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RESEARCH ARTICLE

In silico pharmacology and bioavailability of bioactive constituents from *Triclisia subcordata* (Oliv.), an underutilized medicinal plant in Nigeria

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Abstract

Medicinal plants are rich sources of traditional medicines from which many modern medicines are made. *Triclisia subcordata* Oliv. is one among the underutilized medicinal plants in the Southwestern part of Nigeria. Therefore, this study was designed to present comprehensive data from the literature on pharmacological uses of *T. subcordata* and its phytochemistry, and to predict the pharmacology and bioavailability of the phytoconstituents isolated so far from *T. subcordata* through an *in silico* approach. *T. subcordata* has high antioxidant activity and so it isthus used to treat oxidative stress-related diseases such as inflammation and diabetes. It also has antibacterial, antifungal, antimalarial and smooth muscle relaxing properties. It is a potent inhibitor of enzymes such as alpha-amylase and alpha-glucosidase. It has also traditionally been used in cancer treatment. One of the bisbenzylisoquinoline (BBIQ) alkaloids isolated from this plant, cycleanine, showed selectivity for ovarian cancer cell lines. The presence of phytochemicals such as cyanogenic glycosides and tannins in low concentrations in *T. subcordata* has also been reported to make it edible to humans. The results of predicted absorption, distribution, metabolism, excretion and toxicity was analyzed on the webserver 'ADEMTLab 2.0' . Prediction of activity studies for the four bisbenzylisoquinoline alkaloids isolated so far from this plant supported anticancer, antimicrobial, antidiabetic, antiulcer, antimalarial activities as well as muscle relaxant effect. Moreover, new activities including stimulation of leukopoiesis, inhibition of membrane permeability , inhibition of kinase and nicotinic alpha4beta4 receptor agonist properties were also predicted through *in silico* investigation. From our findings, these phytoconstituents could be lead candidates in drug discovery, since this plant is safe for human consumption.

Keywords

Triclisia subcordata, phytochemicals, pharmacology, ADMET, bioavailability

Introduction

Medicinal plants are rich sources of traditional medicines from which many modern medicines are made (1). Medicinal plants have been reported to contain biologically active compounds with therapeutic properties, and

these compounds have been used for the treatment of various diseases in humans over time (2). Plants generate active compounds during secondary metabolism; these compounds are typically responsible for the biological activities exhibited by plants, making them useful in the treatment of specific ailments and infectious diseases (3).

Triclisia subcordata Oliv. which belong to Menispermaceae family, is a doecious plant. Among Yorubas in Nigeria, it is commonly referred to as *Alugbonran*. It is a climber with a caudate leaf apex and base, a hard leaf texture and an alternate stem arrangement. It is found in Nigeria's southwestern region (4). The leaves are simple, reticulate, and alternate, but they can also be lobed or palmately veined (5). It is found primarily in Nigeria, Ghana, the Ivory Coast, Sierra Leone, Senegal and Togo (6). *T. subcordata* is useful in the treatment of inflammatory conditions, hypertension, and abscess. This plant also contains antioxidants which are useful in the development of medications to treat oxidative stress-related diseases in humans such as cancer, diabetes, and inflammation (7,8). Therefore, this study presented comprehensive and up-to-date information on *T. subcordata*'s traditional uses, phytochemical and pharmacological properties, and at the same time predicting the pharmacology and bioavailability of the phytoconstituents isolated so far *silico* approach.

Materials and Methods

Comprehensive information on T. subcordata

An internet search was conducted using various databases including *Google Scholar*, *PubMed*, *Research Gate*, *Science Direct* and various journals to gather information on previously published articles related to this review. This review gathered information from research articles published from 1960 up to 2021. '*Triclisia subcordata*', '*Triclisia*'and '*Triclisia subcordata* Phytochemistry' were used as the keywords for search. The data were organized and *ChemDraw* was used to draw the chemical structures of the compounds. The International Union of Pure and Applied Chemistry (IUPAC) name(s) of the compounds reported in this review was obtained from *PubChem* (https://pubchem.ncbi.nlm.nih.gov).

In silico study

Four alkaloids isolated so far from *T. subcordata* were subjected to several drug-likeness and ADMET filtering analyses. The drug-likeness analysis which includes Ghose, Lipinski, Veber was performed on the *SwissADME* webserver (http://www.swissadme.ch/index.php) (9). The predicted result from *SwissADME* consists of physiochemical properties, drug-likeness, pharmacokinetics, water-solubility, lipophilicity and bioavailability Score (9). The predicted absorption, distribution, metabolism, excretion and toxicity study was analysed on webserver ADEMTLab 2.0 (10). The canonical SMILES of the compounds were retrieved from the name and identifies in the section of *PubChem* Database. The prediction of activity spectra for substance (PASS) is a webserver tool that was developed to examine the general biological potential of a compound based on its structure–activity relationship (11). The pharmacological effect of the compounds is predicted through a comparison of the compounds under investigation with a training set of more than 205,000 compounds, revealing more than 7200 biological activities. The predicted results of PASS analysis are summarized as a list of probable biological activities, with a probability of being inactive (Pi) and a probability of being active (Pa).

Results and discussion

Comprehensive information on T. subcordata

Traditional uses of *T.subcordata*

This plant is used locally as a medicine and tying material. The fruits have been reported to be edible and a decoction of the root is used to treat fever and malaria. It is also used as a treatment for rheumatism, arthritis, anaemia and sleeping sickness. Furthermore, the root pulp or root sap is rubbed into scarification and snake-bite wounds. Coughs and bronchial disorders are treated by combining the leaf or root juice with salt in palm wine and drinking it. A sedative effect of the leaf or root decoction on the heart makes it useful as a wash for palpitations. A decoction of the leaves and twigs is drunk, or leaf pulp is rubbed in, to treat oedema of the legs (12,13). The leaves are used as a nasal or ocular instillation and as a purgative or bathe against epilepsy. A decoction of the stem is drunk as a treatment for stomach aches. The stem bark is powdered and applied topically to syphilitic sores and leprosy. The bark pulp is used as a purgative (http://www.prota.org). It has also been used to treat breast cancer in Nigeria, as well as diarrhea and abdominal cramps in Benin (12,13).

