AL-Bahir
Journal for Engineering and Pure Sciences
BJEPS

Volume 4 | Issue 1 Article 4

An Insight into the Physicochemical, Drug-likeness, Pharmacokinetics and Toxicity Profile of Kigelia africana (Lam) Bioactive Compounds

Sulyman Olalekan Ibrahim
Department of Industrial Chemistry, Faculty of Physical Sciences, University of Ilorin, Ilorin, Nigeria

Halimat Yusuf Lukman
Department of Chemical Sciences, College of Natural and Applied Sciences, Summit University, Offa, Nigeria.

Marili Funmilayo Zubair
Department of Industrial Chemistry, Faculty of Physical Sciences, University of Ilorin, Ilorin, Nigeria

Oluwagbemiga Tayo Amusan
Department of Chemical Sciences, Crown-Hill University, Ilorin, Nigeria

Fatimah Ronke Abdulkadri
Department of Chemistry, Faculty of Physical Sciences, University of Ilorin, Ilorin, Nigeria

See next page for additional authors

An Insight into the Physicochemical, Drug-likeness, Pharmacokinetics and Toxicity Profile of Kigelia africana (Lam) Bioactive Compounds

Authors

Sulyman Olalekan Ibrahim, Halimat Yusuf Lukman, Marili Funmilayo Zubair, Oluwagbemiga Tayo Amusan, Fatimah Ronke Abdulkadri, Bashir Lawal, Lateefat Bello Abdulfatah, and Olubunmi Atolani

Source of Funding

Authors received no funding for the work

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper

Data Availability

Data available on request

Author Contributions

The author solely contributed to all aspects of this work, including conceptualization, methodology, data curation, software, formal analysis, writing – original draft preparation, review and editing, and project administration

ORIGINAL STUDY

An Insight into the Physicochemical, Drug-likeness, Pharmacokinetics and Toxicity Profile of *Kigelia Africana* (Lam) Bioactive Compounds

Sulyman O. Ibrahim [a,*], Halimat Y. Lukman [b], Marili F. Zubair [a], Oluwagbemiga T. Amusan [c], Fatimah R. Abdulkadri [d], Bashir Lawal [e], Lateefat B. Abdulfatah [b], Olubunmi Atolani [d]

[a] Department of Industrial Chemistry, Faculty of Physical Sciences, University of Ilorin, Ilorin, Nigeria
[b] Department of Chemical Sciences, College of Natural and Applied Sciences, Summit University, Offa, Nigeria
[c] Department of Chemical Sciences, Crown-Hill University, Ilorin, Nigeria
[d] Department of Chemistry, Faculty of Physical Sciences, University of Ilorin, Ilorin, Nigeria
[e] Department of Medical Laboratory Sciences, Faculty of Medical and Health Sciences, Newgate University, Minna, Nigeria

Abstract

***Kigelia africana* plant is multipurpose plant whose therapeutic potential has been thoroughly investigated. The physicochemical, solubilities, ADMET, pharmacological, and drug-like properties of this plant have not been reported in details. This study makes use of the information that is currently known on the chemical make-up of the plant to forecast its overall toxicity as well as the potential for the phytochemicals it contains to be employed in medication discovery. The study also employed free web servers for the lipophilicity, water solubility, drug-likeness, bioavailability score, medicinal chemistry and toxicological profiling of the compounds of *K. africana*. Artemether, a known antimalaria drug was used to validate the potentials of the phytochemicals to serve as precursor to valuable drugs. Findings from our study revealed that a larger percentage of these compounds passed the physicochemical properties analysis, low lipophilicities, high-water solubilities, obeyed the drug-likeness rules, had high gastrointestinal absorption, high blood-barrier permeant, low permeability glycoprotein and hence bioavailable. The toxicological profile additionally showed that majority of the compounds possessed low toxicities and thus can be a potential drug candidate in the drug development industry. The profile of the well-known artemether supported the study's findings that a higher proportion of the *K. africana* compounds have potential drug-like molecules.**

Keywords: Physicochemical, Drug-likeness, Pharmacokinetics, Toxicity profile, *Kigelia africana*

1. Introduction

Over the years, traditional medicine continues to play crucial role in local health care systems especially in low or middle-income regions, underdeveloped or developing countries. In Africa, the high number of traditional practitioners makes herbal medicines easily accessible and affordable [1]. According to the World Health Organization (WHO), 65−80 % healthcare practice integrates traditional medicine at one point or the other leading to an increase in its demand [2]. Various plants parts such as root, stem bark, leaves, flowers, seeds are being used for different medicinal purposes. Due to the advantages of herbal medicine, attention is now shifting from conventional drugs to herbal medicine as also supported by scientific efforts that validate different ethnobotanical and ethnomedicinal uses of these plants.

To bolster drug discovery, authentic data on pharmacokinetics properties of the molecule must be attainable at the earliest which eventually

Received 22 August 2023; revised 6 October 2023; accepted 7 October 2023.
Available online 6 November 2023

* Corresponding author at: Department of Industrial Chemistry, University of Ilorin, P.M.B. 1515, Ilorin, Kwara State, Nigeria.
E-mail address: sulalekan9@gmail.com (S.O. Ibrahim).

https://doi.org/10.55810/2313-0083.1050

contributes to the success or failure of the compound. The present study will be the first of its kind reporting the ADME (Absorption, Distribution, Metabolism and Excretion) properties of *Kigeli africa* using freely available web tool Swiss ADME following the works of [3–7]. Twenty-five [25] isolated compounds reported in their earlier work were screened for ADME and toxicities properties [8].

Kigelia africana (Lam) Benth synonymous to *Kigelia pinnata* has been reported in literature as a multipurpose medicinal plant with many attributes [3]. Locally, the plant is been use for antiulcer [7], antiaging, antioxidant [9], and anti-malarial treatments [10]. It is also globally used in the treatment of genital infections, gynecological disorders [7], renal ailments [11], sickle-cell anemia, psoriasis [12], eczema, central nervous system [13], respiratory ailment, skin complaint, body weakness, leprosy, impetigo, worm infestation [14], scalp, athlete's foot, tumours [15,16] etc., especially in developing nations where orthodox medicine are meager, expensive or inaccessible.

Olawale, Olofinsan [6] described the use of *K. africana* in the treatment of erectile dysfunction using molecular modeling approach. However, there is paucity of information on the ADMET and pharmacokinetics properties of the compounds isolated so far from this wonderful plant which will make it a potential effective drug candidate. This study thus seeks to provide information on the ADMET, pharmacokinetics profile and drug–likeness properties of some of the identified compounds in *K. Africana* for drug discovery and development purposes. The validity of this methods in identifying potential drugs candidate was confirmed using artemether, a known drug for malaria treatment.

2. Materials and methods

2.1. Data mining of K. africana compounds

Bioactive phytochemicals in *Kigelia africana* were obtained from literature work of [3–7]. A dataset of twenty-five [25] compounds were used for this study.

2.2. Physicochemical, lipophilicity and water solubility properties of K. africana compounds

Canonical SMILES formular of the phytochemicals obtained from PerkinElmer ChemDraw was used to determine the properties using SWISSADME available on this site http://www.swissadme.ch/index.php.

