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Therapeutic, Physicochemical, and Pharmaceutical Properties of the Active Compounds Found in Tribulus Terrestris

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ABSTRACT

Introduction: Tribulus terrestris (TT) is rich in bioactive compounds, such as saponins, flavonoids, and alkaloids, which have been researched for their therapeutic properties. Its diuretic effects can help with hypertension and edema, its aphrodisiac properties can aid sexual function, and its antilithic properties can prevent kidney stone formation. This research aimed to study the physicochemical and pharmacological characteristics of TT.

Methods: The PubChem database was used to collect data on the studied compounds, including their formulas and structures. Subsequently, SwissADME software was employed to assess the physicochemical and pharmacological properties of these compounds in TT.

Results: Steroidal saponins and sterols exhibited varying solubility levels in physiological fluids due to their hydrophobic nature and glycosylation patterns. However, flavonoids demonstrated favorable solubility. Compounds, such as (25R)-Spirosta-3,5-dien, β-sitosterol, and stigmasterol had low polarity, whereas Terrestrosin K, Terrestrosin F, Terrestroside B, Protodioscin, and Kaempferol-3-O-rutinoside could form more hydrogen bonds. Steroidal saponins were more readily absorbed in the gastrointestinal tract and could penetrate the BBB.

Discussion: Kaempferol, chrysin, and quercetin showed inhibitory effects on specific cytochrome P450 enzymes. β-sitosterol and stigmasterol had high rates of skin absorption. The bioavailability score ranged from 0.11 to 0.55, and synthetic accessibility scores were generally high.

Conclusion: The steroidal saponins and flavonoids found in TT showed therapeutic potential for conditions, such as hypertension, edema, and sexual dysfunction. Many of them possess favorable pharmaceutical properties for clinical use.

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Introduction

The genus Tribulus, from the family Zygophyllaceae, has approximately 20 species worldwide, with Tribulus terrestris (TT) being a common medicinal herb in India. This annual shrub can be found in various regions, including the Mediterranean, subtropical areas, and deserts (1). Known as Gokshur or puncture vine, it has been used in traditional medicine for its diverse chemical constituents that have shown multiple health benefits, such as anti-inflammatory and anticancer properties (2).

Bioactive compounds of Tribulus terrestris

Phytochemical study of TT has revealed the presence of various bioactive compounds in it, including saponins, flavonoids, glycosides,

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alkaloids, and tannins (3). Saponins, a type of glycoside, have been shown to have anti-inflammatory and antioxidant properties (4). The saponin composition and content of TT from different geographic regions have been found to vary (3).

Sterols

Sterols found in TT include sitosterol, stigmasterol, and campesterol. Bulgarian samples of TT were examined, revealing a group of sterols typical for plants. The author also noted a relatively high percentage of cholesterol (2).

Steroidal Saponins

Steroidal saponins are a group of compounds extensively studied in TT. These saponins consist of a hydrophobic aglycone and a hydrophilic sugar residue, typically categorized as triterpenoid and steroid glycosides or spirostanol and furostanol saponins (5). Various studies have isolated different saponins from TT, such as tigogenin-3-diglucorhamnoside (terrestroside F), neotigogenin, gitogenin, hecogenin, neohecogenin, diosgenin, ruscogenin, chlorogenin, and sarsasapogenin. These studies have also identified sulfated saponins and flavonoid glucosides (6).

The saponin composition has been shown to be influenced by the phenological stage of the plant. For instance, saponin content increases from the pre-flowering to flowering stage and decreases during mass fruit formation. Leaves contain the highest steroid saponin content, followed by fruits and stems (6). Quantitative determination of saponins has been explored in various regions. A study performed in Bulgaria revealed that the levels of protodioscin, prototribestin, dioscin, and rutin were high in populations from southern Bulgaria that used TT (7).

Flavonoids

Flavonoids are a class of compounds commonly found in plants, including TT. These compounds are known for their antioxidant and anti-inflammatory properties and have been shown to offer a range of health benefits. Recent studies have reported the presence of various flavonoids in TT, such as kaempferol, astragalin, kaempferol-3-rhamnoglycoside, tribuluside, and rutin. Other researchers have isolated quercetin, kaempferol, and isorhamnetin from the leaves and fruits of TT (8).

Flavonoid content of TT varied depending on the region in which it was grown (4). A study revealed that the highest levels of quercetin and kaempferol were present in the leaves and fruits of TT grown in Bulgaria, while lower levels were found in samples from Turkey and Iran. The flavonoid content of TT varied depending on the plant part examined. It also showed that TT had the highest content of quercetin and kaempferol in the roots, leaves, and fruits, while isorhamnetin and rutin were only present in the leaves. Moreover, chrysin was exclusively found in the fruits (9).

Furthermore, it found that quercetin levels varied depending on the region and the plant part examined. The highest levels of quercetin were found in the leaves and fruits (10). Flavonoids of TT are mainly derivatives of quercetin, kaempferol, and isorhamnetin. Quercetin, isoquercitrin (11), rutin, quercetin-3-O-gent, quercetin-3-O-gentr, and other flavonoids with quercetin as the basic parent structure have been identified. Isorhamnetin, isorhamnetin-3-O-glu (10, 11), isorhamnetin-3-O-gent, and other flavonoids with isorhamnetin as the basic parent structure have also been found. In addition, kaempferol, kaempferol-3-O-glu, kaempferol-3-O-gent, and other flavonoids with kaempferol as the basic parent structure have been identified as well.

Alkaloids

At least five alkaloids were isolated from the plant, all of which appeared to be β-carboline derivatives. The main alkaloids contained in Australian TT were identified as β-carbolines, harman, and norharman. Synthetic harman and norharman were administered subcutaneously to sheep and caused limb paresis similar to naturally occurring cases of TT staggers. Since alkaloids are among the major constituents of TT, and β-carboline alkaloids may be responsible for the pharmacological effects of this plant, further study of β-carbolines was of interest. β-carbolines are found in marine and terrestrial natural products and exhibit a range of pharmacological activities. Therefore, their biosynthesis and total synthesis are of interest. Toxicity of TT was attributed to the presence of the β-carboline alkaloid and tribulusterine (12, 13).

Lignan Amides and Cinnamic Acid Amides

Tribulus terrestris, as a medicinal plant, has been found to contain a variety of bioactive compounds, including lignan amides and cinnamic acid amides. These compounds have been isolated and identified by several researchers. The lignan amides, such as tribulusamides A and B, have been shown to protect cells from damage caused by tumors induced by D-galactosamine and tumor necrosis factor α (TNF-α). The cinnamic acid amides, including terrestriamide

and 7-methylhydroindanone-1, have also been identified in TT fruits. One notable compound was tribulusamide C, a feruloyl amide derivative that consisted of pyrrolidine-2,5-dione, making it distinct from other lignan amides found in TT fruits. Researchers have isolated metabolites from TT and found that three derivatives of cinnamic acid amides showed inhibition of α-glucosidase activity. These compounds had potential therapeutic applications for various diseases, including cancer and diabetes (6).