Pharmacological activities of T. subcordata

Antioxidant activity

The antioxidant potential of methanol and dichloromethane extracts of *T. subcordata* was determined by evaluating the radical scavenging assay 2,2-diphenyl-1-picrylhydrazyl (DPPH), nitric oxide scavenging activity (NOS), ferric reducing antioxidant potential (FRAP) and total phenolic content (TPC). The methanol extract was discovered to have greater extraction capacity than dichloromethane extract. The extract quantitative analysis revealed that phenolics (593.7±1.34 mg/100 g) and flavonoids (192.6±2.10 mg/100 g) were more in dichloromethane extract than in methanol extract (8).

Anticancer activity

T. subcordata yielded isochondodendrine and 2'-norcocsuline as minor alkaloids in addition to the abundant cycleanine (14). Isochondodendrine and 2'-norcocsuline both demonstrated potent *in vitro* cytotoxicity in four ovarian cancer cell lines (A2780, Igrov-1, Ovcar-8, and Ovcar-4) with IC_{50} values ranging from 3.5-17 µM and 0.8-2.9 µM, respectively (as determined by the sulforhodamine B dye assay) (Uche *et al.,* 2014). In cell growth assays using normal human ovarian epithelial cells, the IC_{50} values for isochondodendrine and 2'-norcocsuline were 10.5 ± 1.2 µM and 8.0 ± 0.2 µM, respectively. These alkaloids

were more effective against cancer cells than against normal cells. The induction of apoptosis by these alkaloids was investigated using caspase activity assays, western blots, and flow cytometry. They activated caspases 3/7, cleaved PARP, increased the subG1 cell cycle phase, and increased both early and late apoptotic cells in ovarian cancer cells. Therefore, isochondodendrine and 2'-norcocsuline are among the least abundant in *T. subcordata*, contributing to its cytotoxic activity and serving as potential hit compounds for future development in the treatment of ovarian cancer (15).

Antimicrobial activity

Extracts of *Triclisia subcordata* Oliv. roots and *Heinsia crinita* (Wennberg) G.Taylor whole plant were used as components of various herbal portions in ethnomedicine in Southwestern Nigeria to treat acute urinogenital infections and infertility. Maceration was used to obtain methanol and hexane extracts of each plant, which were then tested for antimicrobial activity using agar diffusion and micro broth dilution techniques. The extracts were tested against strains of *Staphylococcus aureus*, *E. coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and fungi, including four *Candida* species. The study found that extracts of *H. crinite* and *T. subcordata* had strong antibacterial activity against typed and clinical isolates from Sexually Transmitted Diseases (STD) and meningitis patients. antifungal activity was observed, particularly against *Candida* species which are implicated in candidiasis and vaginal thrush. On the test microorganisms, the methanol extract was more effective than the hexane extract. The research supported the ethnopharmacological applications of these medicinal plants in the treatment of microbial infections (16).

Anti-diabetic activity

Its ethanol and dichloromethane extracts were tested for inhibition of α-glucosidase and α-amylase activities. The plant extract and fractions were found to have mild *in vitro* α-glucosidase and α-amylase inhibitory activities. Therefore, this plant could be used to treat and manage diabetes (8).

Anti-ulcer Activity

In vivo studies were conducted on the anti-ulcer activities of a methanolic extract of its leaves. The plant material extract caused acute toxic effects in rats at doses ranging from 100 to 1600 mg of extract per kg of body weight, but it reduced total acid content, gastric free-HCI and the number of gastric ulcers caused by histamine administration. Cimetidine (100 mg/kg body weight) was less effective than extract at 600 mg/kg body weight in reducing gastric-HCI. Histopathological studies on the stomach revealed that the extract protected tissue from ulcer formation. In rats, the extract also delayed gastric emptying (17).

Muscles relaxant effect

The methanolic leaf extract of *T. subcordata* produced relaxant effects in the rabbit jejunum and rat fundus (stomach), but contractile effects in the rat uterus after macerating dried and pulverized leaves in 50% methanol for 48 hours. A plot of the percent relaxation of the tissue against the log concentration of the extract yielded the effective concentration (EC_{50} = 0.07 mg/mL) of the extract in the rat jejunum. The extract had no observable effects on the guinea pig ileum. Histamine inhibited the effects of the extract on the jejunum, rat fundus, and uterus. The extract's effects appeared to be mediated by H2-receptor-blocking activity (18).

Anti-malaria activity

The anti-plasmodial activity of three alkaloids isolated from *T. subcordata*, cycleanine, isochondodendrine, and 2'-norcocsuline, was investigated in vitro. An SYBR Green 1 fluorescence assay was used to determine the anti-proliferative effects of a chloroquine-resistant *Plasmodium falciparum* strain. These alkaloids demonstrated anti-plasmodial activity *in vitro*, with IC_{50} values in the low micromolar range. Cycleanine suppressed parasitaemia and increased mean survival times in infected mice at oral doses of 25 and 50 mg/kg body weight compared to the control groups. Metabolites and metabolic pathways of cycleanine were also investigated with high-performance liquid chromatography electrospray ionization tandem mass spectrometry. After the intragastric administration of cycleanine, 12 new metabolites were discovered in rats. Cycleanine's metabolic pathways have been shown to include hydroxylation, dehydrogenation, and demethylation (19).

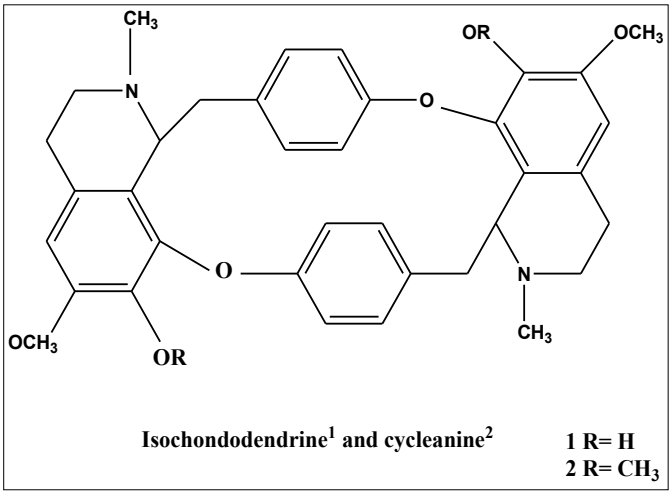
Toxicity of T. subcordata

Natural products contain pharmacologically active compounds that, when consumed in high doses or under certain conditions, can be harmful to human health. As a result, just because medicinal plants are natural does not mean they are not toxic (20). Saponins have been reported to cause haemolysis of red blood cells when injected into the bloodstream (21,22). The presence of secondary metabolites such as cyanogenic glycosides, tannins, and phenols in low concentrations in the plant's leaf extract suggests that the plant may be non-poisonous (23). However, there is currently no available scientific report to support this for *T. subcordata*. Furthermore, the low lipid concentration in *T. subcordata* makes it suitable for people following a low-fat diet (23).

