Pharmacokinetic Properties of Biomass-extracted Substances Isolated by Green Solvents

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According to the literature, approximately 41 nutraceutical compounds have been isolated from different types of biomass using green solvents. It is important to collect information on the pharmacokinetic properties of the nutraceutical substances from biomass isolated according to the published papers. The pharmacokinetic properties of the bioactive substances extracted by green solvents, such as the molecular weight, log*P*, *A*log*P*, H-bond acceptor, H-bond donor, total polar surface area, atom molar refractivity, number of rotatable bonds, number of atoms, rotatable bond count, number of rigid bonds, number of atom rings, and number of H-bonds, were calculated with a drug-likeness tool. In practical terms, the original and most well-known Lipinski's Rule of Five (Ro5) was applied to 28 substances, namely 3-hydroxytyrosol; apigenin; artemisinin; bergapten; bilobalide; biochanin A; caffeic Acid; caffeoylmalic acid; catechins; cinnamic acid; curcumin; daidzei; daidzin; epicatechin; gallic acid; genistein; ginkgolide A; ginkgolide B; levofloxacin; luteolin; naringenin; *p*-coumaric acid; protocatechuic acid; psoralen; quercetin; *trans*-ferulic acid; tyrosol, and vanillin.

Keywords: Green solvents; Deep eutectic solvents; Pharmacokinetic properties; Nutraceutical compounds

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INTRODUCTION

Over the past few decades, a lot of research has been done that has shown biomass feedstocks to have remarkable potential. The revealed potential is associated with the isolation of biologically and pharmacologically active substances. Also, these biomass-extracted compounds have numerous promising applications. Several papers have been published on the biological activities, characteristics, and functions of these substances in the pharma and food industries. Biomass is a source of non-polar and polar chemical compounds, such as fats, saturated and unsaturated fatty acids, resins, resin acids, waxes, flavonoids, terpenoids, stilbenes, ligands, alkaloids, and phenolic and polyphenolic compounds. Extracted compounds have antioxidant, antimycotic, cytotoxic, antiviral, antitumor, antimalarial, insecticidal, antimutagenic, tumorigenic, pharmacokinetic activities, and other properties (Jablonsky *et al.* 2017). The physical properties and predicted absorption, distribution, metabolism, and excretion properties of 237 extractives have been discussed in a recently published study by Jablonsky *et al.* (2017). Most of these substances may be used as fine chemicals, and some have already

been used for pharmacological purposes. Extracts isolated from softwood barks contain hundreds of natural products, some of which have cytotoxic (25 identified substances), antioxidant (26 substances), fungicidal (20 substances), and antibacterial (42 substances) properties. Additionally, some of these substances are repellents (nine substances) and antifeedants (two substances), while others may cause growth inhibition (eight substances), increase the activity of pheromones, or act as pheromones (10 substances) (Jablonsky *et al.* 2017). Natural substances play a vital role in the prevention and cure of various diseases, such as cancer, Alzheimer's, Parkinson's disease, and other neuronal dysfunctions. Recently published works have indicated that phytochemicals containing polyphenolic antioxidants might potentially hinder neurodegeneration, and improve memory and cognitive functions (Alam *et al.* 2018).

Information on the pharmacokinetic properties obtained with various prediction software programs could be used to design drug molecules for various applications with an optimum bioavailability and low or null toxicity (Singh 2016). The IUPAC definition of *Pharmacokinetics* is: Process of the uptake of drugs by the body, the biotransformation they undergo, the distribution of the drugs and their metabolites in the tissues, and the elimination of the drugs and their metabolites from the body over a period of time. Knowledge of pharmacokinetic principles helps prescribers adjust dosage more accurately and rapidly (IUPAC 1997). In the field of biomass and biowaste valorization, a number of techniques associated with green solvents are used, and their strong and weak points have been evaluated and reviewed (Mbous *et al.* 2017; Shishov *et al.* 2017; Zainal-Abidin *et al.* 2017; Fernández *et al.* 2018; Jablonsky *et al.* 2018).

