ANNALS OF "DUNAREA DE JOS" UNIVERSITY OF GALATI
MATHEMATICS, PHYSICS, THEORETICAL MECHANICS
FASCICLE II, YEAR XVI (XLVII) 2024, No. 1
DOI: https://doi.org/10.35219/ann-ugal-math-phys-mec.2024.1.01

Characterization of flavonoids: an explorative review

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Abstract
Flavonoids represent a significant dietary resource for humans. Due to their diverse molecular structures, unique bifunctionalities, minimal side effects and rich pharmacological profiles, flavonoids have become valuable targets for drug design. The objective of this paper is to conduct a systematic review of the various types of flavonoids and their physico-chemical properties.

Keywords: flavonoids, molecular descriptors, molecular structure.

1. INTRODUCTION

Flavonoids are part of the class of polyphenols that are found in some vegetables, fruits, seeds, in various medicinal plants, as well as in drinks. Though flavonoids have typically been regarded as non-nutritive compounds, their beneficial effects have recently gained significant attention in the healthcare field [1].

Flavonoids are found in plants and color them in vibrant and intense shades, encompassing most of the blue, violet, or emerald green hues found in leaves, flowers, roots, and especially in fruits. Natural compounds of flavonoids are involved in UV radiation absorption, symbiotic nitrogen fixation, and floral pigmentation. Additionally, they act as chemical messengers, physiological regulators, and cell cycle inhibitors [2].

Flavonoids are phenolic compounds that contain a pyranic heterocycle in their molecule, condensed with two benzene rings. The benzene rings have hydroxyl groups as substituents, which determine the phenolic character of these compounds. The chemical structure of flavonoids consists of a skeleton of 15 carbon atoms, C6-C3-C6, formed by two benzene rings, (A) and (C), connected by a pyranic heterocycle (B) [3].

Due to their diverse molecular structures, unique bifunctionalities, minimal side effects and rich pharmacological profiles, flavonoids have become valuable targets for drug design. Medical studies conducted over the years demonstrate that flavonoids can act on cancer cells by preventing cell division as well as by inhibiting the enzymes involved in cell activation [4].

The objective of this paper is to explore the physico-chemical properties of three flavonoids: resokaempferol, tectochrysin and kaempferol.

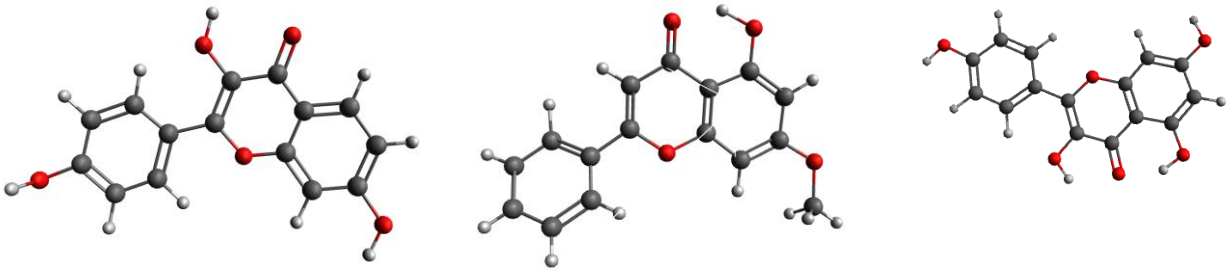
2. EXPERIMENTAL

The process of discovering new drugs is complex, lengthy and expensive. One of the steps of drug development is establishing their bioavailability, therefore we have conducted this study. For our *in-silico* screening, we have used the alvaMolecule2.0.6 software and ADMETlab 3.0 web platform,

which is renowned for its accuracy and extensive capabilities in predicting ADMET properties. Using these advanced tools, we conducted a thorough analysis that included screening 19 physico-chemical properties such as: molecular weight (MW), the number of hydrogen bond acceptors (nHA), the number of hydrogen bond donors (nHD), the number of rotatable bonds (nRot) and the number of rings (nRing).