2.3. Structural optimization and toxicity profiling of K. africana compounds

PerkinElmer ChemDraw software was used to draw the molecular structures of various phytochemicals, the Canonical SMILES formular was then obtained using the same software. The Resulting Canonical SMILES formular was the used to determine the ADME properties using SWISSADME available on this site http://www.swissadme.ch/index.php. The Toxicities profile was done using the Canonical SMILES formula using Protox II available on this site https://tox-new.charite.de/protox_II/index.php?site=compound_input.

3. Results and discussion

The process of drug discovery and development involves several stages such as target identification, target validation, lead identification and optimization among others [17]. In this study, the first stage which is target identification for potential druggable compounds was investigated using the bioinformatics (data mining and computer-aided drug design) approach. Currently, computer-aided drug development (CADD) has facilitated the estimation of drug absorption, distribution, metabolism, and excretion (ADME). They provide reliable data relatively rapidly and support experimental methods [18,19]. The percentage of pharmacokinetics-related failures in the clinical phase has been found to be significantly reduced by the first assessment of ADME properties in the discovery phase [19,20].

Phytochemicals are gaining more attention due to their various benefits in drug development, they are rich in drug candidate molecules, less toxic and produce minimum side effects compared to the synthetic drugs [21]. The structures of the phytochemical compounds identified in *Kigelia africana* is presented in Fig. 1. The plant contained several compounds including kigelinone, isokigelinone, kigelinol, pinnata, isopinnata, avanafil, caffeic acid, luteolin, naphthodione, metronidazole, sitosterol, quinine among others. These compounds have been reported to be pharmacologically active [22]. Avanafil is reportedly active against erectile dysfunction [6].

The physicochemical properties of compounds are indicators of the probable success of such compounds as drug candidates. It is believed that compounds with high molecular weight and lipophilicity present poor drug-like potential [23].

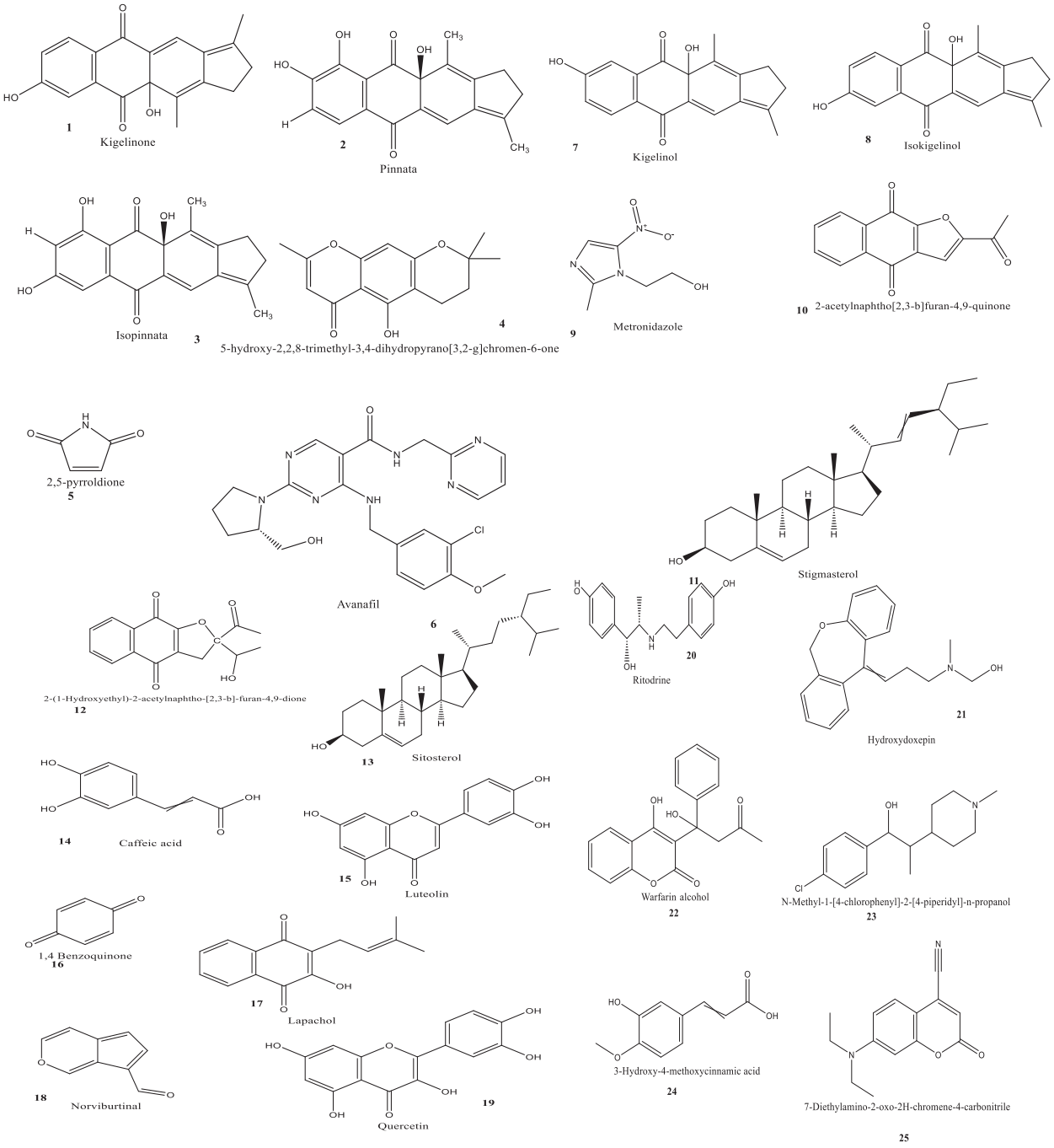

Fig. 1. Structures of Phytochemicals in Kigelia africana.

The Lipinski rule of five gives a guide on oral bioavailability which states that the compound should have no more than 5 hydrogen bond donors and 10 hydrogen bond acceptors and molecular weight <500 $gmol^{-1}$ and a log P < 5 [24]. Tables 1 and 2 show the physicochemical properties and lipophilicity characteristics of the phytochemicals in *Kigelia africana* respectively. Interestingly, all the compounds met the physicochemical conditions, avanafil has the highest molecular weight of 483.95 $gmol^{-1}$ while 2,5-pyrroldione shows the least molecular weight of 97.07 $gmol^{-1}$. Equally, the amount of hydrogen bond donor and hydrogen bond acceptors of the phytochemicals are within the number recommended for potential dugs and for available generic drugs. The total polar surface area

Table 1. Physicochemical properties of the phytochemicals in Kigelia africana.