This work focused on the use of deep eutectic solvents (DESs), natural deep eutectic solvents (NADESs), and low-transition temperature mixtures (LTTMs) from recently published works to extract compounds from biomass and evaluated their pharmacokinetic properties.

EXPERIMENTAL

This paper is not of experimental character. Rather, it evaluates theoretically the pharmacokinetic properties of known compounds exhibiting potential for pharmaceutical application as drugs. All the mentioned compounds were previously extracted using DESs by the following authors from the mentioned kinds of plant-based biomass: *Trachycarpus fortune* (protocatechuic acid, catechins, epicatechin, and caffeic acid) (Fu *et al.* 2017); onions, olives, tomatoes, and pears (3-hydroxytyrosol, *p*-coumaric acid, apigenin, gallic acid, naringenin, caffeic acid, tyrosol, luteolin, and *trans*-ferulic acid) (Fernández *et al.* 2018); spike samples (genistein, daidzein, genistin, biochanin A, and daidzin) (Bajkacz and Adamek 2017); *Ginkgo biloba* (ginkgolide A, ginkgolide B, bilobalide, and ginkgolide C) (Su *et al.* 2017); *Ficus carica* L. (caffeoylmalic acid, rutin, psoralen, and bergapten) (Wang *et al.* 2017); *Moringa oleifera* Lam. leaves (chlorogenic acid, multiflorin B, apigenin C-glycoside, quercetin glycoside, and kaempferol malonylglucoside) (Karageorgou *et al.* 2017); olive (*Olea europaea*) leaves (oleuropein and luteolin) (Dedousi *et al.* 2017); *Platycladi cacumen* (myricitrin, quercitrin, amentoflavone, and hinokiflaveno) (Zhuang *et al.* 2017); *Artemisia annua* leaves (Cao *et al.* 2017); food and herbal tea samples (curcumin) (Aydin *et al.* 2018); pigeon pea roots

(genistin, genistein, and apigenin) (Cui *et al*. 2015); Tartary buckwheat hull (rutin) (Huang *et al*. 2017); and vanillin pods (vanillin) (González *et al*. 2018).

Basic Pharmacokinetic Parameters

The basic pharmacokinetic properties of the extractive substances, including the molecular weight (M_w), partition coefficient (log*P*), octanol-water partition coefficient (*A*log*P*), H-bond acceptor (HBA), H-bond donor (HBD), total polar surface area (TPSA), atom molar refractivity (AMR), number of rotatable bonds (nRB), rotatable bond count (RC), number of rigid bonds (nRigidB), and number of hydrogen bonds (nHB), were calculated with the drug-likeness tool (DruLiTo 2018) (NIPER S.A.S., Nagar, India). All of the rules were applied independently of each other. The calculations were performed according to standard procedures described elsewhere (DruLiTo 2018).

Table 1. Parameters and Criteria for all the Rules and Filters

Filters/Rules	Criteria	Calculation
Lipinski´s rules	No. of Hydrogen bond donors ≤ 5 No. of Hydrogen bond acceptor ≤ 10 Molecular weight ≤ 500 ClogP ≤ 5	
MDDR-like rule	No. of Rings ≥ 3 No. of Rigid bonds ≥ 18 No. of Rotatable bonds ≥ 6	
Veber´s rule	No. of Rotatable bonds ≤ 10 Polar surface area ≤ 140	
Ghose filter	logP (-0.4 – 5.6) Molar refractivity (40 – 130) Molecular weight (160 – 480) Number of Atoms (20 – 70) Polar surface area < 140	
BBB rule	No. of hydrogen bonds (8-10) Molecular weight (400 -500) No acids	
CMC-50 like rule	AlogP (1.3 – 4.1) Molecular refractivity (70 – 110) Molecular weight (230 – 390) Number of Atoms (30 – 55)	
wQED	Molecular weight AlogP No. of Hydrogen-bond acceptors No. of Hydrogen-bond donors No. of Rotatable bonds Polar surface area No. of Aromatic bond count No. of Structural alerts	$wQED = \exp(\frac{\sum_{i=1}^{n} w_i \ln\ d_i}{\sum_{i=1}^{n} w_i})$ where *d* is the individual desirability function, *w* is the weight applied to each function and *n* is the number of descriptors (Bickerton *et al*. 2012)
UwQED	Molecular weight AlogP No. of Hydrogen-bond acceptors No. of Hydrogen-bond donors No. of Rotatable bonds Polar surface area No. of Aromatic bond count No. of Structural alerts	$UwQED = \exp(\frac{1}{n}\sum_{i=1}^{n} \ln\ d_i)$ where *d* is the individual desirability function, and *n* is the number of descriptors (Bickerton *et al*. 2012)

