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Review Article

BIOAVAILABILITY PROBLEMS OF PHYTOSTEROLS: A SYSTEMATIC REVIEW

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ABSTRACT

Phytosterols (PS) are biologically active steroidal compounds obtained from plant foods and cholesterol is found in animals**.** They have a prominent role in reducing the low-density lipoprotein (LDL) cholesterol levels, thus decreasing the risk of many diseases. PSs also have anti-cancer, antioxidant, antiulcer, immunomodulatory, antibacterial, antifungal effects and modulate inflammation by promoting the wound healing and inhibition of platelet aggregation. The most challenging part concerned about phytosterols was bioavailability. Phytosterol's absorption and the concentration of circulation over the body were lesser in human intestine compared to cholesterol because of its selectivity and return through intestinal transporters**.** We searched PubMed, Scopus, Embase, Google scholar and major conference proceedings. Sixteen such therapeutically potent plant steroids were studied in this systematic review to assess the bioavailability issues of phytosterols. Swiss ADME web tool that gives free access to a pool of fast yet robust predictive models for physicochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry friendliness was used for the study.

Keywords: Phytosterols, Absorption, Bioavailability, Steroidal compounds

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INTRODUCTION

Phytosterols (PS) are biologically active steroidal compounds obtained from plant foods and cholesterol is found in animals [1, 2]. Beta-sitosterol, campesterol, and stigmasterol are the common phytosterols in plant and animal diet such as edible oils, nuts, cereals and citrus fruits [3, 4]. These steroids have a common cholesterol skeleton with different side chains. Phytosterols eminently regulates plenitude of plant physiological process leading to proper growth of the plant [5]. Phytosterols have several health applications but could not be derived by humans; should be obtained from plants and animals as a part of diet. The biological and therapeutic activity of phytosterols depends on their formulation and solubility nature. Researches provide supporting evidences that PSs and their derivatives have multiple pharmacological properties and human-wellness-promoting abilities. They have a prominent role in reducing the low-density lipoprotein (LDL) cholesterol levels, thus decreasing the risk of many diseases [6-8]. PSs also have anti-cancer, antioxidant, antiulcer, immunomodulatory, antibacterial, antifungal effects and modulate inflammation by promoting the wound healing and inhibition of platelet aggregation [9-11].

Therapeutic potential of phytosterols

PSs as an additive therapy proves to have a good therapeutic potential in non-alcoholic fatty liver disease showing improvement in LDL cholesterol and liver enzymes [12]. They act by reducing intestinal absorption of cholesterol and thus regulate the LDL-cholesterol levels in humans. This mechanism is mediated by certain mechanisms like 1) Reducing the amount of cholesterol for absorption by solubilising it in the intestinal lumen, 2) Modifications in the expression of Niemann-Pick C1-like 1 protein which reduce cholesterol transport and promote its efflux from the enterocytes to the intestinal lumen, 3) Trans intestinal cholesterol excretion (TICE) removes the cholesterol from body [13]. In a preclinical study, male C57BL/6 J mice were administered with 3.1% PS and high-fat diet supplementation for three weeks shown a decrease in very-low density lipoprotein (VLDL) secretion [14]. PSs play a crucial role in neurodegenerative diseases. Phytosterols crosses the blood brain barrier and modifies the pathways related to neurodegeneration in the brain. Campesterol, beta sitosterol and stigmasterol are used as a prognostic biomarker for the neurodegenerative disorders like Alzheimer's disease [15]. Study performed by Rui *et al.* had documented that a high-cholesterol diet reduce the cognitive performance in animal models [16]. In this study, rats were fed for 6 mo with a high cholesterol diet and 2% g/100 g PS has shown reduced serum lipid levels, improved cognitive performance, triggered an increase in pyramidal cells number. Plasma and hepatic triglycerides (TG) levels were altered by the treatment with phytosterols in laboratory animals. In a study performed by Rideout *et al.*, Syrian golden hamsters fed with a high-fat diet and 2% w/w PSs for 6 w and their TG in blood plasma were found to be decreased [17].