Phytochemicals	MW	Heavy atoms	Aromatic heavy atoms	Fraction Csp3	Rotatable bonds	H-bond acceptors	H-bond donors	MR	TPSA
Kigelinone	308.33	23	6	0.26	0	4	2	85.55	74.6
Pinnata	339.36	25	6	0.3	0	5	3	92.45	94.83
Isopinnata	322.35	24	6	0.3	0	4	2	90.52	74.6
5-hydroxy-2,2,8-trimethyl-3,4-dihydropyrano[3,2-g]chromen-6-one	260.29	19	10	0.4	0	4	1	73.28	59.67
2,5-pyrroldione	97.07	7	0	0	0	2	1	25.87	46.17
Avanafil	483.95	34	18	0.35	10	7	3	131.01	125.39
Kigelinol	308.33	23	6	0.26	0	4	2	85.55	74.6
Isokigelinol	308.33	23	6	0.26	0	4	2	85.55	74.6
Metronidazole	171.15	12	5	0.5	3	4	1	43.25	83.87
2-acetylnaphtho[2,3-b]furan-4,9-quinone	240.21	18	11	0.07	1	4	0	62.21	64.35
Stigmasterol	412.69	30	0	0.86	5	1	1	132.75	20.23
2-(1-Hydroxyethyl)-2-acetylnaphtho-[2,3-b]-furan-4,9-dione	286.28	21	6	0.31	2	5	1	73.46	80.67
Sitosterol	414.71	30	0	0.93	6	1	1	133.23	20.23
Caffeic acid	180.16	13	6	0	2	4	3	47.16	77.76
Luteolin	286.24	21	16	0	1	6	4	76.01	111.13
1,4-Benzoquinone	108.09	8	0	0	0	2	0	28.29	34.14
Lapachol	242.27	18	6	0.2	2	3	1	69.38	54.37
Norviburtinal	146.14	11	9	0	1	2	0	40.72	30.21
Quercetin	302.24	22	16	0	1	7	5	78.03	131.36
Ritodrine	287.35	21	12	0.29	6	4	4	83.13	72.72
Hydroxydoxepin	295.38	22	12	0.26	4	3	1	88.84	32.7
Warfarin alcohol	324.33	24	16	0.16	4	5	2	89.63	87.74
N-methyl-1-[4-chlorophenyl]-2-[4-piperidyl]-n-propanol	267.79	18	6	0.6	3	2	1	80.73	23.47
3-Hydroxy-4-methoxycinnamic acid	194.18	14	6	0.1	3	4	2	51.63	66.76
7-Diethylamino-2-oxo-2H-chromene-4-carbonitrile	242.27	18	10	0.29	3	3	0	71.02	57.24
Artemether	298.37	21	0	1	1	1	0	76.07	46.15

MW- Molecular weight, MR-Molar refractivity, TPSA: Total Polar Surface Area, H-bond − Hydrogen bond.

Table 2. Lipophilicity characteristics of the phytochemicals in Kigelia africana.

Phytochemicals	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P	Consensus Log P
Kigelinone	2.08	1.15	2.87	1.62	3.45	2.23
Pinnata	−5.73	1.04	3	1.02	3.96	0.66
Isopinnata	2.27	1.51	3.18	1.85	3.96	2.55
5-hydroxy-2,2,8-trimethyl-3,4-dihydropyrano[3,2-g]chromen-6-one	3.01	3.09	2.91	1.31	3.72	2.81
2,5-pyrroldione	0.5	−0.29	−1.18	−0.58	0.34	−0.24
Avanafil	3.66	2.58	1.56	0.89	2.44	2.22
Kigelinol	2.08	1.15	2.87	1.62	3.45	2.23
Isokigelinol	1.73	1.15	2.87	1.62	3.45	2.16
Metronidazole	1.16	−0.02	0.09	−1.19	−1.62	−0.32
2-acetylnaphtho[2,3-b]furan-4,9-quinone	1.83	2.28	2.26	0.09	3.31	1.95
Stigmasterol	5.08	8.56	7.8	6.62	6.86	6.98
2-(1-Hydroxyethyl)-2-acetylnaphtho-[2,3-b]-furan-4,9-dione	1.94	1.03	1.45	−0.11	2.77	1.42
Sitosterol	5.07	9.34	8.02	6.73	7.04	7.24
Caffeic acid	0.97	1.15	1.09	0.7	0.75	0.93
Luteolin	1.86	2.53	2.28	−0.03	2.03	1.73
1,4-Benzoquinone	0.94	0.2	0.25	−0.23	0.99	0.43
Lapachol	2.37	2.84	3.23	1.32	3.32	2.62
Norviburtinal	1.69	1.43	2.2	0.65	2.56	1.7
Quercetin	1.63	1.54	1.99	−0.56	1.54	1.23
Ritodrine	2.37	2.32	2.03	1.97	2.62	2.26
Hydroxydoxepin	2.88	3.7	3.13	2.95	3.6	3.25
Warfarin alcohol	2.87	2.12	2.61	1.68	3.59	2.57
N-methyl-1-[4-chlorophenyl]-2-[4-piperidyl]-n-propanol	3.17	3.28	2.65	3.05	3.33	3.1
3-Hydroxy-4-methoxycinnamic acid	1.79	1.51	1.39	1	1.26	1.39
7-Diethylamino-2-oxo-2H-chromene-4-carbonitrile	2.43	2.2	2.51	1.52	2.73	2.28
Artemether	3.35	3.53	2.84	2.6	1.75	2.81

(TPSA) is a physicochemical property that describes the relationship of compound with incidence of adverse events [25].

The partial coefficient (P) is a measure of how a compound dissolves in a mixture of water and non-polar/organic solvent whereas the log10 value of P (LogP) describes the negative value for hydrophilic compounds and a positive value for lipophilic compounds, it is a component of Lipinski's rule of 5 guide; log P < 5; best between 1.35 and 1.8 for better oral and intestinal absorption. The low consensus log P (Clog P) also plays significant role in molecular discovery activities across a wide range of fields. All of the phytochemicals except stigmasterol and sitosterol had a higher Clog P value, 6.98 and 7.24 respectively. The low Clog P value indicates low lipophilic abilities and as such less likelihood to be used as a topical drug and more likely as an oral drug [26]. The lipophilicity study revealed that all the identified compounds had a ClogP <3 except sitosterol (7.24) and stigmasterol (6.98) while hydroxydoxepin and N-methyl-1-[4-chlorophenyl]-2-[4-piperidyl]-n-propanol had values slightly higher than 3 (3.25 and 3.12 respectively). These values portray their low solubility in the system but potentiate them more as a topical drug while others that showed low lipophilicity would likely pass as internally used drugs.

The phytochemical water solubility characteristics is a crucial consideration since it guarantees that at least a minimal concentration of them will be present in the circulatory system, meaning higher absorption in the body. These characteristics influence its use for drug formulation and handling during drug development for easy absorption especially via oral administration [27]. The different models for evaluating water solubility include the ESOL-Ali and SILICOS-IT are usually predicted with the SWISSADME. The first two differ in seminal general solubility equation as they exclude melting point parameters; all demonstrate strong linear correlation between predicted and experimental values [28]. SwissADME predicts solubility (log S) using topological and fragmental approaches, where a value of −10 or below is deemed insoluble and a value of −4 or above is considered soluble. Table 3

Table 3. Water solubility characteristics of phytochemicals in Kigelia africana.