RESULTS AND DISCUSSION

Biomass extractive compounds are widely applied in the food, pharma, wood, furniture, and chemical industries, and they serve many purposes. The development and wide utilization of new green solvent systems (DES, NADES, and LTTM) in obtaining value-added substances support their introduction into various fields, such as the food, chemical, pharmaceutical, cosmetic, and waste processing industries. Case studies have documented instances of isolating interesting compounds by more selective ways. Substances isolable from natural sources (algae, plants, food leftovers, waste from industrial processing of biomass, *etc.*) by green solvents, particularly solvents originating from natural metabolites, have a chance to be utilized in pure and applied pharmacological research of new drugs and their use in practical applications. Bioactive compounds formed in plants result from complex metabolic processes, and their extraction hides some potential benefits. These benefits come from the compounds present in the contexture of plants and fruits that are extracted by naturally occurring substances (NADESs) and are thus fully compatible with the extracted material. The extracted substances may thus show better properties than those extracted by conventional solvents. Polyphenolic substances in particular, but also other types of compounds have remarkably important physiological properties. From this viewpoint, it is important to collect information on the pharmacokinetic properties of substances isolated by green solvent systems.

In a broad sense, the basic pharmacokinetic properties of bioactive substances extracted by DESs, NADESs, and LTTMs include the M_w, log*P*, *A*log*P*, HBA, HBD, TPSA, AMR, nRB, RC, nRigidB, and nHB. The values of these properties were calculated by DruLiTo techniques (Daina *et al.* 2017). The log*P* is a key parameter in studies into the environmental fate of chemicals and for the molecular hydrophobicity. Hydrophobicity affects the drug/cure absorption, bioavailability, hydrophobic drug interaction with a receptor, molecule metabolism, and toxicity (Swamy *et al.* 2011). A log*P* value less than 5 was prioritized for a drug-likeness feature. Restrictions for using the HBA, HBD, log*P*, and M_w were stipulated by Lipinski *et al.* (2001), which helped in introducing other parameters, *e.g.*, those characterizing the experimental data on transport. An interesting and useful parameter is the knowledge of the behaviour of polar atoms in a molecule that defines the TPSA, according to Lipinski's rule of five or simply the rule of five (Ro5), which is a rule of thumb to evaluate the drug-likeness or determine whether a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. This parameter predicted the absorption of substances and transport data. Calculations with DruLiTo are dependent on various drug-likeness rules, namely Lipinski's rule, Veber's rule, Ghose filter, the BBB rule, CMC-50 like rule, and quantitative estimate of the drug-likeness (QED). Taking these rules and restrictions into account allows for a direct research orientation to determine selected substances that have the required parameters and apply them in a purposefully specified field of application or for further research (Daina *et al.* 2017).