PSs has the ability of promoting glucose metabolism by activating the AMP-activated kinase (AMPK) or peroxisome proliferator-activated receptors (PPARs) in transcriptional regulation pathways [18]. A limited rise in blood glucose scale after oral administration of high glucose concentration and increased insulin response was observed. Study performed on zucker diabetic fatty rats by giving 5-campestenone (0.6%) as dietary supplement has shown minimal rise in blood glucose scale with improved insulin response. ß-sitosterol (20 µM) administration also leads to rise in glucose intake by GLUT4 translocation to the plasma membrane [19]. A study in Db/Db mice fed with 0.3% 5-campestenone for eight weeks has documented a sharp decline in the blood glucose levels and inhibition of glucose elimination [20].

Phytosterols have anticancer properties which stimulates apoptosis by interaction with cell targets. A preclinical study on rats shows that beta sitosterol isolated from *Asclepias curassavica* L. has dose related effectiveness in colon rectal cancer [21]. Researches proved ß-sitosterol supplementation cause apoptosis by leading to an increase in FAS protein expression, caspase 8 and tumor necrosis factor in MCF-7 and MDA-MB-231 breast cancer cells [22]. ß-sitosterol and daucosterol from *Grewia tiliaefolia* have the ability to promote apoptosis in A549 lung cancer cells by arresting the cell cycle at the G2/M phase [23]. ß-sitosterol interferes with the DNA fragmentation in the cervical cancer cells in a dose dependent manner.

Phytosterols being similar in structure competes with cholesterol for absorption in the intestine and reduces the LDL cholesterol absorption leading to lipid lowering property [24]. Many formulations with suitable drug delivery vehicles are analysed for oral delivery of phytosterols without affecting its therapeutic efficacy. Formulations of phytosterols incorporated in lecithin micelles, water-dispersible phytosterols with fatty acids and polysorbate composition were able

to reduce the serum LDL-cholesterol more efficiently [25, 26]. Nano emulsions, nanoparticles, micro particles, microcapsules, and micelles are some of the formulation approaches used for phytosterols delivery [27]. However, besides increased therapeutic efficacy, the safety and tolerability of these formulations are concerned to phytosterols oxidation products. The prevention of phytosterols oxidation products in the formulation is the major challenge. The studies regarding the ability to reduce phytosterol oxidation products are insufficient [28].

Bioavailability of phytosterols

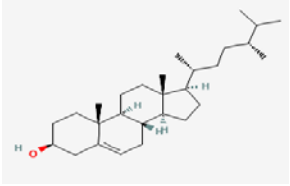
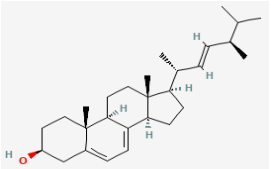
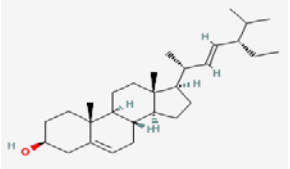
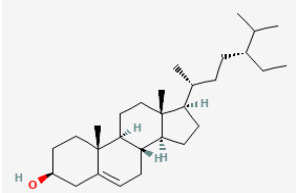
The most challenging part concerned about phytosterols was bioavailability. Phytosterols absorption and the concentration of circulation over the body were lesser in human intestine compared to cholesterol because of its selectivity and return through intestinal transporters [29]. The absorption of the phytosterols are influenced by several factors like solubility, chemical structure, type of phytosterol as steryl glycoside, sterol or stanol, hydrogenation process, preparation and genetic factors. Despite its studies on wide variety of interesting pharmacologic effects the bioavailability of phytosterols remain as a limiting aspect [30]. The presence of polycyclic nucleus, hydroxyl group at C-3 and C-17 side chain in the structure of phytosterols. The physical and chemical modification of phytosterols enhances the bioavailability. A biologically active substance could be customized into a nano scale delivery system in order to reach its target site. Chemical modification of PSs could be done by esterification and physical modification by microencapsulation. Low solubility and high melting point affects the bioavailability. Physical changes by encapsulation of phytosterols in nanodelivery systems favours dissolution in gastrointestinal tract and improve the bioavailability [31].