Pharmacological Activities

Tribulus terrestris has been found to possess a wide range of pharmacological activities, including diuretic, aphrodisiac, antiurolithic, libido-enhancing, immunomodulatory, antidiabetic, absorption enhancer, hypolipidemic, analgesic, antispasmodic, and anticancer properties. Tribulus terrestris contains bioactive compounds consisting of saponins and flavonoids. Steroidal saponins have been shown to protect cells from damage caused by tumors induced by TNF-α (14-22).

Diuretic properties of TT are attributed to nitrates and essential oils in its fruits and seeds. These oils induce positive diuresis in rats, similar to the standard diuretic drug furosemide. The TT essential oils are associated with fluid retention and hypertension (14). Studies on TT have demonstrated its pro-erectile effects on rabbit corpus cavernosum smooth muscle *ex vivo*. Extract of TT has been shown to increase the release of nitric oxide from the endothelium and nitrergic nerve endings, supporting its reputation as an aphrodisiac (15-17). Tribulus terrestris also has antilithic properties, preventing the formation of kidney stones. In a urolithiasis-induced rat model, the ethanolic extract of TT fruits displayed dose-dependent protection against calculogenic material deposition and restored various biochemical parameters in urine, serum, and histopathology of the urinary bladder (16). Steroidal saponins found in TT have pro-erectile effects, enhancing sexual function by increasing blood flow to the genitals. In clinical trials, TT supplementation improved desire and sexual interest in postmenopausal women with hypoactive sexual desire disorder (17).

Saponins isolated from TT enhance the nonspecific immune response by increasing phagocytosis. Alcoholic extracts of the entire plant elevate humoral antibody titers and delayed hypersensitivity response, indicating a potential enhancement of specific immune responses (18). Hypoglycemic properties of TT are attributed to its saponin content, inhibiting gluconeogenesis and reducing serum glucose, triglyceride, and cholesterol levels in diabetic mice. With a potential role for TT in diabetes management, it has the ability to enhance the absorption of metformin hydrochloride in an *ex vivo* model. The aqueous extract of TT fruits has displayed hypolipidemic activity in rats, reducing cholesterol, triglycerides, Low-density lipoprotein, very low-density lipoprotein, and atherogenic index while increasing high-density lipoprotein levels. These findings suggest that TT may contribute to cardiovascular health by managing lipid profiles (20).

Methanolic extracts of TT have demonstrated dose-dependent analgesic effects in mouse models, potentially acting through central and/or peripheral mechanisms (21). Although opioid receptors do not appear to be involved in these effects, the lyophilized saponin mixture of TT has shown promise in reducing peristaltic movements in rabbit jejunum preparations, indicating a therapeutic role in the treatment of gastrointestinal spasms. The TT extracts exhibit chemopreventive properties against 7,12-Dimethylbenz[a]anthracene and croton oil-induced papillomagenesis in mice (20, 22). The present study delved into the physicochemical and pharmacological properties of the active compounds present in TT.

Materials and Method

Predicting Physicochemical Properties and Pharmacokinetics

The SwissADME web tool has become a valuable resource for drug development researchers, offering a comprehensive platform for the prediction of key physicochemical properties and pharmacokinetic parameters. Through its user-friendly interface and reliable predictive models, such as BOILED-Egg and iLOGP, researchers can quickly and accurately forecast critical parameters without the need for extensive computational expertise or specialized software. The present research team has extensively used SwissADME online software, proving it to be an indispensable asset in the discovery and development of novel therapeutic agents (23-26).

Methods

A thorough literature review was conducted to evaluate the medicinal usage of TT in traditional medicine management. A comprehensive search of databases, including PubMed, ScienceDirect, and Scopus, was performed using relevant keywords related to herbal and traditional medicine. The molecular models of the studied compounds of the TT plant were obtained from the PubChem database (23). Primary outcomes of these

studies were analyzed, and the physicochemical properties and pharmacokinetics compounds found in TT were calculated using the SwissADME online software. This investigation aimed to clarify the potential of TT as a therapeutic agent in herbal medicine. The reliable predictive models and user-friendly interface of the database provided valuable insights into the bioavailability, absorption, distribution, metabolism, and excretion of the compound (23-30).

Results

Physicochemical properties of studied compounds

Steroidal saponins and sterols often have low solubility in physiological fluids, but their suitable hydrophobicity allows them to pass through biological membranes. Conversely, the more these compounds are glycosylated, the higher their solubility in physiological fluids. Flavonoids and their glycosylated compounds have favorable solubility in physiological fluids. The compounds with the lowest polar levels were (25R)-Spirosta-3,5-dien, β-sitosterol, and Stigmasterol. The compounds Terrestrosin K, Terrestrosin F, Terrestroside B, Protodioscin, and Kaempferol-3-O-rutinoside have the highest intensity of creating hydrogen bonds among the studied compounds (Tables 1 and 2).

Pharmaceutical Properties of Studied Compounds

Among the studied compounds, steroidal saponins often have high digestive absorption, while sterols and flavonoids have low digestive absorption. Steroidal saponins can typically cross the blood-brain barrier (BBB), unlike flavonoids and compounds with large glycosylated parts. Among the sterol compounds, β-sitosterol and stigmasterol have the highest rate of skin absorption, while the other steroidal saponins have lower skin absorption. Kaempferol, chrysin, perlolyrine, and quercetin compounds have the most inhibitory effect on cytochrome P450 enzymes, while steroidal saponins generally do not have this effect. The bioavailability score for all compounds is medium to low, with an average of 55%. Synthetic accessibility for most compounds is higher than 5.0, making them difficult to obtain through laboratory synthesis (Tables 2 and 3 and Figure 1).

Discussion

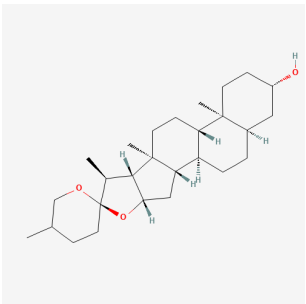
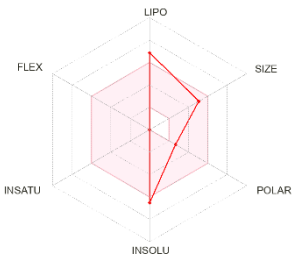
Physicochemical properties