Compounds	ESOL				Ali				SILICOS-IT			
	Log S (ESOL)	Solubility		Class	Log S (Ali)	Solubility		Class	Log S SILICOS-IT	Solubility		Class
		mg/ml	mol/L			mg/ml	mol/L			mg/ml	mol/L	
Kigelinone	−2.67	6.60E-01	2.14E-03	S	−2.31	1.51E+00	4.88E-03	S	−4.51	9.46E-03	3.07E-05	MS
Pinnata	−2.78	5.67E-01	1.67E-03	S	−2.62	8.11E-01	2.39E-03	S	−4.89	4.34E-03	1.28E-05	MS
Isopinnata	−2.97	3.42E-01	1.06E-03	S	−2.68	6.66E-01	2.07E-03	S	−4.89	4.12E-03	1.28E-05	MS
5-hydroxy-2,2,8-trimethyl-3, 4-dihydropyrano[3,2-g]chromen-6-one	−3.79	4.22E-02	1.62E-04	S	−4.01	2.54E-02	9.76E-05	MS	−4.76	4.52E-03	1.74E-05	MS
2,5-pyrroldione	−0.26	5.34E+01	5.51E-01	VS	−0.22	5.85E+01	6.03E-01	VS	−0.27	5.26E+01	5.42E-01	S
Avanafil	−4.2	3.07E-02	6.34E-05	MS	−4.86	6.65E-03	1.38E-05	MS	−7.43	1.79E-05	3.70E-08	PS
Kigelinol	−2.67	6.60E-01	2.14E-03	S	−2.31	1.51E+00	4.88E-03	S	−4.51	9.46E-03	3.07E-05	MS
Isokigelinol	−2.67	6.60E-01	2.14E-03	S	−2.31	1.51E+00	4.88E-03	S	−4.51	9.46E-03	3.07E-05	MS
Metronidazole	−1	1.72E+01	1.00E-01	VS	−1.29	8.74E+00	5.11E-02	VS	−0.41	6.69E+01	3.91E-01	S
2-acetylnaphtho[2,3-b] furan-4,9-quinone	−3.15	1.69E-01	7.05E-04	S	−3.27	1.29E-01	5.39E-04	S	−4.8	3.82E-03	1.59E-05	MS
Stigmasterol	−7.46	1.43E-05	3.46E-08	PS	−8.86	5.71E-07	1.38E-09	PS	−5.47	1.40E-03	3.39E-06	MS
2-(1-Hydroxyethyl)-2-acetylnaphtho-[2,3-b]-furan-4,9-dione	−2.34	1.30E+00	4.54E-03	S	−2.31	1.39E+00	4.85E-03	S	−3.73	5.38E-02	1.88E-04	S
Sitosterol	−7.9	5.23E-06	1.26E-08	PS	−9.67	8.90E-08	2.15E-10	PS	−6.19	2.69E-04	6.49E-07	PS
Caffeic acid	−1.89	2.32E+00	1.29E-02	VS	−2.38	7.55E-01	4.19E-03	S	−0.71	3.51E+01	1.95E-01	S
Luteolin	−3.71	5.63E-02	1.97E-04	S	−4.51	8.84E-03	3.09E-05	MS	−3.82	4.29E-02	1.50E-04	S
1,4-Benzoquinone	−0.64	2.50E+01	2.31E-01	VS	−0.48	3.62E+01	3.34E-01	VS	−0.32	5.15E+01	4.76E-01	S
Lapachol	−3.25	1.38E-01	5.68E-04	S	−3.64	5.55E-02	2.29E-04	S	−3.96	2.69E-02	1.11E-04	S
Norviburtinal	−2.19	9.51E-01	6.51E-03	S	−1.67	3.13E+00	2.14E-02	VS	−3.21	8.95E-02	6.12E-04	S
Quercetin	−3.16	2.11E-01	6.98E-04	S	−3.91	3.74E-02	1.24E-04	S	−3.24	1.73E-01	5.73E-04	S
Ritodrine	−3.11	2.23E-01	7.76E-04	S	−3.49	9.39E-02	3.27E-04	S	−4.53	8.50E-03	2.96E-05	MS
Hydroxydoxepin	−4.14	2.13E-02	7.21E-05	MS	−4.08	2.47E-02	8.37E-05	MS	−5.59	7.59E-04	2.57E-06	MS
Warfarin alcohol	−3.42	1.25E-01	3.84E-04	S	−3.59	8.27E-02	2.55E-04	S	−5.74	5.85E-04	1.80E-06	MS
N-methyl-1-[4-chlorophenyl]-2-[4-piperidyl]-n-propanol	−3.62	6.49E-02	2.42E-04	S	−3.45	9.55E-02	3.57E-04	S	−3.81	4.20E-02	1.57E-04	S
3-Hydroxy-4-methoxycinnamic acid	−2.11	1.49E+00	7.68E-03	S	−2.52	5.86E-01	3.02E-03	S	−1.42	7.43E+00	3.83E-02	S
7-Diethylamino-2-oxo-2H-chromene-4-carbonitrile	−2.94	2.77E-01	1.14E-03	S	−3.04	2.23E-01	9.20E-04	S	−4.62	5.76E-03	2.38E-05	MS
Artemether	−3.85	4.24E-02	1.42E-04	S	−4.18	1.96E-02	6.55E-05	MS	−2.04	2.75E+00	9.20E-03	S

S − Soluble, MS − Moderately Soluble, VS − Very Soluble, PS − Partially Soluble.

Table 4. Pharmacokinetics properties of phytochemicals in Kigelia africana.

Phytochemicals	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)
Kigelinone	High	Yes	Yes	Yes	Yes	No	No	Yes	−7.36
Pinnata	High	No	Yes	No	No	No	No	No	−7.63
Isopinnata	High	Yes	Yes	Yes	Yes	No	No	Yes	−7.19
5-hydroxy-2,2,8-trimethyl-3, 4-dihydropyrano[3,2-g]chromen-6-one	High	Yes	No	Yes	Yes	No	Yes	Yes	−5.69
2,5-pyrroldione	High	No	No	No	No	No	No	No	−7.1
Avanafil	High	No	Yes	No	Yes	Yes	Yes	Yes	−7.42
Kigelinol	High	Yes	Yes	Yes	Yes	No	No	Yes	−7.36
Isokigelinol	High	Yes	Yes	Yes	Yes	No	No	Yes	−7.36
Metronidazole	High	No	No	No	No	No	No	No	−7.36
2-acetylnaphtho[2,3-b]furan-4, 9-quinone	High	Yes	No	Yes	Yes	No	No	Yes	−6.15
Stigmasterol	Low	No	No	No	No	Yes	No	No	−2.74
2-(1-Hydroxyethyl)-2-acetylnaphtho-[2,3-b]-furan-4,9-dione	High	No	No	Yes	No	No	No	No	−7.32
Sitosterol	Low	No	No	No	No	No	No	No	−2.2
Caffeic acid	High	No	No	No	No	No	No	No	−6.58
Luteolin	High	No	No	Yes	No	No	Yes	Yes	−6.25
1,4-Benzoquinone	High	No	No	No	No	No	No	No	−6.82
Lapachol	High	Yes	No	Yes	Yes	No	No	No	−5.76
Norviburtinal	High	Yes	No	Yes	No	No	No	No	−6.18
Quercetin	High	No	No	Yes	No	No	Yes	Yes	−7.05
Ritodrine	High	Yes	Yes	No	No	No	Yes	Yes	−6.41
Hydroxydoxepin	High	Yes	No	Yes	No	No	Yes	No	−5.47
Warfarin alcohol	High	No	No	No	No	No	No	No	−6.77
N-methyl-1-[4-chlorophenyl]-2-[4-piperidyl]-n-propanol	High	Yes	No	No	No	No	Yes	No	−5.6
3-Hydroxy-4-methoxycinnamic acid	High	Yes	No	No	No	No	No	No	−6.41
7-Diethylamino-2-oxo-2H-chromene-4-carbonitrile	High	Yes	No	Yes	Yes	No	No	No	−6.22
Artemether	High	Yes	No	Yes	No	No	No	No	−5.61