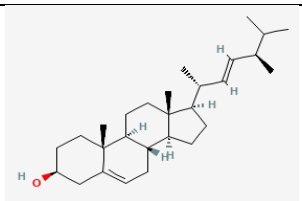
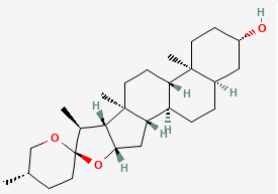
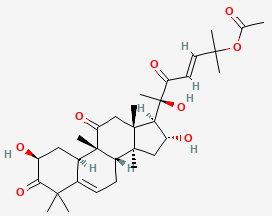
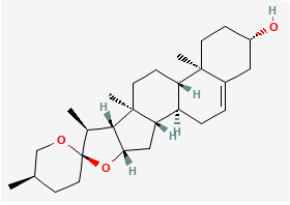
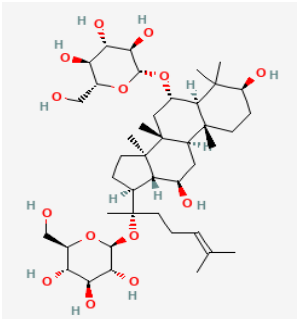
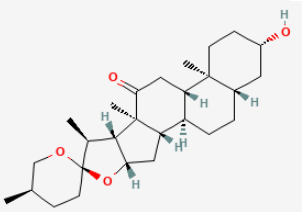
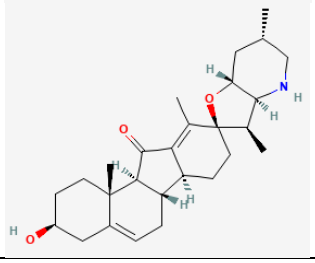
Systematic review of phytosterols selected for the study

16 phytosterols were selected in this study and the structures were obtained using chimera software table 1. The drug-likeness parameters like molecular weight and size, melting and boiling points, hydrogen bonding will determine the pharmacological behaviour a compound in aspects of its bioavailability, toxicity, metabolic activity, etc. Molinspiration cheminformatics tool is employed to evaluate the drug likeness properties of the selected phytosterol compounds [32]. The "drug likeness" is defined as the balance between molecular and structural properties of a chemical compound that determines whether that compound is considered as a "drug" [33]. Log P value is calculated for all the 16 selected compounds. The positive log P value indicates that the lipophilic nature (need to cross BBB). Most of the compounds exhibited high logP values indicating better lipophilic nature; except digitonin has negative value and 5 other compounds have log P values less than 5. The water solubility values of all the compounds were found to be negative; thus indicating their low hydrophilic nature table 2.

Swiss ADME software is employed in order to understand the pharmacokinetic and toxicity parameters of a lead compound in the initial drug discovery process itself so as to avoid hindrances in the later stages [34]. The ADME/Toxicity properties depend on the physicochemical parameters namely lipophilicity (logP), molecular weight, polar surface area, molar refractivity and water solubility. The intestinal absorption of orally active drug like compound is mostly assessed by Caco-2 cell model and MDCK (Madin Darby canine kidney) cell. The results of Caco-2 model were almost compatible with the standard human intestinal absorption values. The blood brain barrier penetration of a compound explains its therapeutic ability in the central nervous system; whereas, drug efficacy and disposition is well explained by the *in vitro* plasma protein binding model. Most of the compounds have their plasma protein binding values low; thus indicating their free distribution nature. Formulation and ease of handling of a chemical compound depends on its water solubility. Oral absorption of a drug is proportional to its water solubility; while, a parenteral drug must be highly water soluble to deliver its active constituents in small volumes. All the PSs shows negative values and hence moderately water soluble table 2.

Table 1: Physical properties

Plant steroids	Structure	Molecular formula	Molecular weight	Synonym	Log p	Boiling point	Melting point	Phase of the study	Therapeutic uses
Campesterol [1]		$C_{28}H_{48}O$	400.7	Campesterin, Campest-5-en-3beta-ol, Ergost-5-en-3-beta-ol	9.972	489.00 to 490.00 °C	157.5 °C	Observational studies [2, 3]	Diagnosis of sitosterolemia [4], for the prevention of cancers and cardio metabolic diseases [5], cholesterol absorption biomarker [6]
Ergosterol [7]		$C_{28}H_{44}O$	396.6	Provitamin D2, Ergosterin, ergosta-5,7,22-trien-3-ol	8.86	250 °C at 0.01 mmHg	170 °C		Biological precursor of vitamin D2, antirachitic vitamin
Stigmasterol [8]		$C_{29}H_{48}O$	412.7	Beta-stigmasterol, stigmasta-5,22-dien-3-ol, stigmasterin	9.43	501.1±19.0 °C at 760 mmHg	170 °C	Animal study [9], observational human studies [10-12]	Cholesterol lowering activity, anti-inflammatory action [13], anti-oxidant action [10]
Beta-Sitosterol [14]		$C_{29}H_{50}O$	414.7	Beta-sitosterol, Cupreol, cinchol, harzol, Rhamnol, Azuprostat, Prostatol, sobatum, beta-sitosterin	10.482	498 to 501 °C @760 mmHg	143.5 °C	Animal studies [15], observational human studies [16-19]	Anti-oxidant activity, anti-cancer property [15], mitigation of benign prostatic hyperplasia [18], cholesterol lowering activity [17].