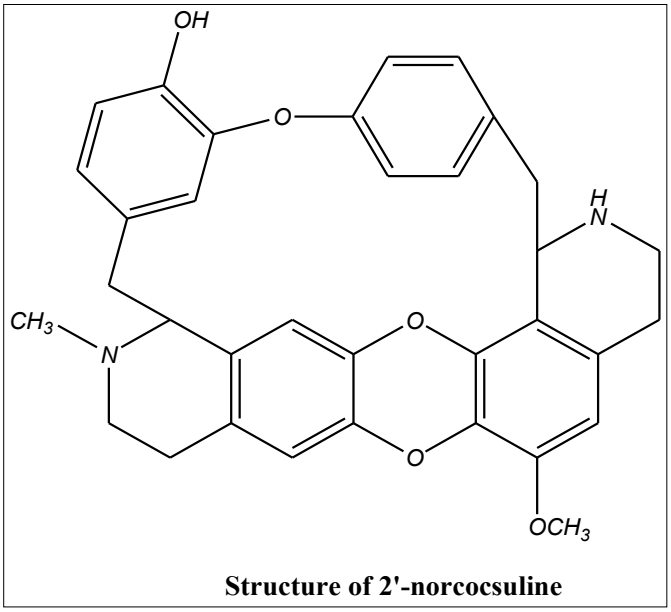
Phytochemistry of T. subcordata

The most common phytochemicals found in medicinal plants are essential oils, alkaloids, flavonoids, terpenoids, carotenoids, saponins, and phytosterols (24,25). These phytochemicals can be obtained from barks, leaves, flowers, roots, fruits, and seeds among other sources (26). The presence of alkaloids was found in large quantities in the root extract of *T. subcordata*, as were tannins and saponins, but in small amounts (16). Okpara *et al*. (23) discovered saponin and flavonoids in high concentrations in *Triclisia* leaf extract, while alkaloids were only moderately present. Phenols, tannins, and cyanogenic glycosides were also present, but only in trace amounts, from the quantitative analysis. Saponins, flavonoids, alkaloids, phenol, tannins, and cyanogenic glycoside were discovered in *T. subcordata* phytochemical screening, which may be responsible for its medicinal uses (23). Akinwumi *et al*. (8) also dis-

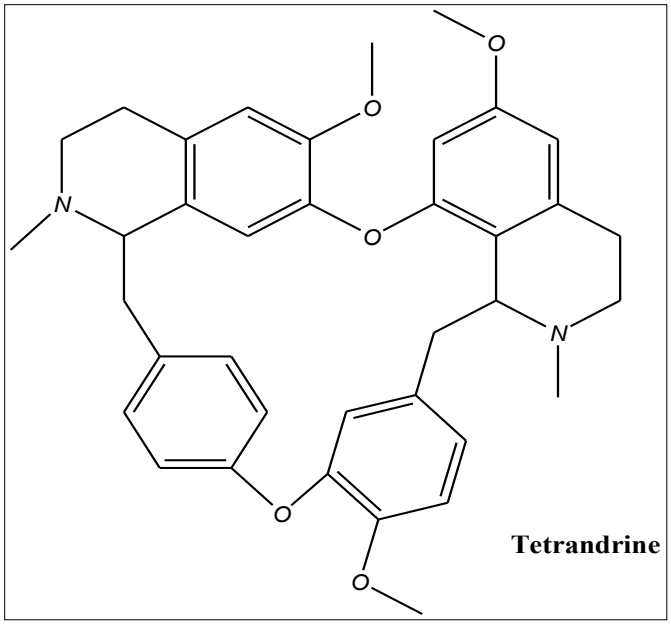
covered saponin, tannin, steroid, flavonoid, phenolic, and alkaloid compounds in the plant's methanol and dichloromethane extracts. According to Okpara *et al*. (23), its leaves contain a higher percentage of flavonoids and saponins than tannins and phenolics. Abo *et al*. (16) reported the presence of tannin, saponin, and alkaloids in a methanol extract of Triclisia root. The methanol extract of the leaf sample contains more phytochemicals than the dichloromethane extract, with saponin being the most abundant and alkaloid being the least abundant (8). The presence of secondary metabolites such as anthraquinones, saponin, tannins, alkaloids, and phenolic compounds was revealed by phytochemical analysis of the powdered leaf sample and extract. Its leaf contains pharmacologically significant flavonoids, saponins, and alkaloids (23). The results of Sonibare and Adebodun's (4) phytochemical screening tests on the powdered sample and crude extract of T. subcordata leaves revealed the presence of saponins, tannins, and alkaloids, but no flavonoids. Four bisbenzylisoquinoline (BBIQ) alkaloids have been isolated from T. subcordata so far. Uche *et al*. (14,15,19) isolated isochondodendrine, cycleanine, tetrandrine, and 2'-norcocsuline from *T. subcordata*. The IUPAC names of isochondrodendrine, cycleanine, 2'-norcocsuline, and tetrandine, the four alkaloids isolated so far from this plant (Figure 1), are presented in Table 1.



Isochondodendrine[1] and cycleanine[2] 1 R= H 2 R= CH_3



Structure of 2'-norcocsuline



Tetrandrine

Fig. 1. Compounds isolated from *T. subcordata* so far

In silico study

In silico drug-likeness and ADMET properties of compounds isolated from *T. subcordata*

One of the major problems that are encountered in the process of drug design and development is the possible toxicity that is associated with potential drug candidates, this informed the need for toxicological and drug ability assessment of compounds using the more rapid, simple, and economic feasible computational technique (27). The four compounds (iso-chondrodendrine, cycleanine, 2'-norcocsuline, and tetrandine) that have been isolated so far from *T. subcordata* were subjected to the predictive drug-likeness and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) filtering analyses. The results of the predictive filtering analysis for compounds are presented in Table 2, while Figure 2 presented the radar plot of *in silico* physicochemical of compounds isolated from *T. subcordata:* (a) Isochondrodendrine (b) Cycleanine (c) 2'-Norcocsuline (d) Tetrandine.