The results obtained in the evaluation of 41 compounds by means of the mentioned rules or screenings are displayed in Table 2. From the data, 28 of the 41 compounds were extracted by DESs, NADEs, or LTTMs and met the requirement of Lipinski's rule. From Lipinski's rule, further development of extraction using DESs,

NADESs, and LTTMs should be oriented for substances meeting the following requirements: $M_w \leq 500$; log$P \leq 5$; HBD ≤ 5; and HBA ≤ 10 (Table 1, bold compounds). The TPSA determines the bioavailability of natural substances per Veber's rule for good oral bioavailability, which stipulates a number of rotatable bonds less than or equal to 10 and a TPSA less than or equal to 140 Å (Veber *et al.* 2002). When using a Ghose filter, the substances should fulfil the following requirements: M_w of 160 g/mol to 480 g/mol; log*P* of 0.4 to 5.6; atom count of 20 to 70; and refractivity of 40 to 130. There were up to 28 compounds that satisfied these requirements. Exploiting the virtual screening tool DruLiTo, the substances were evaluated by taking other rules and filters into account (Table 3). From the entire set of compounds, 28 compounds followed the Ro5 parameters, while 13 compounds (amentoflavone; apigenin 8-C-glycoside; genistin; ginkgolide C; hinokiflaveno; chlorogenic acid; kaempferol malonylglucoside; multiflorin B; myricitrin; oleuropein; quercetin diglycoside; quercitrin; and rutin) violated more than one of the rules. The latter substances can create problems in oral bioavailability. Twenty-five compounds out of the 41 compounds were orally bioavailable, which fulfilled the desired criteria of the Ghose Filter and Veber's rule. They are denoted "1" to have passed the criterion for the given rule in Table 3. To be able to develop new drugs from these extractable compounds, the compounds should not only have a specific biological activity, but also have to exhibit therapeutic properties and the preferred pharmacokinetic profiles (Jablonsky *et al.* 2017). Lipinski´s Ro5 is used most commonly the assessment of drug-likeness, mainly traction in early-stage drug discovery because it is predictive, intuitive, and simple (Bickerton *et al.* 2012). An interesting parameter is QED. It can be used to rank chemical structures by their merit relative to target functions, which in this case are the properties of oral drugs. QED provides a different concept and generally unfavourable property may be tolerated such as are other parameters favourable. Thirty-three compounds out of the 41 compounds fulfilled the UwQED rules and 36 compounds were favourable for wQED rule (Tables 3 and 4).