Plant steroids	Structure	Molecular formula	Molecular weight	Synonym	Log p	Boiling point	Melting point	Phase of the study	Therapeutic uses
Brassicasterol [20]		$C_{28}H_{46}O$	398.7	Brassicasterin, ergosta-5,22E-dien-3-ol	9.679	488 to 489 °C@760 mmHg	150-151 °C	*In vitro* and in silico studies [21]	Anti-infective property, cerebrospinal fluid biomarker for Alzheimer's disease [22]
Sarsasapogenin [23]		$C_{27}H_{44}O_3$	416.6	Parigenin, Sarsagenin, Sarsapogenine	6.210	516.60 °C @760 mmHg	200-201.5 °C	*In vitro* studies [24]	Anti-tumor and anti-depressant activity [24], anti-amyloidogenic action in Alzheimer [25]
Cucurbitacin B [26]		$C_{32}H_{46}O_8$	558.7	Amarine, Datisca principle B, Cucurbitacin B hydrate		546.74 °C	184-186 °C	*In vitro* and *in vivo* [27, 28]	Anticancer activity [28, 29], inhibits colon cancer [27]
Diosgenin [30]		$C_{27}H_{42}O_3$	414.6	Nitogenin, dioscoreasapogenin, 3beta-hydroxy-5-spirostene	6.602	527.11 °C	205.5 °C	observational human studies [31-33]	Anticancer activity, anti-inflammatory and, anti-infective activity [34], neuroprotective action in Alzheimer's and Parkinson disease, enhances cognitive function [35]
Ginsenoside Rg1 [36]		$C_{42}H_{72}O_{14}$	801.0	Sanchinoside C1, Panaxoside A, dammarane, -D-glucopyranoside	1.670	902.70 °C @ 760 mmHg	315-318 °C	*In vitro* studies[37]	Antidiabetic effect, anti-inflammatory, hepatoprotective and Neuroprotective, Anti-angiopathy[37]
Hecogenin [38]		$C_{27}H_{42}O_4$	430.6	Hocogenin	4.22	548.9±50 °C at 760 mmHg	266.5 °C	Animal studies [39]	Anti-helminthic activity [39], anti-oxidant, anti-inflammatory action and gastro protective action [40]
Jervine [41]		$C_{27}H_{39}O_3$	425.6	Iervin, Jerwiny, 11-Ketocyclopamine	3.46	592.5±50 °C at 760 mmHg	243.5-244.5 °C	*In vitro* studies	It is teratogen that inhibits smoothened an integral part of hedgehog signalling pathways [42]