The physiochemical analysis for the compounds reveals that all four compounds (iso-chondrodendrine, cycleanine, 2'-norcocsuline, and tetrandine) fulfilled the requirement for the physicochemical analysis using the Lipinski Egan and Veber filters, thereby suggesting favourable physicochemical/drugable properties (28,29,30,31). Although two of the compounds 2'-norcocsuline and tetrandine did not pass the Pfizer Rule that state that a medically active drug with Content: logP > 3; TPSA < 75 is likely to be toxic (32). All the compounds had a good bioavailability score of 0.55 according to Abbot Bioavailability score (33). Satisfactory Lipinski, Egan, and Veber properties indicate good absorption or permeation and good oral bioavailability respectively (34). All four compounds demonstrated a positive and high probability of human intestinal absorption and substrate of the permeability-glycoprotein (P-gp) (35). The compounds are suggested to be less absorbed into the bloodstream due to the capability of P-gp to pump them back into the intestinal lumen, bile ducts, urine-conducting ducts, and capillaries respec-

Table 1. Pharmacological uses of alkaloids isolated from *T. subcordata* so far

Common name	IUPAC name¶	Pharmacological activities	References
Isochondodendrine	(11*R*,26*R*)-5,20-dimethoxy-10,25-dimethyl-2,17-dioxa-10,25-diazaheptacyclo[26.2.2.2^{13,16}.1^{3,7}.1^{18,22}.0^{11,36}.0^{26,33}] hexatriaconta-1(31),3(36),4,6,13,15,18(33),19,21,28 (32),29,34-dodecaene-4,19-diol	Cytotoxicity and apoptosis in ovarian cancer cell lines (A2780, IGROV-1, OVCAR-8, and OVCAR-4); anti-plasmodial activities; Treatment of dysmenorrhea; Antimicrobial activity	(22,40, 41, 42)
2'-norcocsuline	Nil	Cytotoxicity and apoptosis in ovarian cancer cell lines (A2780, IGROV-1, OVCAR-8, and OVCAR-4); Anti-plasmodial activities	(22, 42)
Tetrandrine	(1*S*,14*S*)-9,20,21,25-tetramethoxy-15,30-dimethyl-7,23-dioxa-15,30-diazaheptacyclo [22.6.2.2^{3,6}.1^{8,12}.1^{14,18}.0^{27,31}.0^{22,33}]hexatriaconta-3(36),4,6 (35),8,10,12(34),18,20,22(33),24,26,31-dodecaene	Calcium channel blocker, effective against silicosis, hypertension, inflammation and lung cancer without any toxicity, Anti-microbial activity; Anti-cancer activity.	(43,44)
Cycleanine	(11*R*,26*R*)-4,5,19,20-tetramethoxy-10,25-dimethyl-2,17-dioxa-10,25-diazaheptacyclo [26.2.2.2^{13,16}.1^{3,7}.1^{18,22}.0^{11,36}.0^{26,33}]hexatriaconta-1(31),3 (36),4,6,13,15,18(33),19,21,28(32),29,34-dodecaene	Anti-plasmodial activity; Uterotonic effect; Anti-convulsant; Anti-cancer activity.	(42, 45,46,47)

Obtained using PubChem (https://pubchem.ncbi.nlm.nih.gov)

tively (36). The *in silico* blood-brain barrier (BBB) test predicts the blood-brain barrier penetration of the molecule. Many parasites including viruses have been reported to infect the brain, thus indicating its ability to cross the blood-brain barrier (BBB) (37). The four phytochemicals displayed properties that suggest their ability to cross the BBB, hence their potential to function as therapeutics for brain cells or clearance of infection in the brain. The Clear-

Table 2. *In silico* physicochemical and ADMET properties of compounds isolated from *T. subcordata*

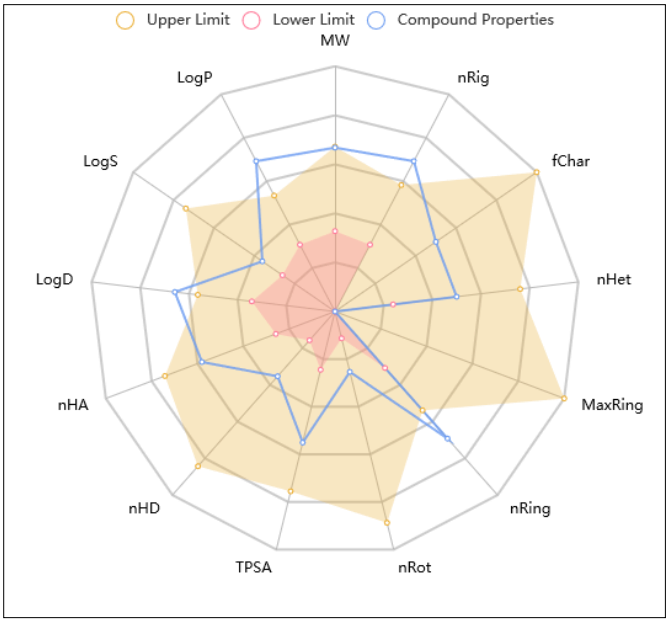
Descriptors	Isochondro-dendrine	Cycleanine	2'-Norcocsuline	Tetrandine	Comment
a) Physicochemical properties					
Molecular weight (g/mol)	594.700	622.3	548.230	622.750	
Num. heavy atoms	44.000	46.000	41.000	46.000	
Num. arom. Heavy atoms	24.000	24.000	21.000	24.000	
Num. Rings	10.000			8.000	
Num. rotatable bonds	2.000	4.000	1.000	4.000	
Num. H-bond acceptors	8.000	8.000	7.000	8.000	
Flexibility	0.048			0.095	
Hydrogen bond donor	2.000	0.000	2.000	0.000	
LogP	5.099	5.120	4.500	4.870	
Molar Refractivity	177.140	186.070	163.790	186.070	
TPSA (Å^2)	83.860	61.86	72.420	61.860	
Drug-likeness					
Lipinski	Yes	Yes	Yes	Yes	
Pfizer Rule	Yes	Yes	No	No	
Egan	Yes	Yes	Yes	Yes	
Veber	Yes	Yes	Yes	Yes	
Bioavailability Score	0.550	0.550	0.550	0.550	
(b) ADMET					
Absorption (Probability)					
HIA	0.010 (Yes)	0.009 (Yes)	0.070 (Yes)	0.007 (Yes)	
Caco-2 Permeability Cm/s	-5.245 (No)	-5.146 (Yes)	-5.735 (No)	-5.618 (No)	Optimal > -5.15
P-glycoprotein Substrate	0.057 (Yes)	0.676 (Yes)	0.060 (Yes)	0.192 (Yes)	Category 1: substrate; Category 0: Non-inibitor
P-glycoprotein Inhibitor	0.999 (No)	1.000 (No)	0.998 (No)	1.000 (No)	Category 1: inhibitor; Category 0: Non-inibitor
Distribution (Probability)					
Blood-Brain Barrier	0.162 (Yes)	0.284 (Yes)	0.049 (Yes)	0.287 (Yes)	Category 1: BBB+; Category 0: BBB-;
PPB %	87.820 (Yes)	66.19 (Yes)	83.48 (Yes)	71.77 (Yes)	Optimal: < 90%.
VD L/kg	0.819 (Yes)	0.848 (Yes)	0.699 (Yes)	0.926 (Yes)	Optimal: 0.04-20L/kg