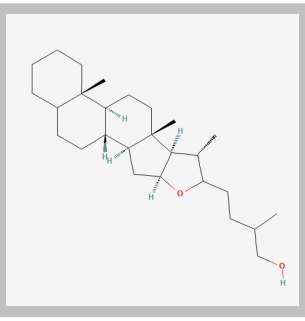
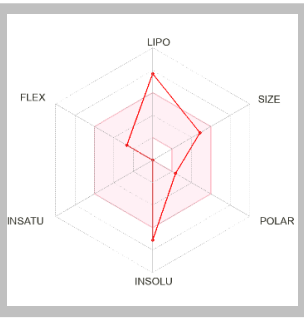
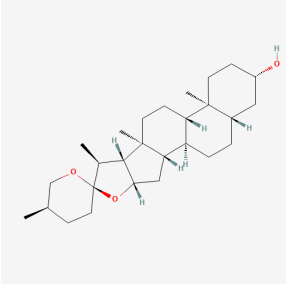
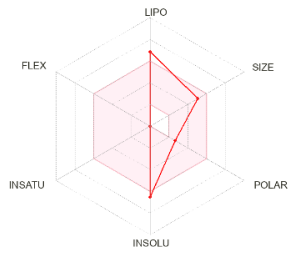
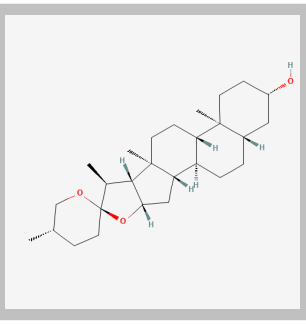
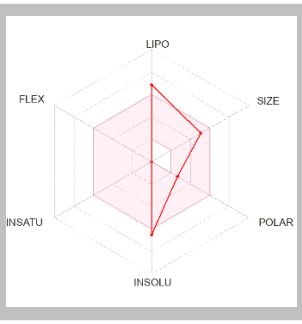
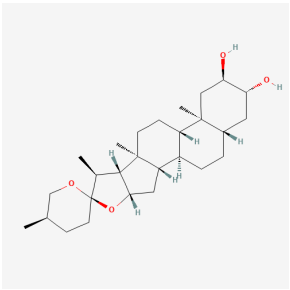
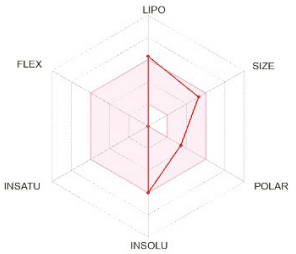
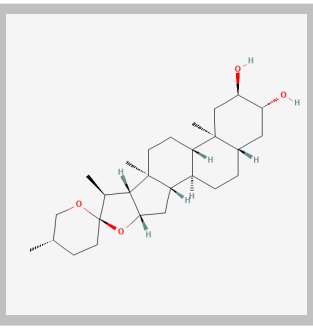
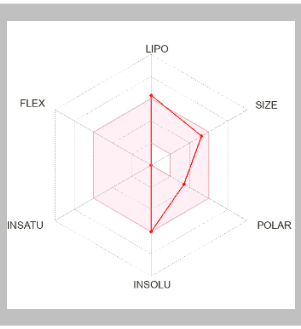
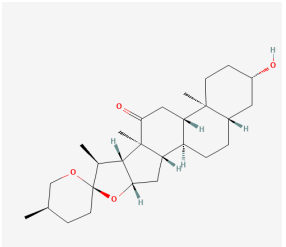
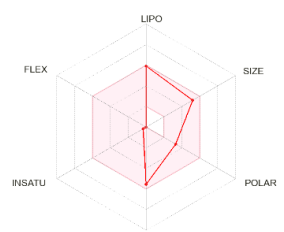
Steroidal saponins generally exhibited higher solubility in physiological fluids due to their steroidal backbone and glycosylation patterns, facilitating easier absorption and transport within the body. However, sterols had lower solubility but could still permeate biological membranes due to their hydrophobic nature. Flavonoids, being less hydrophobic, demonstrated favorable solubility in physiological fluids. Compounds with lower polarity, such as (25R)-Spirosta-3,5-dien, β-sitosterol, and stigmasterol, displayed higher lipophilicity and lower solubility in aqueous environments. Conversely, more polar compounds, like Terrestrosin K, Terrestrosin F, Terrestroside B, Protodioscin, and Kaempferol-3-O-rutinoside exhibited higher solubility in water-based fluids. Terrestrosin K, Terrestrosin F, Terrestroside B, Protodioscin, and Kaempferol-3-O-rutinoside were capable of forming a higher number of hydrogen bonds, contributing to their increased polarity and solubility in water (24-26).

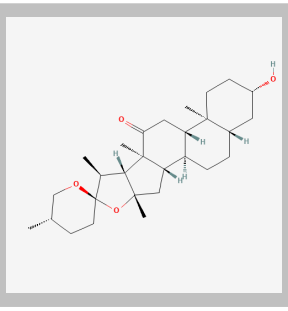
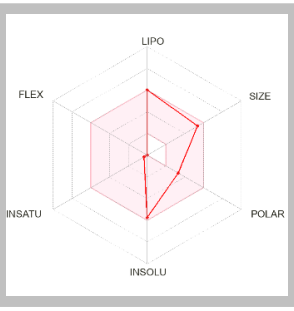
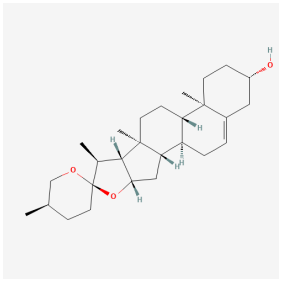
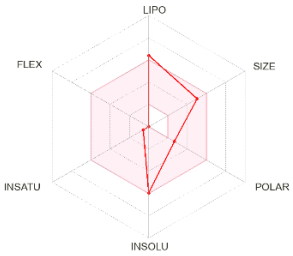
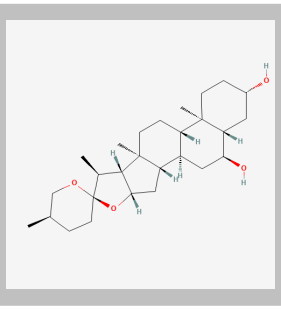
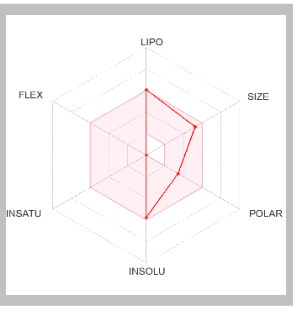
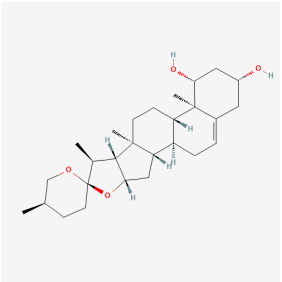
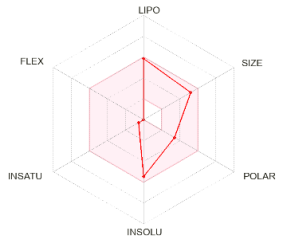
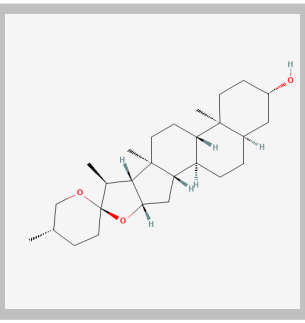
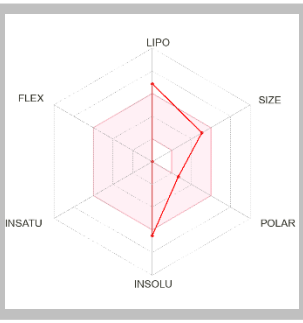
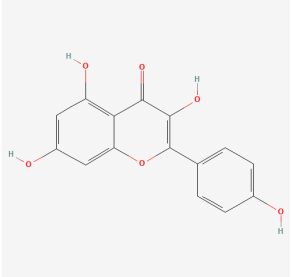
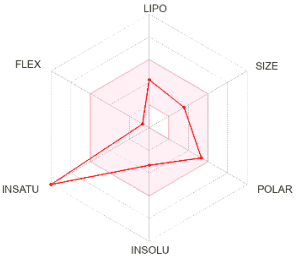
Pharmaceutical properties

