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IN-SILICO ADMET PREDICTION OF PHYTOCHEMICALS IN *CAMELLIA SINENSIS AND CITRUS SINENSIS*

V. Sathya* and V.K. Gopalakrishnan

Department of Bioinformatics, Karpagam University, Coimbatore, Tamil Nadu, India

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Correspondence to Author:

V. Sathya

Assistant Professor, Department of Bioinformatics, CMS College of Science and Commerce, Coimbatore , Tamil Nadu, India

E-mail: sathyasuhijohn@gmail.com

ABSTRACT: *Camellia sinensis and Citrus sinensis* are treasuries of medicinal properties. The compounds present in these plants can deliver potential therapeutic drug. Most of the drugs in clinical development fail to commercialize because of poor ADME and toxicity properties. The main aim of the study is pharmacokinetic investigation and toxicity property, the most causes of high attrition rates in drug development and it should be considered as early as possible in the drug discovery process.

INTRODUCTION: *Camellia sinensis*, the tea plant, is a member of the Theaceae family. It is an evergreen shrub or tree can grow to heights of 30 feet appear in clusters or singly. The polyphenols found in tea are more commonly known as flavanols or catechins, and comprise 30-40 percent of the extractable solids of dried green tea leaves. The main catechins in green tea are epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate (EGCG). The polyphenols present in tea have demonstrated significant antioxidant, anti-carcinogenic, anti-inflammatory, thermogenic, probiotic, and antimicrobial activity [1, 2].

Citrus sinensis, Sweet Orange, a hesperidium belongs to the Rutaceae family [3.] Besides sugars, acids, and polysaccharides, oranges are an important source of phytochemicals such as phenolics, vitamin C and carotenoids.

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These compounds also known as nutraceuticals provides health benefits due to a risk reduction of chronic illness such as cancer and cardiovascular disease [4, 5].

One of the mechanisms by which these phytochemicals exerts their beneficial effects in human health has been related to their antioxidant activity. Phenolics in fruits and vegetables, as well as vitamin C, are said to be effective antioxidants. It was shown that vitamin C contributes in 100% to the total antioxidant activity [6]. Vitamin C scavenges free radicals such as O_2^-, OH, peroxyl radicals and singlet oxygen, protecting the intracellular and extracellular structures [6, 7]. Carotenoids prevent potentially damaging radical production due to their polyene structure[8]. Both juice and peel contain nutraceuticals, nevertheless it has been demonstrated that they are more abundant in citrus peel [9, 10.]

Evaluation of dug-likeness involves prediction of ADMET (Absorption, Distribution, Metabolism, Excretion, toxicity) properties. Insilico HIA (Human Intestinal Absorption) model and skin permeability model can predict potential drugs for oral delivery and trans-dermal delivery.

In distribution, BBB (Blood Brain Barrier) penetration can give information of therapeutic drug in central nervous system (CNS), PPB (Plasma Protein Binding model in its efficacy).

Toxicity of the compounds analyzes AMES mutagenicity, aerobic biodegradability, developmental toxicity potentials, Carcinogenicity

The "drug-like" is the molecules containing functional groups that have properties consistent with the known drugs. Leads displays properties for development in drug discovery are termed to be "drug-like". Lipinski's rule is the most important satisfactory fact of drug-likeness

Lipinski's Rule, so called "Rule of Five" defined as;

Number of hydrogen bond donors <5 (the sum of OHs and NHs)

Number of hydrogen bond acceptor <10 (the sum of Os and Ns)

Molecular Weight<500 and CLogP <5 (MlogP<4.5)

MATERIALS AND METHODS:

Database Screening for Compound Selection: The chemical compound with anticancer and antiviral activity from two plants were screened from Dr. Duke's Phytochemical and ethnobotanical data (http://ars-grin.gov/duke/). The screening results revealed that there were 34 compounds in citrus sinensis and 41 compounds in camellia sinensis.

ChemSpider: The mol formats or PDB format of compounds were collected from Chemspider (http:// Chemspider.com).

Accelerys Discovery Studio: The compounds were prepared and optimized by ADMET properties which evaluates druglikeness and toxicity for all compounds were predicted using TOPKAT (Toxicity Prediction by Komputer Assisted Technology) to check the mutagenicity and probability values of the compounds.

RESULTS AND DISCUSSION: In *Camellia sinensis*, 18 and 22 compounds were screened for anticancer and antiviral activity respectively. In *Citrus sinensis*, 13 and 21 were screened for anticancer and antiviral activity respectively (**Table 1**). The screened compounds from Dr. Duke Phytochemical and Ethanobotanical database were energy minimized and studied for Lipinski's rule of five (Table 1).