shows the water solubility characteristics of *K. africana* compounds. As anticipated, both Sitosterol (−7.9) and Stigmasterol (−7.46) are weakly soluble due to their non-polar nature, metronidazole (−1), 3-Hydroxy-4-methoxycinnamic acid (−2.11), Kigelinol (−2.67) and Isokigelinol (−2.67) shows the maximum solubilities, the entire phytochemicals are soluble and moderately soluble depicting their bioabsorption potential.

An important step in determining the overall toxicity of a substance is to examine the toxicological profile of the product. Predictive (*in silico*) models have been employed in recent years to assess the potential toxicity of food substances based on their chemical makeup. To forecast and confirm the pharmacological activity and toxicological profile of chemical compounds found in *Kigelia africana* found in the literature, *in silico* (computational) approaches were employed. Protox II software, which integrates, captures, and analyzes compounds from many databases around the world, was used to evaluate the compounds while SWISSADME was used for the ADME, pharmacokinetics and druglike properties of the phytocompounds. In the toxicities profile, the compounds were screened for their ability to induce immune toxicity, ability to cause cancer, ability to affect the cell and general toxicity [29].

The pharmacokinetic parameters including gastrointestinal (GI) absorption, BBB permeability, PGP substrate, inhibitor of Cytochrome P450 isoenzymes, and skin permeation as a Log Kp value are displayed on Table 4. GI absorption of compounds particularly those administered via oral route may be affected by factors such as age, genes, health status, ethnicity and thus affect the pharmacokinetics of drug [30]. Low GI absorption may be attributed to non-polar nature of the compound, thus low solubility in the intestinal lumen and overall their reduced bioavailability [31]. With the exceptions of both sitosterol and stigmasterol, which had minimal GI absorption, the pharmacokinetics and drug similarity studies utilizing SwissADME demonstrated high levels of GI absorption for all other phytochemicals.

The blood vessels which line the vascular central nervous system are the blood−brain barrier (BBB) and specifically regulates transport of molecules between the brain and blood; the BBB prevents circulation of drugs to the brain [32]. Thirteen [13] of the enlisted compounds (52 %) are permeable to the BBB while the remaining twelve [12] (48 %) namely pinnata, 2,5-pyrroldione, avanafil, metronidazole, 2-(1-Hydroxyethyl)-2-acetylnaphtho-[2,3-b]-furan-4,9-dione, sitosterol, stigmasterol, caffeic acid, luteolin, quercetin and warfarin alcohol are not BBB permeant. Small molecule compounds may be able to cross this barrier provided their molecular weight is < 400 g/mol and hydrogen bond formation <8. The "No" BBB permeant observed in avanafil, stigmasterol and sitosterol is corroborated by their high molecular weight which were >400 g/mol, other molecules with no BBB permeant may be due to difference in other parameters. The "Yes" indicates possibly movement across the BBB for pharmacological effects pertaining brain diseases. Additionally, the permeability glycoprotein (Pgp) substrate is a transporter expressed primarily in the intestine functions to protect the central nervous system against foreign substances by sending them back into the intestinal lumen to restrict the absorption of the substance. However, overexpression of the Pgp substrate results in multidrug-resistant malignancy [28,33,34]. Fortunately, most of the compounds are not Pgp substrate depicting their potential bioavailability except ritodrine, isokigelinol, kigelinol, avanafil, issopinnata and pinnata.

The biotransformation or metabolism of drug into polar excretable form is initially (phase 1) carried out by the cytochrome P450 super family of five isoenzymes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4) (Ilieva et al., 2018). The predictors for the isoenzymes CYP2C9, CYP2D6 and CYP3A4 present fewer inhibitory compounds compared to CYP1A2, CYP2C19. Hence, most of the compounds are not likely to affect cytochrome P450 reactions in drug metabolism. The fewer the inhibition the better the phase 1 reaction of drug biotransformation in the liver would occur.

A multivariate linear regression called the skin permeability coefficient (Log Kp) shows how permeant a molecule is to the skin. The less permeant the molecule is to the skin, the lower the log Kp (with Kp in cm/s). The skin permeability standard compass is −8.0 to −1.0 [28].

All the phytochemicals show appreciable permeability in the range of −2.2 cm/s to −7.63 cm/s. Pinnata had the lowest log Kp (−7.63 cm/s), followed by avanafil (−7.42 cm/s). kigelinone, kigelinol, isokigelinol and metronidazole had the same value of −7.36 cm/s, other compounds had lesser negative values with stigmasterol and sitosterol shows the best permeability coefficient of and −2.7 and −2.2 cm/s respectively indicating excellent transdermal medicinal and aesthetic prospects [35,36]. This result is in tandem with the other pharmacokinetics parameters for stigmasterol and sitosterol where they presented low GI, no BBB permeant nor a Pgp substrate. Its inhibitory effect on the cytochrome P450 isoenzymes further

Table 5. Drug-likeness and bioavailability score of phytochemicals in Kigelia africana.

Phytochemicals	Lipinski violations	Ghose violations	Veber violations	Egan violations	Muegge violations	Bioavailability Score
Kigelinone	0	0	0	0	0	0.55
Pinnata	0	0	0	0	0	0.55
Isopinnata	0	0	0	0	0	0.55
5-hydroxy-2,2,8-trimethyl-3, 4-dihydropyrano[3,2-g]chromen-6-one	0	0	0	0	0	0.55
2,5-pyrroldione	0	4	0	0	2	0.55
Avanafil	0	2	0	0	0	0.55
Kigelinol	0	0	0	0	0	0.55
Isokigelinol	0	0	0	0	0	0.55
Metronidazole	0	0	0	0	1	0.55
2-acetylnaphtho[2,3-b]furan-4,9-quinone	0	0	0	0	0	0.55
Stigmasterol	1	3	0	1	2	0.55
2-(1-Hydroxyethyl)- 2-acetylnaphtho-[2,3-b]-furan-4,9-dione	0	0	0	0	0	0.56
Sitosterol	1	3	0	1	2	0.55
Caffeic acid	0	0	0	0	1	0.56
Luteolin	0	0	0	0	0	0.55
1,4-Benzoquinone	0	3	0	0	1	0.55
Lapachol	0	0	0	0	0	0.85
Norviburtinal	0	2	0	0	1	0.55
Quercetin	0	0	0	0	0	0.55
Ritodrine	0	0	0	0	0	0.55
Hydroxydoxepin	0	0	0	0	0	0.55
Warfarin alcohol	0	0	0	0	0	0.55
N-methyl-1-[4-chlorophenyl]-2- [4-piperidyl]-n-propanol	0	0	0	0	0	0.55
3-Hydroxy-4-methoxycinnamic acid	0	0	0	0	1	0.85
7-Diethylamino-2-oxo-2H-chromene-4-carbonitrile	0	0	0	0	0	0.55
Artemether	0	0	0	0	0	0.55

Table 6. Medicinal chemistry properties of phytochemicals in Kigelia africana.