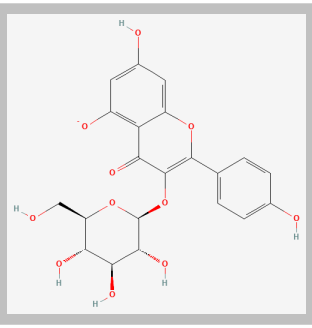
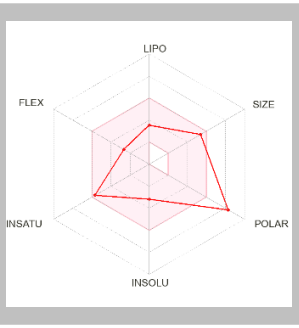
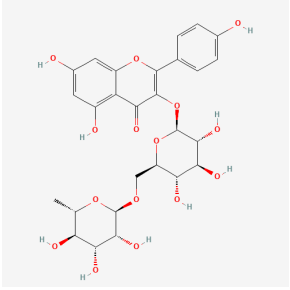
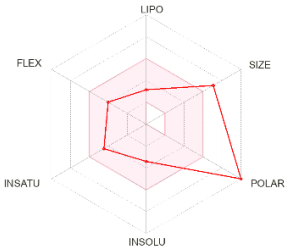
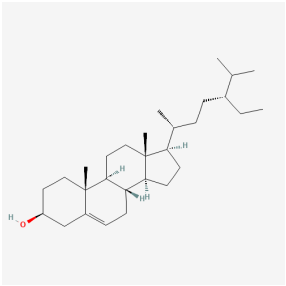
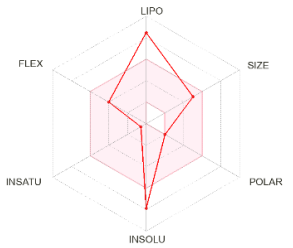
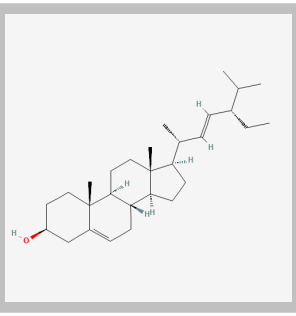
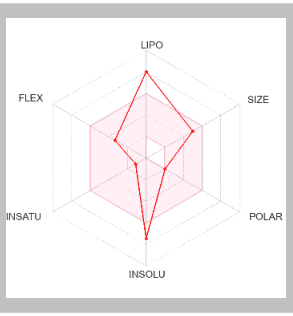
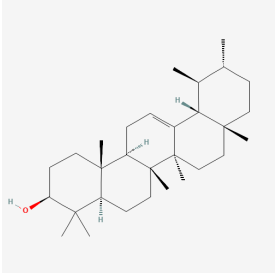
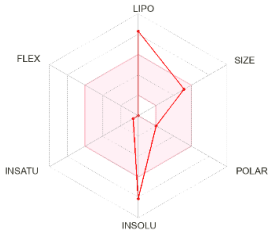
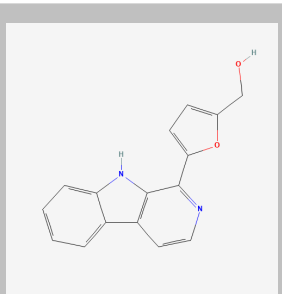
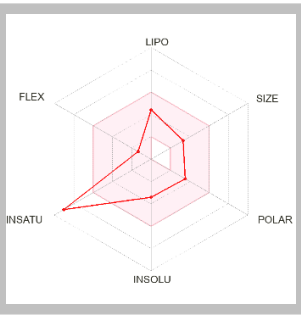
Steroidal saponins typically had high gastrointestinal absorption rates, facilitating their entry into the bloodstream and distribution throughout the body. Sterols and flavonoids generally exhibited lower absorption rates.

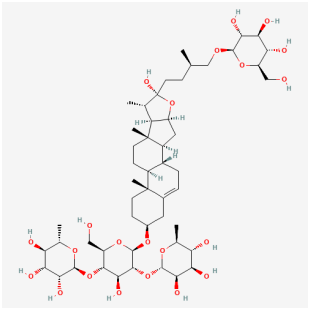
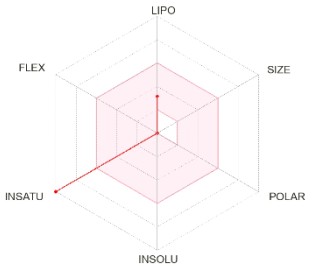
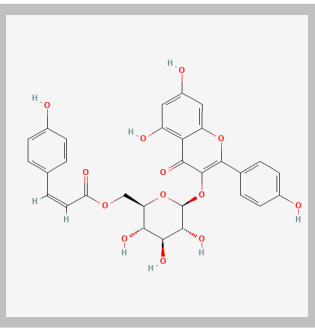
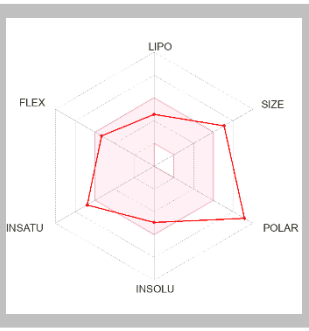
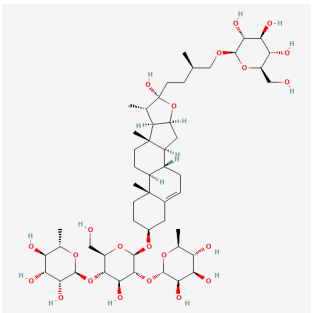
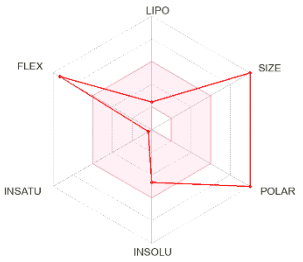
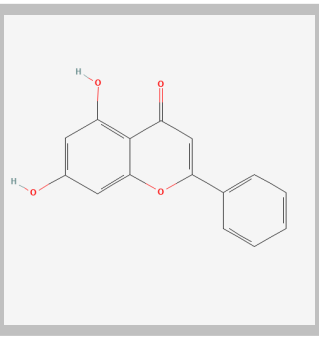
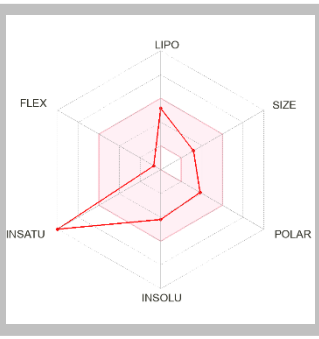
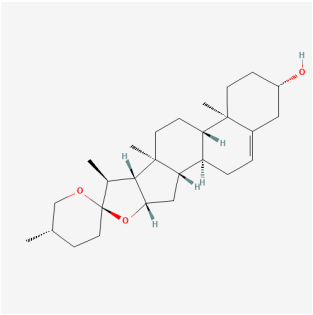
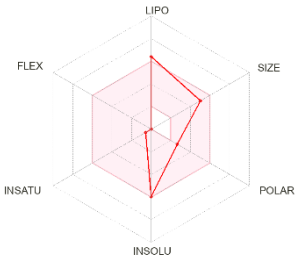
Table 1. Name, International Union of Pure and Applied Chemistry (IUPAC) name, 2-D structure, and radar scale of physicochemical properties of studied compounds