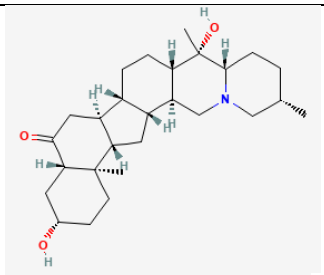
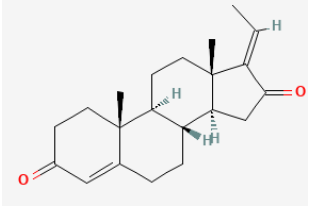
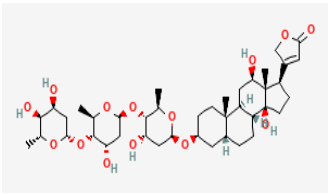
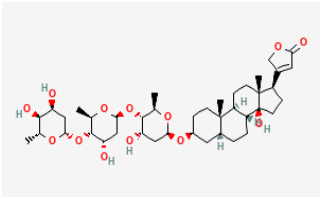
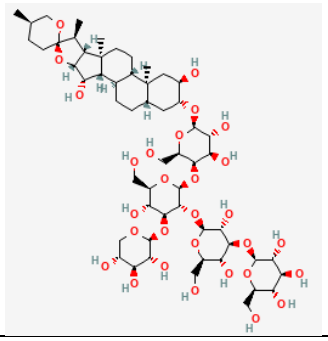
Plant steroids	Structure	Molecular formula	Molecular weight	Synonym	Log p	Boiling point	Melting point	Phase of the study	Therapeutic uses
Peiminine [43]		$C_{27}H_{43}NO_3$	429.6	Verticinone, Fritillarine, Zhebeinone, Raddeanine, Kashmirine, peininine	4.011	567±50 °C at 760 mmHg	212-213 °C	*In vitro* studies [44, 45]	Acts as chemo sensitizer for Adriamycin in gastric cancer [44],
Guggulsterone [46, 47]		$C_{21}H_{28}O_2$	312.45	Guggulsterones EandZ	3.65	463.3±45 °C at 760 mmHg	E isomer-170-171 °C Z isomer-188-190 °C	Observational and Animal study [48, 49]	Provides cardiovascular protective effect by its hypolipidemic, anti-inflammatory and anti-oxidant action [50], anti-cancer property [49]
Digoxin [51]		$C_{41}H_{64}O_{14}$	780.9	Lanoxin, digacin, davoxin, digosin, cardiogoxin, rougoxin, cordioxil, eudigox, lanacrist, vanoxin	2.37	931.60 °C @760.0 mmHg	230-265 °C	Observational studies [52-56]	For treatment of atrial fibrillation[54] chronic heart failure [53]
Digitoxin [57]		$C_{41}H_{64}O_{13}$	764.9	Digitoxoside, unidigin, Digitoksin, cardidigin, carditoxin, coramedan, crystodigin, carditalin, digitalin, digitrin	1.85	902± °C at 760 mmHg	493 to 495 °F 256-257 °C (anhydrous)	Observational studies [58-60], *In vitro* studies and animal study [61]	Antiarrhythmic agent [60], treatment for congestive heart failure [58, 59]
Digitonin [62]		$C_{56}H_{92}O_{29}$	1229.3	Digitin	230-240 °C	788.4 °C	446 to 464 °F	*In vitro* studies [63-66]	Biological detergent [65], induces membrane permeability [63]

Table 2: *In silico* predicted properties

S. No.	Plant steroids	Human intestinal absorption	CaCo-2	Bioavailability score	Ames mutagenesis	Water solubility Log S	Plasma protein biding (100%)	Acute oral toxicity (Kg/mol)	Molar refractivity	Lipophilicity Log $P_{o/w}$ (WLOGP)
1	Campesterol	0.9930	0.6088	0.585	0.8600	-4.81 Moderately soluble	1.109	3.138	128.42	7.63
2	Ergosterol	0.9950	0.6576	0.542	0.8400	-4.692 moderately soluble	1.018	3.706	127.47	7.33
3	Stigmasterol	0.9914	0.5455	0.5571	0.8300	-4.703 Moderately soluble	1.185	3.285	132.75	7.80
4	Sitosterol	0.9930	0.5385	0.5286	0.8700	-4.703 Poorly soluble	1.124	3.414	133.23	8.02
5	Brassicasterol	0.9914	0.6076	0.5714	0.8700	-4.692 Moderately soluble	1.116	3.195	127.95	7.41
6	Sarsasapogenin	0.9294	0.5138	0.5429	0.8100	-5.182 Moderately soluble	0.941	3.252	122.07	5.79