Phytochemicals	PAINS alerts	Brenk alerts	Leadlikeness violations	Synthetic Accessibility
Kigelinone	1	0	0	3.96
Pinnata	1	0	0	4.14
Isopinnata	1	0	0	4.07
5-hydroxy-2,2,8-trimethyl-3,4-dihydropyrano[3,2-g]chromen-6-one	0	0	0	3.04
2,5-pyrroldione	0	1	1	1.88
Avanafil	0	0	2	3.81
Kigelinol	1	0	0	3.96
Isokigelinol	1	0	0	3.96
Metronidazole	0	2	1	2.3
2-acetylnaphtho [2,3-b]furan-4,9-quinone	1	0	1	3.09
Stigmasterol	0	1	2	6.21
2-(1-Hydroxyethyl)-2-acetylnaphtho- [2,3-b]-furan-4,9-dione	1	0	0	4.18
Sitosterol	0	1	2	6.3
Caffeic acid	1	2	1	1.81
Luteolin	1	1	0	3.02
1,4-Benzoquinone	1	1	1	2.87
Lapachol	1	1	1	2.92
Norviburtinal	0	1	1	2.81
Quercetin	1	1	0	3.23
Ritodrine	0	0	0	2.5
Hydroxydoxepin	0	1	1	3.7
Warfarin alcohol	0	1	0	3.8
N-methyl-1-[4-chlorophenyl]-2-[4-piperidyl]-n-propanol	0	0	0	2.53
3-Hydroxy-4-methoxycinnamic acid	0	1	1	1.9
7-Diethylamino-2-oxo-2H-chromene-4-carbonitrile	0	1	1	2.9
Artemether	0	1	1	6.65

Table 7. In silico toxicological profile of phytochemicals in Kigelia africana.

Compound Name	LD_{50} value and Tox Class	Prediction Accuracy (%)	Immunotoxicity	Carcinogenicity	Mutagenicity	Cytotoxicity
Kigelinone	450 mg/Kg 4	67.38	Active (0.79)	Active (0.52)	Active (0.70)	Inactive
Pinnata	1,000 mg/Kg 4	67.38	Active (0.97)	Inactive	Inactive	Inactive
Isopinnata	1000 mg/Kg 5	67.38	Inactive (0.55)	Active (0.52)	Inactive	Inactive
5-hydroxy-2,2,8-trimethyl-3,4-dihydropyrano[3,2-g]chromen-6-one	100 mg/Kg 3	67.38	Inactive	Inactive	Active (0.56)	Inactive
2,5-pyrroldione	80 mg/Kg 3	100	Inactive	Active (0.68)	Active (0.73)	Inactive
Avanafil	1190 mg/Kg 4	54.26	Active (0.86)	Inactive	Inactive	Inactive
Kigelinol	1000/Kg 4	67.38	Active (0.78)	Active (0.51)	Inactive	Inactive
Isokigelinol	1000 mg/Kg 5	68.07	Active (0.88)	Active (0.51)	Inactive	Inactive
Metronidazole	1500 mg/Kg 4	69.26	Inactive	Active (0.87)	Active (0.97)	Inactive
2-acetylnaphtho[2,3-b] furan-4,9-quinone	2400 mg/Kg 5	67.38	Inactive	Active (0.52)	Active (0.57)	Inactive
Stigmasterol	890 mg/Kg 4	70.97	Active (0.99)	Inactive	Inactive	Inactive
2-(1-Hydroxyethyl)-2-acetylnaphtho-[2,3-b]-furan-4,9-dione	2000 mg/Kg 4	68.07	Inactive	Active (0.50)	Inactive	Inactive
Sitosterol	890 mg/Kg 4	70.97	Active (0.99)	Inactive	Inactive	Inactive
Caffeic acid	2980 mg/Kg 5	70.97	Inactive	Active (0.78)	Inactive	Inactive
Luteolin	3919 mg/Kg 5	70.97	Inactive	Active (0.68)	Active (0.51)	Inactive
1,4-Benzoquinone	25 mg/Kg 2	100	Inactive	Active (0.72)	Inactive	Inactive
Lapachol	487 mg/Kg 4	100	Inactive	Inactive	Inactive	Inactive
Norviburtinal	2000 mg/Kg 4	54.26	Inactive	Active (0.63)	Inactive	Inactive
Quercetin	159 mg/Kg 3	100	Inactive	Active (0.68)	Active (0.51)	Inactive
Ritodrine	687 mg/Kg 4	100	Active (0.64)	Inactive	Inactive	Inactive
Hydroxydoxepin	135 mg/Kg 3	72.90	Inactive	Active (0.78)	Inactive	Inactive
Warfarin alcohol	21 mg/Kg 1	70.97	Inactive	Inactive	Inactive	Inactive
N-methyl-1-[4-chlorophenyl]-2-[4-piperidyl]-n-propanol	400 mg/Kg 4	69.26	Inactive	Inactive	Inactive	Inactive
3-Hydroxy-4-methoxycinnamic acid	7900 mg/Kg 6	100	Active (0.95)	Inactive	Inactive	Inactive
7-Diethylamino-2-oxo-2H-chromene-4-carbonitrile	1691 mg/Kg 4	69.26	Inactive	Active (0.50)	Inactive	Inactive
Artemether	567 mg/Kg	100	Active (0.92)	Inactive	Inactive	Inactive

explains that their metabolism into more polar metabolites might be difficult. Pinnata with the highest negative log Kp value presented high GI absorption, no inhibition of the cytochrome P450 isoenzymes, thus easily metabolized into a more polar and easily excretable form.

The SwissADME database evaluation of bioavailability score and drug-likness for compounds were

also conducted, the latter uses five rule-based filters (Lipinski rule of five, Ghose, Veber, Egan and Muegge), each of which has a unique set of characteristics that define whether a molecule qualifies as a drug-like compound [32]. The drug-likness and bioavailability score as well as medicinal chemistry properties result for the *K. africana* compounds are displayed on Tables 5 and 6 respectively.