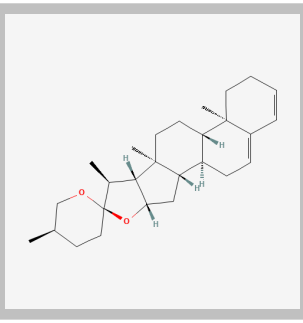
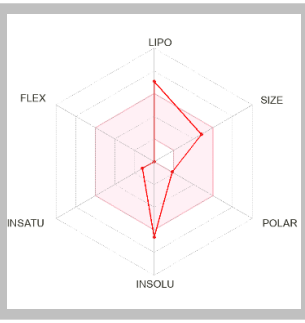
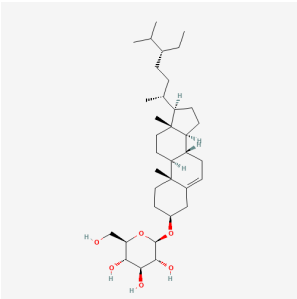
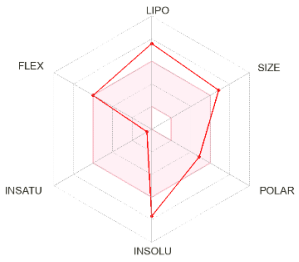
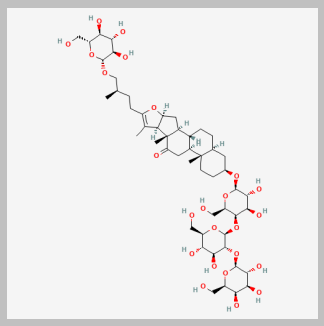
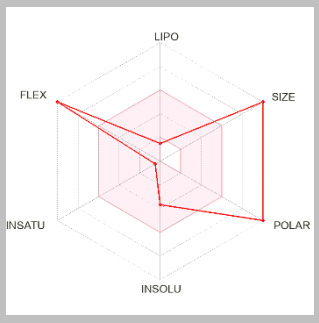
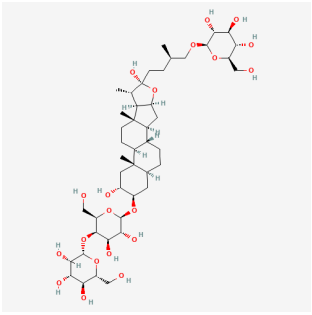
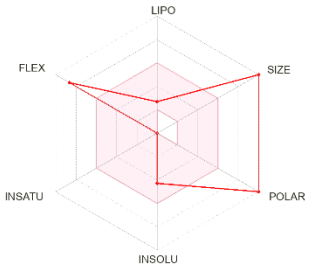
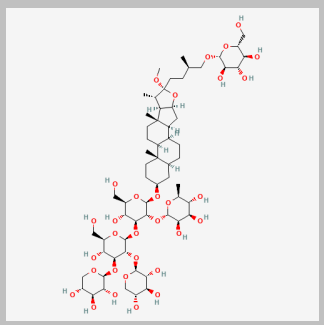
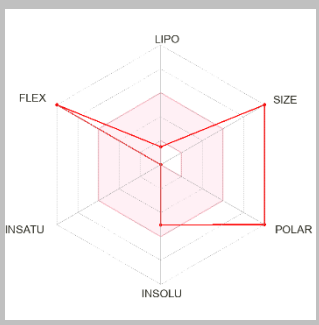
Compound Name	IUPAC Name	2-D Structure	Radar scale of physicochemical propreties
Spirostanol	(1*R*,2*S*,4*S*,6*R*,7*S*,8*R*,9*S*,12*S*,13*S*,16*S*,18*R*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane-6,2'-oxane]-16-ol		

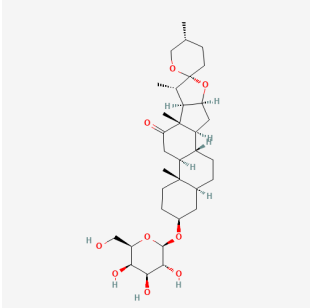
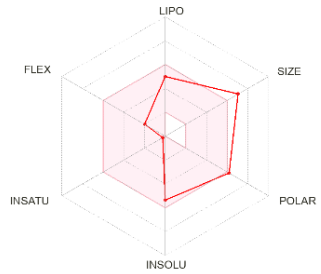
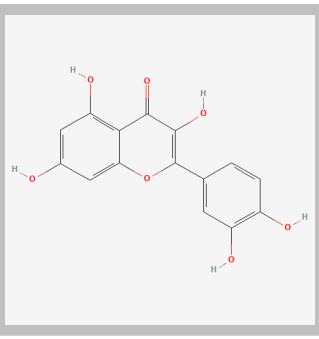
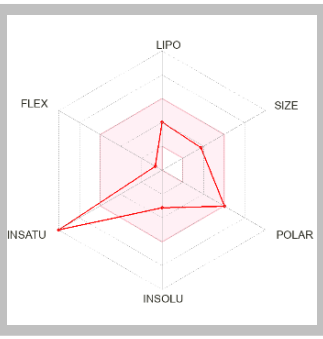
Furostanol	2-methyl-4-[(1*R*,2*S*,4*S*,7*S*,8*R*,9*S*,12*S*,13*S*)-7,9,13-trimethyl-5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosan-6-yl]butan-1-ol		
Tigogenin	(1*R*,2*S*,4*S*,5'*R*,6*R*,7*S*,8*R*,9*S*,12*S*,13*S*,16*S*,18*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane-6,2'-oxane]-16-ol		
Neotigogenin	(1*R*,2*S*,4*S*,5'*S*,6*R*,7*S*,8*R*,9*S*,12*S*,13*S*,16*S*,18*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane-6,2'-oxane]-16-ol		
Gitogenin	(1*R*,2*S*,4*S*,5'*R*,6*R*,7*S*,8*R*,9*S*,12*S*,13*S*,15*R*,16*R*,18*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane-6,2'-oxane]-15,16-diol		
Neogitogenin	(1*R*,2*S*,4*S*,5'*S*,6*R*,7*S*,8*R*,9*S*,12*S*,13*S*,15*R*,16*R*,18*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane-6,2'-oxane]-15,16-diol		
Hecogenin	(1*R*,2*S*,4*S*,5'*R*,6*R*,7*S*,8*R*,9*S*,12*S*,13*S*,16*S*,18*S*)-16-hydroxy-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane-6,2'-oxane]-10-one		