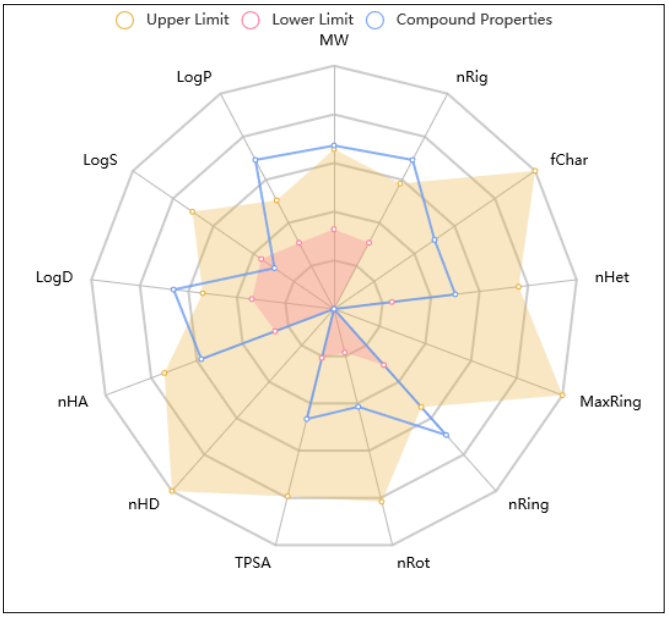
Metabolism (Probability)					
CYP450 1A2 Inhibitor	0.056	0.035	0.101	0.041	Category 1: Inhibitor/substrate; Category 0: Non-inhibitor/ substrate
CYP450 1A2 Substrate	0.966	0.971	0.886	0.971	
CYP450 3A4 Inhibitor	0.037	0.094	0.039	0.101	
CYP450 3A4 Substrate	0.948	0.961	0.943	0.962	
CYP4502C9 Inhibitor	0.049	0.044	0.040	0.024	
CYP450 2C9 Substrate	0.413	0.603	0.432	0.602	
CYP4502C19 Inhibitor	0.059	0.069	0.143	0.062	
CYP450 2C19 Substrate	0.962	0.983	0.903	0.981	
CYP4502D6 Inhibitor	0.026	0.012	0.022	0.010	
CYP450 2D6 Substrate	0.941	0.952	0.944	0.964	
Elimination					
$T_{1/2}$ (Half Life Time)	0.416	0.143	0.141	0.180	long half-life: >3h; short half-life: <3h
CL (Clearance Rate) mL/min/kg	7.227 (Yes)	7.668 (Yes)	5.643 (Yes)	9.019 (Yes)	High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low:
Toxicity					
hERG Blockers	0.958 (No)	0.986 (No)	0.965 (No)	0.987 (No)	Category 1: active; Category 0: inactive
H-HT	0.030 (Yes)	0.030 (Yes)	0.010 (Yes)	0.029 (Yes)	Category 1: H-HT positive (+); Category 0: H-HT negative (-);
AMES Toxicity	0.119 (Yes)	0.019 (Yes)	0.153 (Yes)	0.084 (Yes)	Category 1: AMES positive (+); Category 0: AMES negative (-);
Rat Oral Acute Toxicity	0.146 (Yes)	0.241 (Yes)	0.227 (Yes)	0.216 (Yes)	Category 0: low-toxicity; Category 1: high-toxicity;
Respiratory Toxicity	0.220 (Yes)	0.527 (Yes)	0.414 (Yes)	0.511 (Yes)	Category 1: respiratory toxicants; Category 0: respiratory non-
Carcinogenicity	0.003 (Yes)	0.028 (Yes)	0.045 (Yes)	0.031 (Yes)	Category 1: carcinogens; Category 0: non-carcinogens;
SkinSen	0.848 (No)	0.22 (Yes)	0.925 (No)	0.532 (No)	Category 1: Sensitizer; Category 0: Non-sensitizer;
DILI	0.052 (Yes)	0.105 (Yes)	0.163 (Yes)	0.538 (Yes)	Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI
Other Pharmacokinetics					
GI absorption	High	High	High	High	High

[a]**ADMET**: Absorption, distribution, metabolism, elimination, and toxicity; **GI**: Gastro-intestinal; **BBB**: Blood Brain Barrier; **P-gp**: permeability glycoprotein; **CYP**: cytochrome P450; **hERG**: human Ether-à-go-go-Related Gene; **HIA**: Human Intestinal Absorption; **H-HT**: Human Hepatotoxicity **AMES**: Ames Mutagenicity; **DILI**: Drug Induced Liver Injury; **VD**: Volume Distribution; **PPB**: Plasma Protein Binding.

ance rate is a vital pharmacokinetic parameter that describes, alongside the half-life and the volume of distribution, and hence gives information about the frequency of dosing of a drug. The estimated half-life time (less than 2 hours) and clearance rate fall within the moderate range (35).