Table 2. Drug-likeness Tool Descriptors Calculated by the DruLiTo Application

Compound	M_w	log*P*	*A*log*P*	HB A	HB D	TPSA	AMR	No. RB	No. Atom	RC	No. Rigid Bond	No. Arom Ring	No. HB
3-Hydroxytyrosol	154.06	0.385	-0.112	3	3	60.69	44.68	2	21	1	9	1	6
Amentoflavone	538.09	2.3	-0.839	10	6	173.98	157.86	3	58	6	42	4	16
Apigenin	270.05	1.138	-0.224	5	3	86.99	80.15	1	30	3	21	2	8
Apigenin 8-C-Glycoside	432.11	-0.707	-2.655	10	7	177.14	112.51	3	51	4	31	2	17
Artemisinin	282.15	3.039	0.801	5	0	53.99	61.35	0	42	4	23	0	5
Bergapten	216.04	1.337	-0.317	4	0	44.76	61.53	1	24	3	17	2	4
Bilobalide	326.1	-0.166	-0.447	8	2	119.36	69.57	1	41	4	25	0	10
Biochanin A	284.07	1.364	-0.323	5	2	75.99	83.96	2	33	3	21	2	7
Caffeic Acid	180.04	0.888	0.203	4	3	77.76	50.41	2	21	1	11	1	7
Caffeoylmalic Acid	296.05	0.234	-0.25	8	4	141.36	71.79	7	33	1	14	1	12
Catechins	290.08	0.852	-0.936	6	5	110.38	81.07	1	35	3	22	2	11
Cinnamic Acid	148.05	1.887	1.329	2	1	37.3	47.2	2	19	1	9	1	3
Curcumin	368.13	1.945	0.522	6	2	93.06	111.7	8	47	2	20	2	8
Daidzei	254.06	1.124	0.176	4	2	66.76	77.32	1	29	3	20	2	6
Daidzin	416.11	-0.182	-1.915	9	5	145.91	110.02	4	50	4	29	2	14
Epicatechin	290.08	0.852	-0.936	6	5	110.38	81.07	1	35	3	22	2	11
Gallic Acid	170.02	0.964	-0.721	5	4	97.99	41.77	1	18	1	11	1	9
Genistein	270.05	1.043	-0.387	5	3	86.99	78.92	1	30	3	21	2	8
Genistin	432.11	-0.263	-2.478	10	6	166.14	111.62	4	51	4	30	2	16
Ginkgolide A	408.14	1.176	-0.745	9	2	128.59	90.34	1	53	6	33	0	11
Ginkgolide B	424.14	0.146	-1.318	10	3	148.82	91.44	1	54	6	34	0	13
Ginkgolide C	440.13	-1.095	-2.084	11	4	169.05	92.95	1	55	6	35	0	15
Hinokiflaveno	538.09	2.466	-0.933	10	5	162.98	158.97	4	58	6	41	4	15
Chlorogenic Acid	354.1	-0.7	-1.194	9	6	164.75	85.8	5	43	2	21	1	15
Kaempferol Malonylglucoside	534.1	-0.157	-2.607	14	7	229.74	130.03	8	60	4	33	2	21
Levofloxacin	361.14	1.995	-0.928	7	1	73.32	97.62	2	46	4	27	1	8
Luteolin	286.05	1.486	-0.787	6	4	107.22	81.76	1	31	3	22	2	10
Multiflorin B	594.16	-1.083	-4.018	15	9	245.29	145.57	6	72	5	40	2	24
Myricitrin	464.1	1.15	-3.398	12	8	206.6	116.37	3	53	4	33	2	20
Naringenin	272.07	0.79	-0.154	5	3	86.99	78.53	1	32	3	21	2	8
Oleuropein	540.18	-0.072	-1.593	13	6	201.67	131.67	11	70	3	29	1	19
p-Coumaric Acid	164.05	0.751	0.766	3	2	57.53	48.8	2	20	1	10	1	5
Protocatechuic Acid	154.03	0.616	-0.158	4	3	77.76	40.17	1	17	1	10	1	7
Psoralen	186.03	1.097	0.181	3	0	35.53	54.89	0	20	3	16	2	3
Quercetin	302.04	1.834	-1.244	7	5	127.45	83.44	1	32	3	23	2	12
Quercetin Diglycoside	626.15	-1.207	-5.425	17	11	285.75	148.84	7	74	5	41	2	28
Quercitrin	448.1	0.802	-2.835	11	7	186.37	114.76	3	52	4	32	2	18
Rutin	610.15	-0.735	-4.581	16	10	265.52	147.17	6	73	5	41	2	26

***trans*-Ferulic Acid**	194.06	0.78	0.267	4	2	66.76	55.45	3	24	1	11	1	6
Tyrosol	138.07	0.037	0.452	2	2	40.46	43.07	2	20	1	8	1	4
Vanillin	152.05	0.589	-0.046	3	1	46.53	44.28	2	19	1	9	1	4

Table 3. Application of Different Rules/Filters for the Properties Calculated by the DruLiTo Application