Neohecogenin	(1*R*,2*S*,4*S*,5'*S*,6*R*,7*S*,8*R*,9*S*,12*S*,13*S*,16*S*,18*S*)-16-hydroxy-4,5',7,9,13-pentamethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane-6,2'-oxane]-10-one		
Diosgenin	(1*S*,2*S*,4*S*,5'*R*,6*R*,7*S*,8*R*,9*S*,12*S*,13*R*,16*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icos-18-ene-6,2'-oxane]-16-ol		
Chlorogenin	(1*R*,2*S*,4*S*,5'*R*,6*R*,7*S*,8*R*,9*S*,12*S*,13*R*,16*S*,18*S*,19*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane-6,2'-oxane]-16,19-diol		
Ruscogenin	(1*S*,2*S*,4*S*,5'*R*,6*R*,7*S*,8*R*,9*S*,12*S*,13*R*,14*R*,16*R*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icos-18-ene-6,2'-oxane]-14,16-diol		
Sarsasapogenin	(1*R*,2*S*,4*S*,5'*S*,6*R*,7*S*,8*R*,9*S*,12*S*,13*S*,16*S*,18*R*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane-6,2'-oxane]-16-ol		
Kaempferol	3,5,7-trihydroxy-2-(4-hydroxyphenyl)chromen-4-one		

kaempferol-3 glucoside	7-hydroxy-2-(4-hydroxyphenyl)-4-oxo-3-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl]oxychromen-5-olate		
kaempferol-3-rutinoside	5,7-dihydroxy-2-(4-hydroxyphenyl)-3-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-[[(2*R*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl] oxychromen-4-one		
β-sitosterol	(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-[(2*R*,5*R*)-5-ethyl-6-methyl-heptan-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1*H*-cyclopenta[a] phenanthren-3-ol		
Stigmasterols	(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-[(*E*,2*R*,5*S*)-5-ethyl-6-methyl-hept-3-en-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1*H*-cyclopenta[a] phenanthren-3-ol		
α-Amyrin	(3*S*,4*aR*,6*aR*,6*bS*-,8*aR*,11*R*,12*S*,12*aR*,14*aR*,14*bR*)-4,4,6*a*,6*b*,8*a*,11,12,14*b*-octamethyl-2,3,4*a*,5,6,7,8,9,10,11,12,12*a*,14,14*a*-tetradecahydro-1*H*-picen-3-ol		
Tribulusterine (Perlolyrin)	[5-(9H-pyrido[3,4-b]indol-1-yl) furan-2-yl]methanol		

Protodioscin	(2*S*,3*R*,4*R*,5*R*,6*S*)-2-[(2*R*,3*S*,4*S*,5*R*,6*R*)-4-hydroxy-2-(hydroxymethyl)-6-[[(1*S*,2*S*,4*S*,6*R*,7*S*,8*R*,9*S*,12*S*,13*R*,16*S*)-6-hydroxy-7,9,13-trimethyl-6-[(3*R*)-3-methyl-4-[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxybutyl]-5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icos-18-en-16-yl]oxy]-5-[(2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxyoxan-3-yl]oxy-6-methyloxane-3,4,5-triol		
Tribuloside	[(2*R*,3*S*,4*S*,5*R*,6*S*)-6-[5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxochromen-3-yl]oxy-3,4,5-trihydroxyoxan-2-yl]methyl (*Z*)-3-(4-hydroxyphenyl)prop-2-enoate		
Protodioscin	(2*S*,3*R*,4*R*,5*R*,6*S*)-2-[(2*R*,3*S*,4*S*,5*R*,6*R*)-4-hydroxy-2-(hydroxymethyl)-6-[[(1*S*,2*S*,4*S*,6*R*,7*S*,8*R*,9*S*,12*S*,13*R*,16*S*)-6-hydroxy-7,9,13-trimethyl-6-[(3*R*)-3-methyl-4-[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxybutyl]-5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icos-18-en-16-yl]oxy]-5-[(2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxyoxan-3-yl]oxy-6-methyloxane-3,4,5-triol		
Chrysin	5,7-dihydroxy-2-phenylchromen-4-one		
Yamogenin	(1*S*,2*S*,4*S*,5'*S*,6*R*,7*S*,8*R*,9*S*,12*S*,13*R*,16*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icos-18-ene-6,2'-oxane]-16-ol		

Diosgenin,dehydro ((25R)-Spirosta-3,5-dien)	(1*S*,2*S*,4*S*,5'*R*,6*R*,7*S*,8*R*,9*S*,12*S*,13*R*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosa-16,18-diene-6,2'-oxane]		
Daucosterol, Sitogluside, (β-sitosterol-β-D-glucoside)	(2*R*,3*R*,4*S*,5*S*,6*R*)-2-[[(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-[(2*R*,5*R*)-5-ethyl-6-methylheptan-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1*H*-cyclopenta[a]phenanthren-3-yl]oxy]-6-(hydroxymethyl)oxane-3,4,5-triol		
Terrestrosin K	(1R,2S,4S,8R,9S,12S,13S,16S,18S)-16-[(2R,3R,4R,5R,6R)-5-[(2S,3R,4S,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)-3-[(2S,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyoxan-2-yl]oxy-3,4-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-7,9,13-trimethyl-6-[(3R)-3-methyl-4-[(2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxybutyl]-5-oxapentacyclo[10.8.0.02,9.04,8.013,18]icos-6-en-10-one		
Terrestrosin F	(2R,3R,4S,5S,6R)-2-[(2R)-4-[(1R,2S,4S,6R,7S,8R,9S,12S,13S,15R,16R,18S)-16-[(2R,3R,4R,5R,6R)-3,4-dihydroxy-6-(hydroxymethyl)-5-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyoxan-2-yl]oxy-6,15-dihydroxy-7,9,13-trimethyl-5-oxapentacyclo[10.8.0.02,9.04,8.013,18]icosan-6-yl]-2-methylbutoxy]-6-(hydroxymethyl)oxane-3,4,5-triol		
Terrestroside	(2*S*,3*R*,4*R*,5*R*,6*S*)-2-[(2*R*,3*R*,4*S*,5*R*,6*R*)-5-hydroxy-4-[(2*S*,3*R*,4*S*,5*R*,6*R*)-5-hydroxy-6-(hydroxymethyl)-3,4-bis[[(2*S*,3*R*,4*S*,5*R*)-3,4,5-trihydroxyoxan-2-yl]oxy]oxan-2-yl]oxy-6-(hydroxymethyl)-2-[[(1*S*,2*S*,4*S*,6*R*,7*S*,8*R*,9*S*,12*S*,13*S*,16*S*,18*S*)-6-methoxy-7,9,13-trimethyl-6-[(3*R*)-3-methyl-4-[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxybutyl]-5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosan-16-yl]oxy]oxan-3-yl]oxy-6-methyloxane-3,4,5-triol		