Among the numerous *in silico* toxicity descriptors, *h*ERG channel performs an important function in the re-





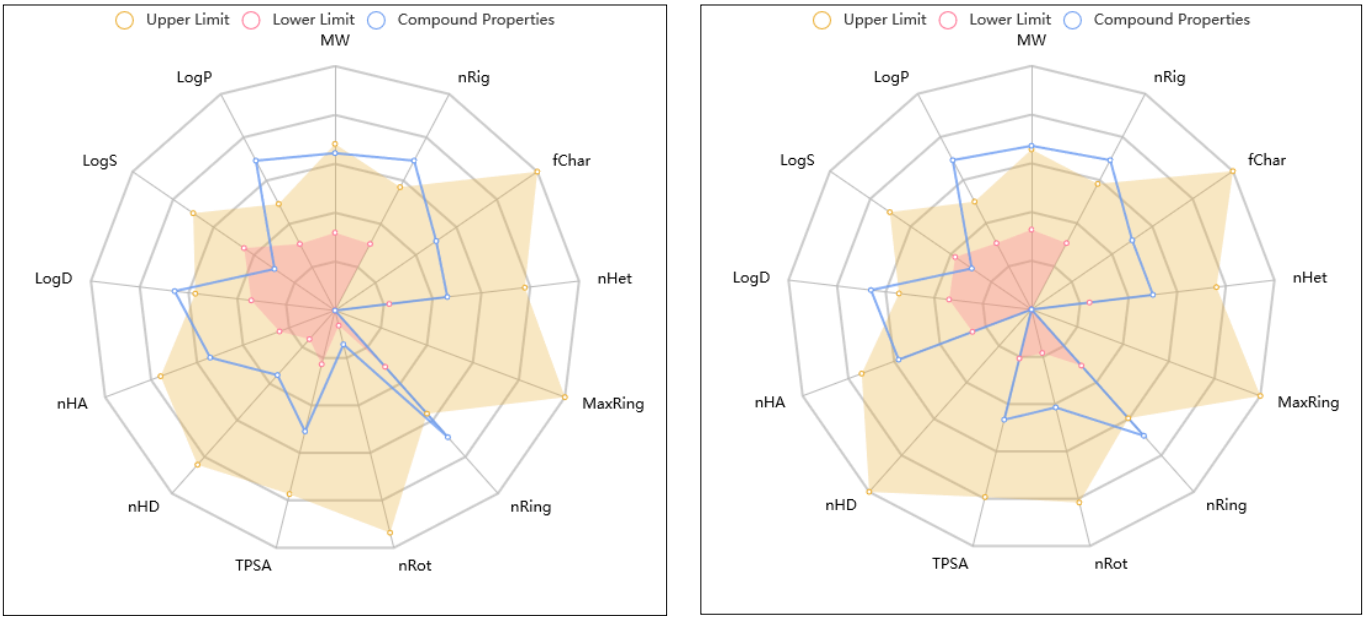


Fig. 2. The radar plot of *in silico* physicochemical of compounds isolated from *T. subcordata:* (**a**) Isochondrodendrine (**b**) Cycleanine (**c**) 2'-Norcocsuline (**d**) Tetrandine. The radar plot demonstrate the physicochemical properties of each compound (in *blue*) and the reference optimal scope (in *red* and *yellow*). The optimal range is provided by ADMET lab 2.0 (35)

polarization and termination stages of action potential in cardiac cells (38), compounds that block the hERG channel have the potential to cause cardiotoxicity (39). All the four compounds did not exhibit the potential of being hERG channel blockers, suggesting that they may not cause *h*ERG channel-related cardiotoxicity. The four compounds did not exhibit mutagenicity or any toxicity based on the predicted rat acute toxicity *in silico*, hence may not cause genetic mutations (35).

The effects of the phytoconstituents on phase I drug metabolism in the liver were also evaluated using several cytochrome P_{450} descriptors. The phytoconstituents demonstrated less inhibitory potential for the various cytochrome P_{450}, and thus may not adversely affect phase I drug metabolism in the liver to a large extent. The four compounds demonstrated a high probability of absorption, subcellular distribution, and low toxicity. The ADME/tox analysis indicated high aqueous solubility, ability to pass the high human intestinal absorption, and low acute oral toxicity with a good bioavailability score.

Bioactivity

The pharmacological activities, mechanisms of action, and computed probabilities for activity surpassing the probability of inactivity (Pa > Pi) were reported in Tables 3, 4, 5, and 6. The Pi and Pa values vary in the range of 0.000–1.000, and, mostly, the addition of Pa and Pi doesn't give one. For a compound, the likelihood of achieving a particular experimental activity is high when Pa > 0.7. A compound is unlikely to demonstrate a particular experimental activity when Pa < 0.5, Tables 3, 4, 5, and 6 show the predicted experimental activity with a Pa ≥ 0.7.

Table 3. Bioactivity prediction report for isochondrodendrine

Pa	Pi	Activity
0.908	0.005	5 Hydroxytryptamine release stimulant
0.904	0.001	Histamine release stimulant
0.889	0001	Oxygen scavenger
0.802	0.003	MAP kinase stimulant
0.774	0.005	Spasmolytic
0.767	0.005	Vasodilator, peripheral
0.759	0.004	Leukopoiesis stimulant
0.749	0.004	Skeletal muscle relaxant
0.755	0.019	Membrane permeability inhibitor
0.736	0.004	Muscle relaxant
0.715	0.003	Neurotransmitter antagonist
0.725	0.016	Nicotinic alpha4beta4 receptor agonist
0.716	0.011	Kinase inhibitor
0.720	0.018	HIF1A expression inhibitor
0.710	0.038	Antineurotic

Table 4. Bioactivity prediction report for cycleanine

Pa	Pi	Activity
0.914	0.001	Histamine release stimulant
0.909	0.005	5 Hydroxytryptamine release stimulant
0.899	0.001	Oxygen scavenger
0.857	0.004	Spasmolytic
0.811	0.015	Nootropic
0.787	0.019	Antineurotic
0.759	0.004	Leukopoiesis stimulant
0.749	0.004	Skeletal muscle relaxant
0.730	0.003	Fibrinogen receptor antagonist
0.728	0.004	Muscle relaxant
0.715	0.009	Antisecretoric
0.706	0.005	MAP kinase stimulant
0.708	0.009	Vasodilator, peripheral
0.706	0.014	Apoptosis agonist
0.708	0.018	Nicotinic alpha4beta4 receptor agonist