Our result showed that with the exception of 2, 5-pyrroldione which showed 4 violations of rules a drug-like compound must possess according to Veber rule, other compounds obeyed the rule. Two compounds; sitosterol and stigmasterol showed 1 (Lipinski), 3 (Ghose), 1 (Egan) and 2 (Muegge) drug-like violations while 1,4-Benzoquinone 3 (Ghose), 1 (Muegge), avanafil 2 (Ghose) violations, norviburtinal 2 (Ghose) and 1 (Muegge) violations and 3-Hydroxy-4-methoxycinnamic acid 1 (Muegge) violation. All other phytochemicals showed agreement with Ghose (Amgen), Egan (Pharmacia), Veber (GSK), Lipinski (Pfizer) and Muegge rules a drug-like entity must possess. For a drug or compound to be viable as orally, its bioavailability score must be 0.55 (Martin). Interestingly, findings from this study shows that all compounds the met the condition of a viable oral drug except 2-(1-Hydroxyethyl)-2-acetylnaphtho-[2,3-b]-furan-4,9-dione (0.56), 3-Hydroxy-4-methoxycinnamic acid (0.85), caffeic acid (0.56) and lapachol (0.85). The *in silico* methods successfully identified the FDA-approved anti-malarial drug artemether as a potential source of bioactive principles, demonstrating the accuracy of the methods' predictions of bioactive phytochemicals and the consequent savings in time compared to manually screening millions of potential plant compounds for pharmacologically active principles.

The toxicological profile of a compound in drug development is highly importantly due to some effects they may pose on the health of humans. Mutagenicity depicts toxicity relating to changes in the DNA sequence of an organism either spontaneously or inducible and maybe passed on to offspring [37]. A drug candidate that fails a mutagenicity test is likely to cause chromosomal aberrations, frameshift or point mutations. Mutagenicity is closely related to carcinogenicity as some mutagenic agents can also be carcinogenic and genotoxic. Immunotoxicity on the other hand describes compounds that are toxic to organisms. Several pathological diseases can ensue from these various toxicities, these include inflammation, neurological disorders, aging, diabetes, cardiovascular diseases, organ disorders, cancers of different types among others [38]. The ProTox-II is a free web server that can predict the end points toxicities (acute or targeted) of compounds to be used in drug development as binary (active or inactive), the minimum dose that can cause death in 50 % of a population (LD_{50}) as well as the toxicity classes [39]. The *in silico* toxicological evaluation of *Kigelia africana* phytochemicals is shown on Table 7. The result showed that kigelinone with a lethal dosage of 450 mg/kg has tendency to induce immunotoxicity at a prediction probability of 0.79, Carcinogenicity at a prediction probability of 0.52, and Mutagenicity with a prediction probability of 0.70. Of the twenty-five phytochemicals, lapachol, warfarin alcohol, and N-methyl-1-[4-chlorophenyl]-2-[4-piperidyl]-n-propanol shows no tendencies to induce immunotoxicity, carcinogenicity, mutagenicity and general toxicities. 2,5-pyrroldione shows a fatal LD50 dose of 80 mg/kg, a class 3 toxic substance that is largely known to be toxic if swallowed. Similarly, 1,4-Benzoquinone, a class 2 toxic substances show a fatal dose level of 25 mg/kg, at 100 % prediction accuracy, and capable of inducing carcinogenicity at a prediction probability level of 0.72. Compounds of *K. africana* demonstrated reasonably low toxicity across the end point toxicities reported.

4. Conclusion

Natural products have continually shown to be better potential novel drug candidates due to the abundant active compounds contained in them. *K. africana* is indigenous to Africa has been traditionally used against certain diseases such as cancer, digestive disorders, sexual dysfunctions among others. Scientific efforts have attempted to validate some of these acclaimed traditional medicinal uses. Several important compounds have been isolated to include sterols, flavonoids, caffeic acid, naphthoquinones, fatty acids, norviburtinal, courmarins and lots more. The study's conclusions that a higher percentage of the *K. africana* compounds have potential drug-like molecules were corroborated by the profile of the well-known artemether which can be isolated and used in the development of drugs for which the plant has been pharmacologically reported to be used for. However, further clinical studies on the druggability of these compounds are recommended.

Consent for publication

Not Applicable.

Availability of data and material

All data generated or analyzed during this study are included in this article.

Acknowledgements

Not Applicable.

References

[1] Umeta Chali B, Melaku T, Berhanu N, Mengistu B, Milkessa G, Mamo G, Alemu S, Mulugeta T. Traditional medicine practice in the context of COVID-19 pandemic: community claim in jimma zone, oromia, Ethiopia. Infect Drug Resist 2021:3773–83. https://doi.org/10.2147/IDR.S331434.

[2] Pan S-Y, Litscher G, Gao S-H, Zhou S-F, Yu Z-L, Chen H-Q, Zhang S-F, Tang MK, Sun JN, Ko KM. Historical perspective of traditional indigenous medical practices: the current renaissance and conservation of herbal resources. Evidence-based Compl Altern Med 2014. https://doi.org/10.1155/2014/525340. 2014.

[3] Gabriel OA, Olubunmi A. Comprehensive scientific demystification of Kigelia africana: A review. Afr J Pure Appl Chem 2009;3(9):158–64. https://doi.org/10.5897/AJPAC.9000044.

[4] Atolani O, Olatunji GA, Fabiyi OA, Adeniji AJ, andOgbole OO. Phytochemicals from Kigelia pinnata leaves show antioxidant and anticancer potential on human cancer cell line. J Med Food 2013;16(10):878–85. https://doi.org/10.1089/jmf.2012.0249.

[5] Atawodi SEO, Olowoniyi OD. Pharmacological and therapeutic activities of Kigelia africana (Lam.) Benth. Ann Res Rev Biol 2015:1–17. https://doi.org/10.9734/ARRB/2015/8632.

[6] Olawale F, Olofinsan K, Ogunyemi OM, Karigidi KO, Gyebi GA, Ibrahim IM, Iwaloye O. Deciphering the therapeutic role of Kigelia africana fruit in erectile dysfunction through metabolite profiling and molecular modelling. Inform Med Unlocked 2023;37:101190. https://doi.org/10.1016/j.imu.2023.101190.

[7] Saini S, Kaur H, Verma B, Singh S. Kigelia africana (Lam.) Benth.—an overview. 2009. http://nopr.niscpr.res.in/handle/123456789/4043.

[8] Ranjith D, Ravikumar C. SwissADME predictions of pharmacokinetics and drug-likeness properties of small molecules present in Ipomoea mauritiana Jacq. J Pharmacogn Phytochem 2019;8(5):2063–73.

[9] Olaleye MT, Rocha BJ. Acetaminophen-induced liver damage in mice: effects of some medicinal plants on the oxidative defense system. Exp Toxicol Pathol 2008;59(5):319–27. https://doi.org/10.1016/j.etp.2007.10.003.

[10] Weiss CR, Moideen SV, Croft SL, andHoughton PJ. Activity of extracts and isolated naphthoquinones from Kigelia pinnata against Plasmodium falciparum. J Nat Prod 2000;63(9):1306–9. https://doi.org/10.1021/np000029g.