Compound	Lipinski's Rule	Ghose Filter	CMC-50 Like Rule	Veb-er's Rule	MDDR Like Rule	BBB Like-ness	Uw QED	W QED
3-Hydroxytyrosol	1	0	0	1	0	1	1	1
Amentoflavone	0	0	0	0	0	0	1	1
Apigenin	1	1	0	1	0	1	1	1
Apigenin 8-C-Glycoside	0	1	0	0	0	0	1	1
Artemisinin	1	1	0	1	0	1	1	1
Bergapten	1	1	0	1	0	1	1	1
Bilobalide	1	1	0	1	0	0	1	1
Biochanin A	1	1	1	1	0	1	1	1
Caffeic Acid	1	1	0	1	0	0	1	1
Caffeoylmalic Acid	1	1	0	0	0	0	1	1
Catechins	1	1	0	1	0	0	1	1
Cinnamic Acid	1	0	0	1	0	1	1	1
Curcumin	1	1	1	1	0	1	1	1
Daidzei	1	1	0	1	0	1	1	1
Daidzin	1	1	0	0	0	0	1	1
Epicatechin	1	1	0	1	0	0	1	1
Gallic Acid	1	0	0	1	0	0	1	1
Genistein	1	1	0	1	0	1	1	1
Genistin	0	0	0	0	0	0	1	1
Ginkgolide A	1	1	0	1	0	0	1	1
Ginkgolide B	1	1	0	0	0	0	1	1
Ginkgolide C	0	0	0	0	0	0	1	1
Hinokiflaveno	0	0	0	0	0	0	0	1
Chlorogenic Acid	0	0	0	0	0	0	1	1
Kaempferol Malonylglucoside	0	0	0	0	1	0	0	0
Levofloxacin	1	1	1	1	0	0	1	1
Luteolin	1	1	1	1	0	0	1	1
Multiflorin B	0	0	0	0	1	0	0	0
Myricitrin	0	1	0	0	0	0	0	1
Naringenin	1	1	0	1	0	1	1	1
Oleuropein	0	0	0	0	1	0	0	0
p-Coumaric Acid	1	1	0	1	0	0	1	1
Protocatechuic Acid	1	0	0	1	0	1	1	1
Psoralen	1	1	0	1	0	1	1	1
Quercetin	1	1	1	1	0	0	1	1
Quercetin Diglycoside	0	0	0	0	1	0	0	0
Quercitrin	0	1	0	0	0	0	0	1
Rutin	0	0	0	0	1	0	0	0
trans-Ferulic Acid	1	1	0	1	0	0	1	1
Tyrosol	1	0	0	1	0	0	1	1
Vanillin	1	0	0	1	0	0	1	1

UwQED – Unweighted Quantitative Estimate of Druglikeness; wQED –Weighted Quantitative Estimate of Druglikeness; The substance that is passed through the filter "1" or violated rules "0"

Table 4. Summary Results of Total Number of the Candidate Among the Molecules Passing and Violating all the Rules

Selected Filters	Total Number of Molecule Filter	Total Number of Molecule Violated the Rules
Lipinski's Rule	28	13
Ghose Filter	25	16
CMC-50 Like Rule	5	36
Veber's Rule	25	16
MDDR Like Rule	5	36
BBB Likeness	12	29
UwQED	33	8
wQED	36	5

CONCLUSIONS

1. The computed pharmacokinetic properties of biomass-extracted substances are key parameters for further progress and spreading of breakthrough technology for the extraction of biologically and pharmacologically active substances.
2. Twenty-eight compounds out of the 41 compounds considered were orally bioavailable, which fulfilled the desired criteria of the Ro5 (3-Hydroxytyrosol; Apigenin; Artemisinin; Bergapten; Bilobalide; Biochanin A; Caffeic Acid; Caffeoylmalic Acid; Catechins; Cinnamic Acid; Curcumin; Daidzei; Daidzin; Epicatechin; Gallic Acid; Genistein; Ginkgolide A; Ginkgolide B; Levofloxacin; Luteolin; Naringenin; p-Coumaric Acid; Protocatechuic Acid; Psoralen; Quercetin; trans-Ferulic Acid; Tyrosol and Vanillin) and 25 compounds fulfilled the desired criteria of the Ghose Filter and Veber's rule.

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REFERENCES CITED

Alam, A., Tamkeen, N., Imam, N., Farooqui, A., Ahmed, M. M., Tazyeen, S., Ali, S., Malik, M. Z., and Ishrat, R. (2018). "Pharmacokinetic and molecular docking studies of plant-derived natural compounds to exploring potential anti-Alzheimer activity," in: *In Silico Approach for Sustainable Agriculture*, D. K. Choudhary, M. Kumar, R. Prasad, and V. Kumar (eds.), Springer, Singapore, Singapore, pp. 217-238.

