be used to determine solubility.

Note needs to be taken that no research on the plant *Eichhornia crassipes* extracts or any part thereof has this far looked at drug-like poperties stated above, besides studying their bioactivities.

Conclusion

The findings from this research show that there is need for robust determination of compounds from the *E. crassipes*, not just leaves, but also roots and stems, which are likely to give these known and other unknown compounds with a likelihood to have anticancer activities. The chemistry of these compounds needs to be studied further to determine their suitability as strong potential drug leads by looking at their drug-like properties. This way, it will be easier for drug developers and project managers to narrow down to compounds from *E. crassipes* that are already known to be viable drug candidate interms of drug-like properties and proceed to confirmation of cytotoxicity determination and clinical trial. These properties will also assist in drug modifications wherever necessary, in structural activity relationships.

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