Table 5. Bioactivity prediction report for 2'-Norcocsuline

Pa	Pi	Activity
0.942	0.003	Spasmolytic
0.901	0.001	Histamine release stimulant
0.898	0.003	Muscle relaxant
0.843	0.002	Leukopoiesis stimulant
0.836	0.002	Oxygen scavenger
0.796	0.007	Nicotinic alpha4beta4 receptor agonist
0.791	0.003	Skeletal muscle relaxant
0.713	0.004	Antitussive

Table 6. Bioactivity prediction report for tetrandrine

Pa	Pi	Activity
0.925	0.001	Oxygen scavenger
0.881	0.004	Spasmolytic
0.862	0.008	5 Hydroxytryptamine release stimulant
0.828	0.003	Leukopoiesis stimulant
0.805	0.003	Skeletal muscle relaxant
0.789	0.003	Muscle relaxant
0.762	0.002	Fibrinogen receptor antagonist
0.769	0.010	Apoptosis agonist
0.758	0.005	Vasodilator, peripheral
0.762	0.025	Nootropic
0.761	0.024	Antineurotic
0.719	0.005	MAP kinase stimulant

Conclusion

This review of *Triclisia subcordata* phytochemical analysis, biological activities and toxicology has highlighted the important therapeutic potentials of *T. subcordata* in the treatment of various diseases and ailments affecting mankind. The plant has been shown to have antimicrobial, anticancer, antiulcer and antioxidant properties. The presence of some important phytochemicals in this plant extract has been linked to these biological activities. The results of predicted absorption, distribution, metabolism, excretion, and toxicity as well as prediction of activity studies for the four bisbenzylisoquinoline (BBIQ) alkaloids isolated so far supported all the activities reported for this plant, moreover, new activities including leukopoiesis stimulant, membrane permeability inhibitor, nicotinic alpha-4 beta-4 receptor agonist and kinase inhibitor were also predicted. These data presented these phytoconstituents as lead candidates in drug discovery since this plant is safe for human consumption.

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Authors contributions

ADO and GAG conceived the study and participated in its design and coordination. ADO, TRO, GAG, BAO, and OAO drafted and revised the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interests to declare.

Ethical issues: None.

References

1. Dar RA, Shahnawaz M, Rasool S, Qazi PH. Natural product medicines: A literature update. J phytopharmacol. 2017;6(6):349-51. www.phytopharmajournal.com/Vol6_Issue6_06.pdf
2. Aye MM, Aung HT, Sein MM, Armijos C. A review on the phytochemistry, medicinal properties and pharmacological activities of 15 selected Myanmar medicinal plants. Molecules. 2019;24 (2):293. https://doi.org/10.3390/molecules24020293
3. Singh B, Sharma RA. Secondary metabolites of medicinal plants, 4 Volume set: ethnopharmacological properties, biological activity and production strategies. John Wiley & Sons; 2020
4. Sonibare MA, Adebodun SA. Macroscopic and microscopic evaluation of *Triclisia subcordata* Oliv.(Menispermaceae) towards its standardization. Nig. J. Pharm. Res. 2018;14 (2):189-96.
5. Ajugwo AO, Ezimah AC, Awah FM, Mounbegna PE, Azikiwe CC. Phytochemical and antimicrobial properties of the aqueous root extract of Triclisia dictyophylla. Asian J. Med. Sci. 2013;4 (1):15-20. https://www.nepjol.info/index.php/AJMS/article/view/7846
6. Trease G, Evans WC. Pharmacognosy. 11th edn. Brailliar Tiridel. Can. Macmillian.publishers; 1989.
7. Tiam ER, Ngono Bikobo DS, Abouem A, Zintchem A, Mbabi Nyemeck N, Moni Ndedi ED *et al*. Secondary metabolites from *Triclisia gilletii* (De Wild) Staner (Menispermaceae) with antimycobacterial activity against Mycobacterium tuberculosis. Nat. Prod. Res. 2019;33(5):642-50. https://doi.org/10.1080/14786419.2017.1402324
8. Akinwunmi OA, Adekeye DK, Olagboye SA. Phytochemical quantification, in vitro antioxidant and antidiabetic potentials of methanol and dichloromethane extracts of *Triclisia subcordata* (Oliv) leaves. TPR. 2020;4(1):17-24.
9. 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):1-13. https://doi.org/10.1038/srep42717
10. Yang H, Lou C, Sun L, Li J, Cai Y, Wang Z *et al*. admetSAR 2.0: web-service for prediction and optimization of chemical ADMET properties. Bioinformatics; 2018;35(6):1067-1069. https://doi.org/10.1093/bioinformatics/bty707
11. Lagunin, A., Stepanchikova, A., Filimonov, D., & Poroikov, V. PASS: prediction of activity spectra for biologically active substances. Bioinformatics. 2000;16(8);747-748. https://doi.org/10.1093/bioinformatics/16.8.747
12. Gbadamosi IT, Erinoso SM. A review of twenty ethnobotanicals used in the management of breast cancer in Abeokuta, Ogun State, Nigeria. Afr. J. Pharm. Pharmacol. 2016;10(27):546-64. https://doi.org/10.5897/AJPP2015.4327
13. Ayena AC, Chegnimonhan V, Guidi TC, Adoukonou-Sagbadja H, Karou S, Mensah GA *et al*. Biodiversity of plants used in the treatment of gastroenteritis in southern Benin. Астраханский медицинский журнал. 2016;11(3):145-54.
14. Uche FI, Abed M, Abdullah MI, Drijfhout FP, McCullagh J, Claridge TW *et al*. O9 Isolation, identification and anti-cancer

activity of minor alkaloids from *Triclisia subcordata* Oliv. Biochem. Pharmacol. 2017;139:112.