Aydin, F., Yilmaz, E., and Soylak, M. (2018). "Vortex assisted deep eutectic solvent (DES)-emulsification liquid-liquid microextraction of trace curcumin in food and herbal tea samples," *Food Chem.* 243, 442-447. DOI: 10.1016/j.foodchem.2017.09.154

Bajkacz, S., and Adamek, J. (2017). "Evaluation of new natural deep eutectic solvents for the extraction of isoflavones from soy products," *Talanta* 168, 329-335. DOI: 10.1016/j.talanta.2017.02.065

Bickerton, G. R., Paolini, G. V., Besnard, J., Muresan, S., and Hopkins, A. L. (2012). "Quantifying the chemical beauty of drugs," *Nature Chemistry* 4(2), 90-98. DOI: 10.1038/NCHEM.1243

Cao, J., Yang, M., Cao, F., Wang, J., and Su, E. (2017). "Well-designed hydrophobic deep eutectic solvents as green and efficient media for the extraction of artemisinin from *Artemisia annua* leaves," *ACS Sustain. Chem. Eng.* 5(4), 3270-3278. DOI: 10.1021/acssuschemeng.6b03092

Cui, Q., Peng, X., Yao, X.-H., Wei, Z.-F., Luo, M., Wang, W., Zhao, C.-J., Fu, Y.-J., and Zu, Y.-G. (2015). "Deep eutectic solvent-based microwave-assisted extraction of genistin, genistein and apigenin from pigeon pea roots," *Sep. Purif. Technol.* 150, 63-72. DOI: 10.1016/j.seppur.2015.06.026

Daina, A., Michielin, O., and Zoete, V. (2017). "SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules," *Sci. Rep.-UK* 7. DOI: 10.1038/srep42717

Dedousi, M., Mamoudaki, V., Grigorakis, S., and Makris, D. P. (2017). "Ultrasound-assisted extraction of polyphenolic antioxidants from olive (*Olea europaea*) leaves using a novel glycerol/sodium-potassium tartrate low-transition temperature mixture (LTTM)," *Environments* 4(2), 31. DOI: 10.3390/environments4020031

DruLiTo (2018). http://www.niper.gov.in/pi_dev_tools/DruLiToWeb/DruLiTo_Download.html, Accessed on October 10th, 2018.

Fernández, M. d. l. Á., Espino, M., Gomez, F. J. V., and Silva, M. F. (2018). "Novel approaches mediated by tailor-made green solvents for the extraction of phenolic compounds from agro-food industrial by-products," *Food Chem.* 239, 671-678. DOI: 10.1016/j.foodchem.2017.06.150

Fu, N., Lv, R., Guo, Z., Guo, Y., You, X., Tang, B., Han, D., Yan, H., and Row, K. H. (2017). "Environmentally friendly and non-polluting solvent pretreatment of palm samples for polyphenol analysis using choline chloride deep eutectic solvents," *J. Chromatogr. A* 1492, 1-11. DOI: 10.1016/j.chroma.2017.02.036

González, C. G., Mustafa, N. R., Wilson, E. G., Verpoorte, R., and Choi, Y. H. (2018). "Application of natural deep eutectic solvents for the "green" extraction of vanillin from vanilla pods," *Flavour Frag. J.* 33(1), 91-96. DOI: 10.1002/ffj.3425

Huang, Y., Feng, F., Jiang, J., Qiao, Y., Wu, T., Voglmeir, J., and Chen, Z.-G. (2017). "Green and efficient extraction of rutin from tartary buckwheat hull by using natural deep eutectic solvents," *Food Chem.* 221, 1400-1405. DOI: 10.1016/j.foodchem.2016.11.013

IUPAC. (1997). *Compendium of Chemical Terminology*, 2nd Ed. (the "Gold Book"). Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford. DOI: 10.1351/goldbook