S. No.	Plant steroids	Human intestinal absorption	CaCo-2	Bioavailability score	Ames mutagenesis	Water solubility Log S	Plasma protein biding (100%)	Acute oral toxicity (Kg/mol)	Molar refractivity	Lipophilicyity Log $P_{o/w}$ (WLOGP)
7	Cucurbitacin B	0.9895	0.7257	0.6571	0.7200	-4.504 Moderately soluble	1.008	5.214	150.94	3.50
8	Diosgenin	0.9482	0.5112	0.6143	0.9100	-6.909 Moderately soluble	1.039	2.97	121.59	5.71
9	Ginsenoside	0.6476	0.8777	0.7571	0.7400	-4.303	0.853	3.993	205.81	1.12
10	Hecogenin	0.9357	0.5126	0.6429	0.7800	-4.59 Moderately soluble	0.774	3.012	122.27	4.97
11	Jervine	0.9789	0.5523	0.5143	0.6700	-3.999 Moderately soluble	0.96	3.327	127.21	3.80
12	Peiminine	0.9638	0.5621	0.5857	0.7000	-2.445 Soluble	1.008	3.332	128.33	3.51
13	Gugglusterone	0.9950	0.8896	0.5714	0.9500	-4.367	0.976	2.922	93.54	4.64
14	Digoxin	0.8851	0.9372	0.7143	0.7400	-4.336 Soluble	0.536	5.056	196.10	2.22
15	Digitoxin	0.8851	0.9257	0.8286	0.7500	-5.066 Soluble	1.055	5.237	194.94	3.25
16	Digitonin	-0.7034	0.8742	0.7571	0.7529	-3.414	0.733	5.015	280.34	-6.50

Table 3: Experimental pharmacokinetics

S. No.	Phytosteroids	AUC	Cmax	Tmax	t1/2	Volume of distribution	Clearance	Species	Route of administration	No. of subjects (n)	Dose	Bioavailability
1	Campesterol [69]	AUC_{0-t} 120±46.1 ng. h/ml	1250±512 ng/ml	72 (36-72 range) (h)	-	-	-	Rats	Oral	4	500 mg/kg insadol extract	-
2	Ergosterol [70]	$AUC_{(0-36h)}$ 22.29±5.08 (g h ml^{-1})	22.27±0.19 (g/ml)	8.00±1.18 (h)	5.90±1.41 (h)	-	-	Rat	Oral	6	100 mg/kg	-
3	Stigmasterol [69]	$AUC_{(0-\infty)}$ 21.8±7.86 ng h/ml	246±38.2 ng/ml	15(9 to72 range) (h)	-	-	-	Rat	Oral	4	500 mg/kg insadol extract	-
4	Beta-sitosterol [71]	$AUC_{0-\infty}$ 0.19 ng. h/ml	1.8 pg/ml	17.33 (h)	72.4 (h)	-	-	Humans	Oral	12	3.8-4.2 µg in 15 ml solution	0.41%
5	Sarsasapogenin [72]	AUC_{0-48} 17405±4398 ng h/ml	2114±362 ng/ml	6 (h)	8.7±2.2 (h)	-	-	Rats	Oral	6	25 mg/kg	-
6	Cucurbitacin B [73]	$AUC_{0-\infty}$ 52.42±29.58	31.24±10.50 µg/l	0.60±0.22 (h)	N/A	-	-	Rats	Oral	6	4 mg/kg	10.25±5.63 %
7	Diosgenin [74]	$AUC_{0-\infty}$ 4.475±0.06 µg h/ml	0.5773±0.012 µg/ml	1 (h)	7.563±0.21 (h)	-	2.5143±0.09 ml/h/kg	Rats	Oral	6	15 mg/kg	9±0.2 %
		$AUC_{0-\infty}$ 4.957±0.44 µg h/ml	0.6122±0.1 µg/ml	-	7.930±0.37 (h)	2.539±0.57 ml/kg	0.222±0.05 ml/h/kg	Rats	Intravenous single dose	6	1.5 mg/kg	-
8	Ginsenoside [75]	$AUC_{0-\infty}$ 279.70±81.84 µg/l. h	35.38±10.33 µg/l	4.29±0.76 (h)	3.09±1.64 (h)	848.16±487.89 L/kg	189.36±43.49 L/h/kg	Rats	Oral	6	50 mg/kg	4.23 %
		$AUC_{0-\infty}$ 661.31±151.78 µg/l. h	534.97±105.40 µg/l	-	6.35±4.04 (h)	69.23±41.13 L/kg	7.88±1.99 L/h/kg		Intravenous	6	5 mg/kg	
9	Jervine [76]	$AUC_{0-\infty}$ 5547.95±558.34 µg/l. h	233.30±30.37 ng/l	1.20±0.73 (h)	11.09±2.35 (h)	115.24±19.46 L/kg	7.26±0.68 L/h/kg	Rats	Oral	6	40 mg/kg	
		$AUC_{0-\infty}$ 1289.67±318.46 µg/l. h	138.40±19.31 ng/l	0.13±0.08 (h)	8.35±5.15 (h)	44.15±18.11 L/kg	4.03±0.80 L/h/kg		Intravenous	6	5 mg/kg	60.02
10	Peiminine [77]	$AUC_{0-\infty}$ 367.2±22.35 ng h/l	68.80±1.63 ng/ml	1.83±0.72 (h)	3.012±0.16 (h)			Beagle dog	Oral	12	1 g/kg *Fritillariaussuriensis powder*	
11	E-Guggluste rone [78]	$AUC_{0-\infty}$ 40.36±6.47 ng. h/ml			0.23±0.01 (h)	41.87±3.95 L/kg	129.06±13.81L/h/kg	Rabbit	Intravenous	3	10 mg/kg	
	Z-Guggulsterone	$AUC_{0-\infty}$ 20.34±6.2 ng. h/ml			0.35±0.10 (h)	145.09±60.6 L/kg						
12	Digoxin [79]	$AUC_{(0-24h)}$ 25.4±6.0 ng. h/ml	$AUC_{(0-\infty)}$ 61±13.1 ng. h/ml	3.7±1.7 ng/ml	1.6±1.2 (h)	38±6.1 (h)		Human	Oral	7	1 mg	
13	Digitoxin [80]				138 (h)			Human study	Oral	6	1 mg	81.5±19.7%
					156 (h)	0.47±0.07 L/kg	2.44±0.82 ml/min		Intravenous			