The molecular weight (MW), ideally falling within the range of 100 to 600, significantly influences the drug's solubility and permeability [5]. The number of hydrogen bond acceptors (nHA) and donors (nHD), ideally ranging from 0 to 12 and 0 to 7, respectively, affects the binding affinity and specificity [5]. The rotatable bonds (nRot), ideally varying from 0 to 11, increase molecular flexibility, which helps the molecule fit into receptor sites more effectively [5]. The number of rings (nRing) and the maximum ring size (MaxRing), ranging between 0 and 6, and 0 and 18, respectively, have a significant impact on molecular stability and rigidity [5]. The solubility (LogS) and the octanol-water partition coefficient (LogP) have a significant role in predicting how a molecule distributes between aqueous and lipid environments [5].

The 3D molecular structures of the studied compounds, presented in Figure 1, were generated with the Avogadro software.



a) b) c)

Fig. 1. 3D molecular structures for: a) resokaempferol, b) tectochrysin, c) kaempferol.

We further analyzed the properties of these flavonoids by employing the name, chemical formula or isomeric SMILES notation, as displayed in Tabel 1.

Table 1. Chemical characteristics of the studied flavonoids

Chemical characteristic	Resokaempferol	Tectochrysin	Kaempferol
Synonyms:	3,7-dihydroxy-2-[4-[(2S,5S)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyphenyl]chromen-4-one	5-hydroxy-7-methoxy-2-phenylchromen-4-one	3,5,7-trihydroxy-2-(4-hydroxyphenyl)chromen-4-one
Chemical formula	$C_{21}H_{20}O_{10}$	$C_{16}H_{12}O_4$	$C_{15}H_{10}O_6$
Isomeric SMILES notation	C1=CC(=CC=C1C2=C(C(=O)C3=C(O2)C=C(C=C3)O)O)O[C@H]4C(C([C@@H](C(O4)CO)O)O)O	COC1=CC(=C2C(=C1)OC(=CC2=O)C3=CC=CC=C3)O	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O

3. RESULTS AND DISCUSSION

The physico-chemical properties of the studied compounds are displayed in Table 2. The results, obtained by using the ADMETlab 3.0 web platform, illustrate their bioavailability profiles. All three compounds are within the acceptable molecular weight (MW) range, thereby fulfilling one of the criteria for good absorption and permeability. The number of hydrogen bond acceptors (nHA) and donors (nHD) also fall within the optimal ranges, with kaempferol having an increased number of hydrogen bond acceptors and donors, which suggests that this compound might form more hydrogen bonds with the target protein. All three flavonoids have low rotatable bonds (nRot), meaning that they

might have limited flexibility, influencing their fitting in the active site of target protein. The stability and the rigidity of the molecules, necessary for the effectiveness of interaction with the protein are given by the number of rings (nRing). All three molecules are within the optimal range.

Table 2. Physico-chemical properties for the three analyzed flavonoids

Physicochemical Property	Resokaempferol	Tectochrysin	Kaempferol
Molecular Weight	270.240	268.260	286.05
Van der Waals volume	265.186	273.692	273.977
Density	1.018	0.979	1.044
nHA	5	4	6
nHD	3	1	4
nRot	1	2	1
nRing	3	3	1
MaxRing	10	10	10
nHet	5	4	6
fChar	0	0	0
nRig	18	18	18
Flexibility	0.056	0.111	0.056
Stereo Centers	0	0	0
TPSA	90.900	59.670	111.13
LogS	-3.828	-4.390	-3.648
LogP	2.073	3.850	1.965
Melting point	288.744	184.312	302.081
Boiling point	378.783	331.085	383.666
Ui	3.906	3.906	

4. CONCLUSIONS

The physico-chemical profiles suggest that they have the potential to be good inhibitors, but their efficacy would ultimately need to be validated through biological assays and clinical trials. The data obtained (chemical properties and bioavailability) confirm that all the three compounds meet the requirements to qualify as drugs.

However, the effectiveness of these compounds as inhibitors and their potential in cancer therapy still depend on their therapeutic index, which balances efficacy against toxicity.

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