Agavoside A	(1R,2S,4S,5'R,6R,7S,8R,9S,12S,13S,16S,18S)-5',7,9,13-tetramethyl-16-[(2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl]oxyspiro[5-oxapentacyclo[10.8.0.02,9.04,8.013,18]icosane-6,2'-oxane]-10-one		
Quercetin	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one		

Steroidal saponins were more likely to cross the BBB, compared to flavonoids. Some steroidal saponins were substrates of P-glycoprotein, which could impact their absorption and distribution, particularly in the central nervous system and other tissues where this transporter was active. Kaempferol, chrysin, and quercetin demonstrated inhibitory effects on CYP1A2, CYP2C9, CYP2D6, and CYP3A4 enzymes, influencing drug metabolism and potential drug-

Table 2. Physicochemical properties of the compounds under study

Studied compounds	Molecular Weight	Heavy atoms	Fraction Csp3	Rotatable bonds	H-bond acceptors	H-bond donors	MR (Molar Refractivity)	TPSA(topological polar surface area)	Implicit log P	XLOGP3	Estimated solubility Log S	Estimated solubility Solubility (mg/ml)	Estimated solubility Class
Spirostanol	416.64	30	1.00	0	3	1	122.07	38.69	4.58	6.49	-6.51	1.28e-04	Poorly soluble
Furostanol	402.65	29	1.00	4	2	1	123.06	29.46	4.74	7.98	-7.10	3.20e-05	Poorly soluble
Tigogenin	416.64	30	1.00	0	3	1	122.07	38.69	4.53	6.49	-6.51	1.28e-04	Poorly soluble
Neotigogenin	416.64	30	1.00	0	3	1	122.07	38.69	4.53	6.49	-6.51	1.28e-04	Poorly soluble
Gitogenin	432.64	31	1.00	0	4	2	123.23	58.92	4.12	5.52	-6.00	4.33e-04	Moderately soluble
Neogitogenin	432.64	31	1.00	0	4	2	123.23	58.92	4.17	5.52	-6.00	4.33e-04	Moderately soluble
Hecogenin	430.62	31	0.96	0	4	1	122.27	55.76	4.11	4.83	-5.55	1.21e-03	Moderately soluble
NEOHECOGENIN	444.65	32	0.96	0	4	1	127.11	55.76	4.16	5.01	-5.75	7.85e-04	Moderately soluble

(25R)-Spiros-ta-3,5-dien	Yamo-genin	Tribulusterine (Perlolyrine)	Chrysin	Tribulo-side	Protodi-oscin	Stigmas-terol	β-sitosterols	Kaempferol-3-O-ru-tinoside	kaempferol-3 glucoside	Kaempferol	Sarsasapo-genin	Ruscogenin	Chlorogenin	Dios-genin
396.61	414.62	264.28	254.24	594.52	1049.20	412.69	414.71	594.52	447.37	286.24	416.64	430.62	432.64	414.62
29	30	20	19	43	73	30	30	42	32	21	30	31	31	30
0.85	0.93	0.06	0.00	0.20	0.96	0.86	0.93	0.44	0.29	0.00	1.00	0.93	1.00	0.93
0	0	2	1	8	14	5	6	6	4	1	0	0	0	0
2	3	3	4	13	22	1	1	15	11	6	3	4	4	3
0	1	2	2	7	13	1	1	9	6	4	1	2	2	1
119.96	121.59	77.43	71.97	149.51	252.16	132.75	133.23	139.36	106.24	76.01	122.07	122.76	123.23	121.59
18.46	38.69	62.05	70.67	216.58	346.06	20.23	20.23	249.20	193.11	111.13	38.69	58.92	58.92	38.69
4.69	4.43	2.36	2.27	1.56	4.48	5.08	5.05	0.79	1.44	1.70	4.51	4.32	4.30	4.49
6.90	5.67	2.23	3.52	2.47	-1.25	8.56	9.34	0.02	0.72	1.90	6.49	4.70	5.15	5.67
-6.65	-5.98	-3.42	-4.19	-4.93	-4.63	-7.46	-7.90	-3.42	-3.17	-3.31	-6.51	-5.47	-5.77	-5.98
8.96e-05	4.31e-04	1.01e-01	1.64e-02	6.94e-03	2.44e-02	1.43e-05	5.23e-06	2.24e-01	3.00e-01	1.40e-01	1.28e-04	1.46e-03	7.40e-04	4.31e-04
Poorly soluble	Moderate-ly soluble	Soluble	Moderate-ly soluble	Mod-erately soluble	Mod-erately soluble	Poorly soluble	Poorly soluble	Soluble	Soluble	Soluble	Poorly soluble	Moderately soluble	Moderately soluble	Mod-erately soluble

Daucosterol, Sitogluside	576.85	41	0.94	9	6	4	165.61	99.38	5.17	7.74	-7.70	1.15e-05	Poorly soluble
Terres-trosin K	1079.18	75	0.94	16	24	14	253.48	383.36	4.58	-2.87	-3.67	2.32e-01	Soluble
Terrestros-in F	937.07	65	1.00	13	20	13	223.73	327.60	3.88	-0.81	-4.28	4.90e-02	Moderately soluble
Terrestroside B	1345.47	93	1.00	20	31	17	311.35	473.13	4.32	-2.90	-5.03	1.24e-02	Moderately soluble
Agavoside A	592.76	42	0.97	3	9	4	154.65	134.91	4.58	3.24	-5.36	2.60e-03	Moderately soluble
Quercetin	302.24	22	0.00	1	7	5	78.03	131.36	1.63	1.54	-3.16	2.11e-01	Soluble

drug interactions. β-sitosterol and stigmasterol exhibited the highest rates of skin absorption among the studied sterols, which was relevant for topical applications. The bioavailability score for these compounds ranged from 0.11 to 0.55, with an average of 55%, indicating medium to low bioavailability. The synthetic accessibility scores were generally high, with most compounds

Table 3. Pharmaceutical properties of studied compounds.