Jablonsky, M., Nosalova, J., Sladkova, A., Haz, A., Kreps, F., Valka, J., Miertus, S., Frecer, V., Ondrejovic, M., Sima, J., *et al.* (2017). "Valorisation of softwood bark through extraction of utilizable chemicals. A review," *Biotechnol. Adv.* 35(6), 726-750. DOI: 10.1016/j.biotechadv.2017.07.007

Jablonsky, M., Škulcová, A., Malvis, A., and Šima, J. (2018). "Extraction of value-added components from food industry based and agro-forest biowastes by deep eutectic solvents," *J. Biotechnol.* 282, 46-66. DOI: 10.1016/j.jbiotec.2018.06.349

Karageorgou, I., Grigorakis, S., Lalas, S., and Makris, D. P. (2017). "Enhanced extraction of antioxidant polyphenols from *Moringa oleifera* Lam. leaves using a biomolecule-based low-transition temperature mixture," *Eur. Food Res. Technol.* 243(10), 1839-1848. DOI: 10.1007/s00217-017-2887-1

Lipinski, C. A., Lombardo, F., Dominy, B. W., and Feeney, P. J. (2001). "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings," *Adv. Drug Deliver. Rev.* 46(1-3), 3-26. DOI: 10.1016/S0169-409X(00)00129-0

Mbous, Y. P., Hayyan, M., Hayyan, A., Wong, W. F., Hashim, M. A., and Looi, C. Y. (2017). "Applications of deep eutectic solvents in biotechnology and bioengineering—Promises and challenges," *Biotechnol. Adv.* 35(2), 105-134. DOI: 10.1016/j.biotechadv.2016.11.006

Shishov, A., Bulatov, A., Locatelli, M., Carradori, S., and Andruch, V. (2017). "Application of deep eutectic solvents in analytical chemistry. A review," *Microchem. J.* 135, 33-38. DOI: 10.1016/j.microc.2017.07.015

Singh, D. (2016). "Defining desirable natural product derived anticancer drug space: Optimization of molecular physicochemical properties and ADMET attributes," *ADMET and DMPK* 4(2), 98-113. DOI: 10.5599/admet.4.2.291

Su, E., Yang, M., Cao, J., Lu, C., Wang, J., and Cao, F. (2017). "Deep eutectic solvents as green media for efficient extraction of terpene trilactones from *Ginkgo biloba* leaves," *J. Liq. Chromatogr. R. T.* 40(8), 385-391. DOI: 10.1080/10826076.2017.1309661

Swamy, R. N., Gnanamani, A., Shanmugasamy, S., Gopal, R. K., and Mandal, A. B. (2011). "Bioinformatics in crosslinking chemistry of collagen with selective cross linkers," *BMC Research Notes* 4, 399-406. DOI: 10.1186/1756-0500-4-399

Veber, D. F., Johnson, S. R., Cheng, H.-Y., Smith, B. R., Ward, K. W., and Kopple, K. D. (2002). "Molecular properties that influence the oral bioavailability of drug candidates," *J. Med. Chem.* 45(12), 2615-2623. DOI: 10.1021/jm020017n

Wang, T., Jiao, J., Gai, Q.-Y., Wang, P., Guo, N., Niu, L.-L., and Fu, Y.-J. (2017). "Enhanced and green extraction polyphenols and furanocoumarins from Fig (*Ficus carica* L.) leaves using deep eutectic solvents," *J. Pharmaceut. Biomed.* 145, 339-345. DOI: 10.1016/j.jpba.2017.07.002

Zainal-Abidin, M. H., Hayyan, M., Hayyan, A., and Jayakumar, N. S. (2017). "New horizons in the extraction of bioactive compounds using deep eutectic solvents: A review," *Anal. Chim. Acta* 979, 1-23. DOI: 10.1016/j.aca.2017.05.012

Zhuang, B., Dou, L. L., Li, P., and Liu, E. H. (2017). "Deep eutectic solvents as green media for extraction of flavonoid glycosides and aglycones from *Platycladi Cacumen*," *J. Pharm. Biomed. Anal.* 134, 214-219. DOI: 10.1016/j.jpba.2016.11.049

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