In silico toxicity prediction holds a great importance in the early drug discovery process as 30-40% of the drug compounds would be rejected at the development stage due to their unidentified toxicities. Ames test is a simple and reliable method to test mutagen city of a compound [35]. It utilises bacterium *Salmonella typhimurium* strains that carry mutations in genes for histidine synthesis. The lead compound is tested whether it has the ability to cause a reversion to growth on a histidine free medium. The values in the Ames test result have shown their minimal toxicity.

Bai *et al.*, 2018 assessed the *in vivo* pharmacokinetic (PK) properties of the phytosterol compounds [36, 37]. In this study, male wistar rats of 250-280 gm weight were procured housed in stainless steel cages (3 rats/cage) with room temperature and 12-h light/dark cycle. The rats were fed with standard pellets for a week and were fasted overnight before the commencement of experiments. Pentobarbital (50 mg/kg I. P) to anesthetize the rats, carotid artery cannulated and the blood samples collected in heparin tubes for 0, 15, and 30 min and 1, 2, 4, 6, 8, 10, 12, and 24 h after the oral administration of PSs individually. The blood samples were centrifuged (16,000g, 5 min) and the plasma was separated and stored at 80 °C. The peak plasma concentrations (Cmax) and the time required to reach Cmax (Tmax) of PSs were recorded. The area under the concentration-time curve (AUC) was calculated from the values obtained during 0 to 24 hr using the trapezoidal rule [37]. The half-life (t1/2) was calculated by using the apparent elimination rate constant obtained from the elimination phase gradient. All the data was expressed as mean SD M and the significance was measured by student's T-test and one-way ANOVA. The significance level was set at p less than 0.05. Using these values, the clearance, volume of distribution and oral bioavailability (BA) were calculated using the non-compartmental analysis (NCA) software PK Solutions version 2.0. All these pharmacokinetic results help the researcher to design the dosing calculations for clinical trials (table 3).

CONCLUSION

In view of the less bioavailability of phytosterols, physical or chemical modification can be applied to increase their bioavailability. Chemical modification has focussed majorly on esterification and physical modification has been attained by microencapsulation method. A physical modification by encapsulation process of phytosterols in nanodelivery system favours dissolution in gastrointestinal tract and enhances the bioavailability. By designing a delivery system, the biologically active substance can be delivered to its specific absorption site. The superiority of this system is that it can decrease the loss of biologically active substances prior to reaching the absorption site to enhance the bioavailability of the compound. The Swiss ADME Web tool used in the study helped in computation of key pharmacokinetic, physicochemical, drug-like and related parameters for one or more molecules. In one attempt, efforts were put in the application to implant free open-access and rapid predictive models exhibiting statistical predictive power, significance, straightforward translation to molecular design and intuitive interpretation,. These methods were adapted from renowned published papers or in-house original methods, especially developed and thoroughly benchmarked. When investigated together, these methods help the researchers to design their studies for improving the bioavailability of phytosterols.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

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