Molecule Name	Gastrointestinal absorption	Blood-brain barrier permeant	P-glycoprotein substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)	Bioavailability score	Synthetic accessibility
Spirostanol	High	Yes	No	No	No	No	No	No	-4.23	0.55	6.88
Furostanol	High	No	No	No	No	No	No	No	-3.09	0.55	5.70
Tigogenin	High	Yes	No	No	No	No	No	No	-4.23	0.55	6.88
Neotigogenin	High	Yes	No	No	No	No	No	No	-4.23	0.55	6.88
Gitogenin	High	Yes	Yes	No	No	No	No	No	-5.02	0.55	7.00
Neogitogenin	High	Yes	Yes	No	No	No	No	No	-5.02	0.55	7.00
Hecogenin	High	Yes	Yes	No	No	No	No	No	-5.50	0.55	6.70
Neohecogenin	High	Yes	Yes	No	No	No	No	No	-5.46	0.55	6.82
Diosgenin	High	Yes	No	No	No	No	No	No	-4.80	0.55	6.94
Chlorogenin	High	Yes	Yes	No	No	No	No	No	-5.28	0.55	6.97
Ruscogenin	High	Yes	Yes	No	No	No	No	No	-5.59	0.55	7.06
Sarsasapogenin	High	Yes	No	No	No	No	No	No	-4.23	0.55	6.88
Kaempferol	High	No	No	Yes	No	No	Yes	Yes	-6.70	0.55	3.14
kaempferol-3 glucoside	Low	No	No	No	No	No	No	No	-8.52	0.11	5.25

Kaempferol-3-O-rutinoside	Low	No	Yes	No	No	No	No	No	-9.91	0.17	6.48
β-sitosterol	Low	No	No	No	No	No	No	No	-2.20	0.55	6.30
Stigmasterol	Low	No	No	No	No	Yes	No	No	-2.74	0.55	6.21
Protodioscin	Low	No	Yes	No	No	No	No	No	-13.59	0.17	10.00
Tribuloside	Low	No	No	No	No	No	No	No	-8.17	0.17	5.96
Chrysin	High	Yes	No	Yes	No	No	Yes	Yes	-5.35	0.55	2.93
Tribulusterine (Perlolyrine)	High	Yes	Yes	Yes	No	No	Yes	Yes	-6.33	0.55	2.98
Yamogenin	High	Yes	No	No	No	No	No	No	-4.80	0.55	6.94
(25R)-Spirosta-3,5-dien	Low	No	No	No	No	Yes	No	No	-3.82	0.55	6.87
Daucosterol, Sitogluside	Low	No	No	No	No	No	No	No	-4.32	0.55	8.02
Terrestrosin K	Low	No	Yes	No	No	No	No	No	-14.92	0.17	10.00
Terrestrosin F	Low	No	Yes	No	No	No	No	No	-12.59	0.17	10.00
Terrestroside B	Low	No	Yes	No	No	No	No	No	-16.57	0.17	10.00
Agavoside A	High	No	Yes	No	No	No	No	No	-7.62	0.55	7.95
Quercetin	High	No	No	Yes	No	No	Yes	Yes	-7.05	0.55	3.23

scoring above 5.0, suggesting that obtaining these compounds through laboratory synthesis may be challenging (24-30).

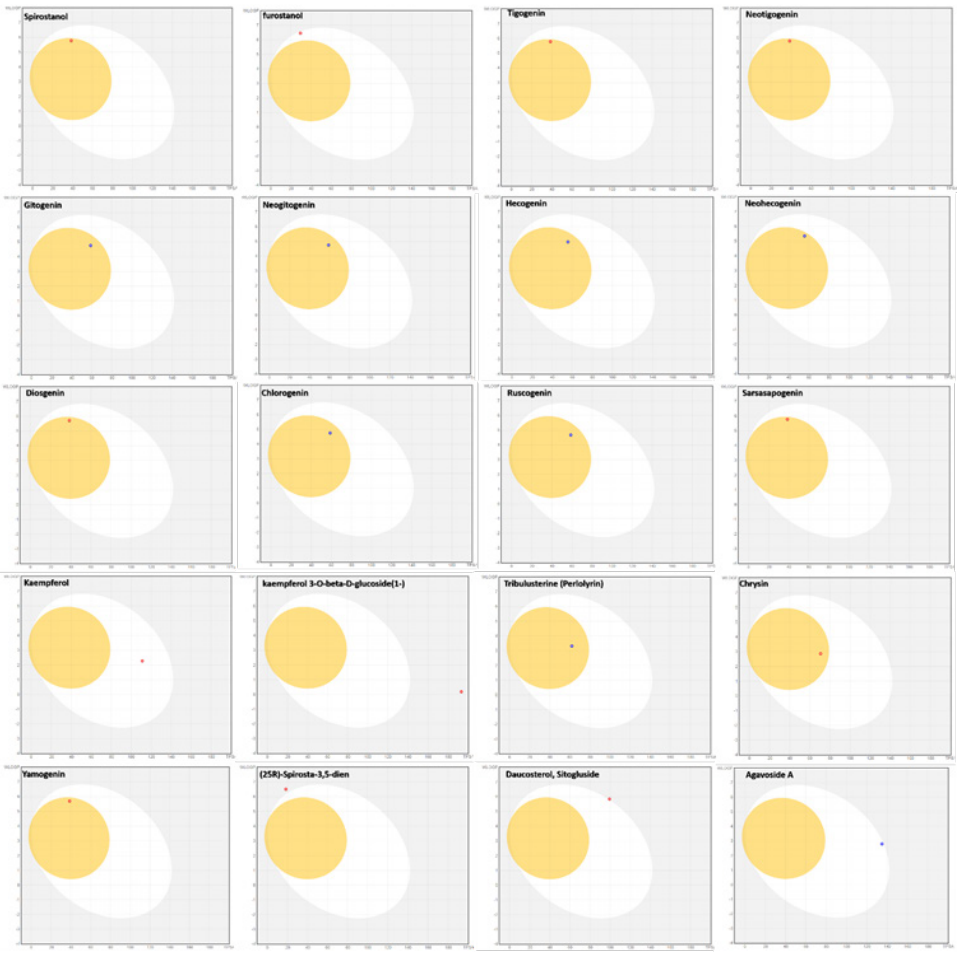


Figure 1. Illustration of the egg plot of the compounds under study. Yellow areas represent compounds capable of passively crossing the blood-brain barrier, and white areas contain compounds that can be passively absorbed by the digestive system. Moreover, blue dots indicate compounds that can enter the central nervous system through P-glycoproteins. In addition, red dots indicate compounds that can exit the central nervous system through P-glycoproteins

Conclusion

Steroidal saponins had higher gastrointestinal absorption rates and could cross the BBB. Kaempferol, chrysin, and quercetin showed inhibitory effects on certain cytochrome P450 enzymes. Moreover, β-sitosterol and stigmasterol had high skin absorption rates. Bioavailability of the studied compounds ranged from 0.11 to 0.55, and synthetic accessibility scores were generally high. Studied compounds, such as steroidal saponins and flavonoids, exhibited favorable physicochemical and pharmacological properties, indicating their potential as therapeutic agents. Efficacy of TT in various clinical applications and the standardization of its preparations were crucial for ensuring its safe and effective use in the treatment of conditions, such as hypertension, edema, and sexual dysfunction.

Conflict of interest

The authors have no conflicts of interest in the study.

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