[11] Owolabi OJ, Omogbai EK, Obasuyi O. Antifungal and antibacterial activities of the ethanolic and aqueous extract of Kigelia africana (Bignoniaceae) stem bark. Afr J Biotechnol 2007;6(14). https://doi.org/10.5897/AJB2007.000-2244.

[12] Olubunmi A, Gabriel OA, Stephen AO, Scott FO. Antioxidant and antimicrobial activity of cuticular wax from Kigelia africana. Fabad J Pharm Sci 2009;34(4):187.

[13] Azu OO. The sausage plant (Kigelia africana): Have we finally discovered a male sperm booster. J Med Plants Res 2013;7(15):903–10. https://doi.org/10.5897/JMPR12.0746.

[14] Idowu A, Popoola O, Alani J, Ipadeola A, andNwekoyo V. Toxicity effect of Kigelia africana aqueous extract on the haematology and histopathology of juvenile Nile Tilapia (Oreochromis niloticus). Agro-Science 2020;19(1):37–42. https://doi.org/10.4314/as.v19i1.6.

[15] Hussain T, Fatima I, Rafay M, Shabir S, Akram M, andBano S. Evaluation of antibacterial and antioxidant activity of leaves, fruit and bark of Kigelia africana. Pakistan J Bot 2016;48(1):277–83.

[16] Falode JA, Akinmoladun AC, Olaleye MT. Ameliorative property of Kigelia africana crude and flavonoid leaf extracts on aluminum-induced hepatotoxicity in albino rats. Comp Clin Pathol 2019;28:1495–506. https://doi.org/10.1007/s00580-019-03004-y.

[17] Deore AB, Dhumane JR, Wagh R, Sonawane R. The stages of drug discovery and development process. Asian J Pharmaceut Res Dev 2019;7(6):62–7. https://doi.org/10.22270/ajprd.v7i6.616.

[18] Sliwoski G, Kothiwale S, Meiler J, Lowe EW. Computational methods in drug discovery. Pharmacol Rev 2014;66(1):334–95. https://doi.org/10.1124/pr.112.007336.

[19] Ndombera F, Maiyoh G, Tuei V. Pharmacokinetic, physicochemical and medicinal properties of n-glycoside anti-cancer agent more potent than 2-deoxy-d-glucose in lung cancer cells. 2019. http://41.89.164.27:8080/xmlui/handle/123456789/632.

[20] Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. Nat Biotechnol 2014;32(1):40–51. https://doi.org/10.1038/nbt.2786.

[21] Satpathy R, andAcharya S. Development of a database of RNA helicase inhibitors (VHIMDB) of pathogenic viruses and in silico screening for the potential drug molecules. EuroBiotech J 2022;6(3):116–25. https://doi.org/10.2478/ebtj-2022-0012.

[22] Sachana R, Chauhanb N, Omarc BJ, andAgrawald S. Therapeutic uses of Kigelia pinnata. Int J Med Plants (Photon) 2013;(105):163–73.

[23] Blomme EA, Will Y. Toxicology strategies for drug discovery: present and future. Chem Res Toxicol 2016;29(4):473–504. https://doi.org/10.1021/acs.chemrestox.5b00407.

[24] Lipinski CA, Lombardo F, Dominy BW, andFeeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 1997;23(1–3):3–25. https://doi.org/10.1016/S0169-409X(96)00423-1.

[25] Hughes JD, Blagg J, Price DA, Bailey S, DeCrescenzo GA, Devraj RV, Ellsworth E, Fobian YM, Gibbs ME, Gilles RW. Physiochemical drug properties associated with in vivo toxicological outcomes. Bioorg Med Chem Lett 2008;18(17):4872–5. https://doi.org/10.1016/j.bmcl.2008.07.071.

[26] Chauhan PN, Sharma A, Rasheed H, Mathur H, Sharma P. Treatment Opportunities and Technological Progress Prospective for Acne Vulgaris. Curr Drug Deliv 2022;20(8):1037–48. https://doi.org/10.2174/1567201819666220623154225.

[27] Ottaviani G, Gosling DJ, Patissier C, Rodde S, Zhou L, andFaller B. What is modulating solubility in simulated intestinal fluids? Eur J Pharmaceut Sci 2010;41(3–4):452–7. https://doi.org/10.1016/j.ejps.2010.07.012.

[28] Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 2017;7(1):42717. https://doi.org/10.1038/srep42717.

[29] Lawal M, Olotu FA, Soliman ME. Across the blood-brain barrier: Neurotherapeutic screening and characterization of naringenin as a novel CRMP-2 inhibitor in the treatment of Alzheimer's disease using bioinformatics and computational tools. Comput Biol Med 2018;98:168–77. https://doi.org/10.1016/j.compbiomed.2018.05.012.

[30] Stillhart C, Vučićević K, Augustijns P, Basit AW, Batchelor H, Flanagan TR, Gesquiere I, Greupink R, Keszthelyi D, andKoskinen M. Impact of gastrointestinal physiology on drug absorption in special populations––An UNGAP review. Eur J Pharmaceut Sci 2020;147:105280. https://doi.org/10.1016/j.ejps.2020.105280.

[31] Alagga AA, Gupta V. Drug absorption StatPearls. StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/books/NBK557405/.

[32] Mahmud S, Paul GK, Biswas S, Kazi T, Mahbub S, Mita MA, Afrose S, Islam A, Ahaduzzaman S, Hasan MR. Phytochemdb: a platform for virtual screening and computer-aided drug designing. Database 2022. https://doi.org/10.1093/database/baac002. 2022, baac002.

[33] Belal A. Drug likeness, targets, molecular docking and ADMET studies for some indolizine derivatives. Die

Pharmazie-An Int J Pharmaceut Sci 2018;73(11):635−42. https://doi.org/10.1691/ph.2018.8061.
[34] Lin JH, andYamazaki M. Role of P-glycoprotein in pharmacokinetics: clinical implications. Clin Pharmacokinet 2003;42:59−98. https://doi.org/10.2165/00003088-200342010-00003.
[35] Putra PP, Abdullah SS, Rahmatunisa R, Junaidin J, Ismed F. Structure, activity, and drug-likeness of pure compounds of Sumatran lichen (Stereocaulon halei) for the targeted ACE2 protein in COVID-19 disease. Pharmaciana 2020;10(1):135. https://doi.org/10.12928/pharmaciana.v10i2.16877.
[36] Ghose AK, Viswanadhan VN, Wendoloski JJ. A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. J Combin Chem 1999;1(1):55−68. https://doi.org/10.1021/cc9800071.
[37] Słoczyńska K, Powroźnik B, Pękala E, andWaszkielewicz AM. Antimutagenic compounds and their possible mechanisms of action. J Appl Genet 2014;55:273−85. https://doi.org/10.1007/s13353-014-0198-9.
[38] Bhattacharya S. Consumer attitude towards green marketing in India. IUP J Mark Manag 2011;10(4):62−70.
[39] Tian B, Wu N, Pan X, Yan C, Sharma VK, Qu R. Ferrate (VI) oxidation of bisphenol E−Kinetics, removal performance, and dihydroxylation mechanism. Water Res 2022;210:118025. https://doi.org/10.1016/j.watres.2021.118025.