15. Uche FI, Drijfhout FP, McCullagh J, Richardson A, Li WW. Cytotoxicity effects and apoptosis induction by bisbenzylisoquinoline alkaloids from *Triclisia subcordata*. Phytother Res. 2016; 30 (9):1533-9.
16. Abo KA, Lawal IO, Ogunkanmi A. Evaluation of extracts of Triclisia suboardata Oliv and Heinsia crinita (Afz) G. Taylor for antimicrobial activity against some clinical bacterial isolates and fungi. *Afr. J. Pharm. Pharmacol.* 2011;5(2):125-31.
17. Asuzu IU, Anaga AO. The antiulcer effect of the methanolic extract of Triclisia subcordata leaves in rats. J. Herbs Spices Med. Plants. 1996;3(3):45-53.
18. Asuzu IU, Okoro UO, Anaga AO. The effects of the methanolic leaf extract of *Triclisia subcordata* Oliv. on smooth muscles. J. Herbs Spices Med. Plants. 1995;2(4):11-8.
19. Uche FI, Drijfhout F, McCullagh J, Richardson A, Li WW. In vivo efficacy and metabolism of the antimalarial cycleanine and improved in vitro antiplasmodial activity of novel semisynthetic analogues. *Antimicrob Agents Chemother.* 2021;65(2-3):1-16
20. Ali R, Rooman M, Mussarat S, Norin S, Ali S, Adnan M, Khan SN. A systematic review on comparative analysis, toxicology, and pharmacology of medicinal plants against Haemonchus contortus. Front. Pharmacol. 2021; 2:644027..
21. Abiodun HA, Oluwatobi SA, Joseph AO, Oyetomiwa OF, Kenechukwu BO. Toxicological evaluation of extract of *Olax subsorpioidea* on albino Wistar rats. *Afr. J. Pharm. Pharmacol.* 2014; 8(21):570-8.
22. Agomuo E, Amadi P, Ogunka-Nnoka C, Amadi B, Ifeanacho M, Njoku U. Characterization of oils from *Duranta repens* leaf and seed. OCL. 2017;24(6):A601.
23. Okpara FN, Nwaichi EO, Akaninwor JO. Proximate Analysis and Phytochemical Screening of *Triclisia subcordata* Oliv Leaf. Int. J. Biochem. Res. 2021;30(8): 1-9.
24. Chanda N, Shukla R, Zambre A, Mekapothula S, Kulkarni RR, Katti K, Bhattacharyya K, Fent GM, Casteel SW, Boote EJ, Viator JA. An effective strategy for the synthesis of biocompatible gold nanoparticles using cinnamon phytochemicals for phantom CT imaging and photoacoustic detection of cancerous cells. Pharm. Res. 2011;28(2):279-91.
25. Bhattacharya A, Tiwari P, Sahu PK, Kumar S. A review of the phytochemical and pharmacological characteristics of *Moringa oleifera*. J. Pharm. Bioallied. Sci. 2018;10(4):181.
26. Yadav RN, Agarwala M. Phytochemical analysis of some medicinal plants. J. Phytol. 2011;3(12): 10-14.
27. Raies AB., Bajic VB. In silico toxicology: computational methods for the prediction of chemical toxicity. Wiley Interdiscip. Rev. Comput. Mol. Sci. 2016;6(2):147-172.
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: 42717.
29. Egan WJ, Merz KM, Baldwin JJ. Prediction of drug absorption using multivariate statistics. J. Med. Chem. 2000; 43(21):3867-3877.
30. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J. Pharmacol. Toxicol. Methods. 2000;44(1):235-249. https://doi.org/10.1016/s1056-8719(00)00107-6
31. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. J. Med. Chem. 2002 45(12):2615-2623.
32. 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):4872-4875.
33. Martin YC. A bioavailability score. J. Med. Chem. 2005;48(9):3164-3170.
34. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. J. Med. Chem. 2002;45(12):2615-2623.
35. Xiong G, Wu Z, Yi J, Fu L, Yang Z, Hsieh C *et al*. ADMETlab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties. Nucleic Acids Res. 2021;49 (W1), W5-W14.
36. Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics. Clin. Pharmacokinet. 2003; 42(1), 59-98.
37. Zanin L, Saraceno G, Panciani PP, Renisi G, Signorini L, Migliorati K, Fontanella MM. SARS-CoV-2 can induce brain and spine demyelinating lesions. Acta Neurochir. 2020;162(7):1491-4.
38. Raschi E, Vasina V, Poluzzi E, De Ponti F. The hERG K+ channel: target and antitarget strategies in drug development. Pharmacol. Res. 2008; 57(3):181-195.
39. Kratz JM, Grienke U, Scheel O, Mann SA, Rollinger JM. Natural products modulating the hERG channel: heartaches and hope. Nat. Prod. Rep. 2017;34(8), 957-980.
40. Am B. D-isochondodendrine in the treatment of dysmenorrhea. Bulletin de la Federation des Societes de Gynecologie et Dobstetrique de Langue Francaise. 1951;3(1):63-4.
41. Otshudi AL, Apers S, Pieters L, Claeys M, Pannecouque C, De Clercq E, Van Zeebroeck A, Lauwers S, Frederich M, Foriers A. Biologically active bisbenzylisoquinoline alkaloids from the root bark of *Epinetrum villosum*. J. Ethnopharmacol. 2005;102(1):89-94.
42. Uche FI, Guo X, Okokon J, Ullah I, Horrocks P, Boateng, J *et al*. In vivo efficacy and metabolism of the antimalarial cycleanine and improved in vitro antiplasmodial activity of novel semisynthetic analogues. Antimicrob. Agents Chemother. 2021; 65(2):e01995-20
43. Bhagya N, Chandrashekar KR. Tetrandrine–A molecule of wide bioactivity. Phytochemistry. 2016;125:5-13.
44. Bhagya NC, Chandrashekar KR. Tetrandrine and cancer–An overview on the molecular approach. Biomed. Pharmacother. 2018;97:624-32.
45. Wambebe C, Gamaniel K, Akah PA, Kapu SD, Samson A, Orisadipe AT *et al*. Central and uterotonic effects of cycleanine. Indian J. Pharmacol. 1997;29(5):366.
46. Sonavane GS, Palekar RC, Kasture VS, Kasture SB. Anticonvulsant and behavioural actions of Myristica fragrans seeds. Indian J. Pharmacol. 2002;34(5):332.
47. Li W. Cytotoxicity effects and apoptosis induction by cycleanine and tetrandrine. Planta Med.: Natural Products and Medicinal Plant Research. 2016;30(9):1533-9