TABLE 1: SCREENING OF COMPOUNDS FROM DATABASE

PLANT	ANTICANCER ACTIVITY	ANTIVIRAL ACTIVITY
Camellia sinensis	Epigallocatechin-Gallate, Alpha-Terpineol, Benzaldehyde, Beta-Carotene, Butyric Acid, Caffeic-Acid, Chlorophyll, Chlorogenic acid, Ferulic acid, Gallic-Acid, Hyperoside, Isoquercitrin, Kaempferol, Lignin, Limonene, Naringenin, Rutin, Tannin	Epicatechin-3-O-Gallate, Epigallocatechin-Gallate, Adenine, Alpha-pinene, Apigenin, Ascorbic acid, Beta-sitosterol, Caffeine, Dammaradienol, Epicatechin, Eugenol, Geranial, Lauric acid, Linalool, Lupeol, Myricetin, Quercetin, Quercitrin, Stigmasterol, Tannic acid, Theaflavin, Theophylline
Citrus sinensis	Alpha-Carotene, Alpha-Terpineol, Alpha-Tocopherol, Beta-Carotene, Butyric-Acid, Caffeic-Acid, Chlorogenic Acid, Diosmin, Ferulic acid, Limonene, Naringenin, Neohesperidin, Rutin	Alpha-Pinene, Ascorbic acid, Beta-sitosterol, Caffeic acid, Caffeine, Chlorine, , Geranial, Hesperidin, Limonene, Linalool, Lithium, Myricetin, Naringenin, Naringin, Neryl-acetate, P-cymene, Quercetin, Rutin, Scutellarein, Stigmasterol, Subaphyllin

There were common compounds found in both the plants which show anticancer and antiviral activity. Thus the results showed that in grand total from the two plants there were about 18 compounds satisfied Lipinski's rule 34 compounds failed due to molecular weight >500, partition coefficient >5, hydrogen bond acceptor >10. ADME and toxicity profile analyzed for the satisfied compounds are tabulated in **table 2**. Based upon the ADMET values from Accelerys Discovery studio, the compounds have good ADME nature (**figure 1**). The toxicity profile of AMES mutagenicity in most compounds was found to be zero. The compounds having AMES and hepatotoxicity values to be 1 may serve as mutagen. Then, Blood brain barrier, Human Intestinal absorption, Aqueous solubility, hepato-

toxicity and CPY2D6 inhibition of the compounds were found to be good and optimal. Hence, these 18 compounds can be further preceded for the docking studies to deliver a novel therapeutic drug against anticancer and antiviral diseases.

TABLE 2: ADMET OF SCREENED COMPOUNDS

Compound	BBB	Absorption	Solubility	Hepatotoxicity	CPY2D6	PPB	AMES Mutagenictiy
Adenine	3	3	5	0	0	0	1
Apigenin	3	0	3	1	1	2	0
Caffeic acid	3	0	4	0	1	0	0
Chlorogenicacid	4	3	4	1	0	2	0
Chlorine	4	1	4	0	0	0	0
Epicatechin	4	0	3	1	1	0	0
Ferulic acid	3	0	4	1	0	0	1
Kaempferol	3	3	4	1	1	2	0
Lauric acid	1	0	3	0	0	1	0
Lignin	1	0	3	0	0	0	0
Limonene	0	0	3	0	0	0	0
Linalool	1	0	3	0	0	0	0
Lithium	4	2	5	0	0	0	0
Myricetin	1	2	4	1	0	1	1
Naringenin	3	0	3	1	1	1	0
Nerylacetate	1	0	3	0	0	0	0
P-Cymene	0	0	3	0	0	2	0
Subaphyllin	3	0	4	0	1	1	0
Scutallarin	3	0	3	1	1	2	1
Quercitin	4	1	3	1	1	2	1

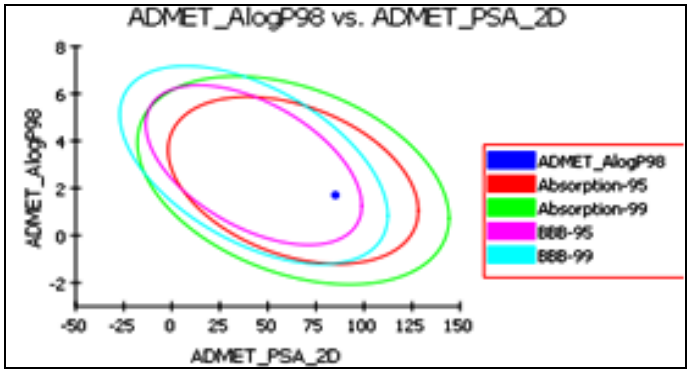

FIG. 1: ADMET OF SATISFIED PHYTOCHEMICALS

CONCLUSION: *Camellia sinensis* and *Citrus sinensis* are treasuries to deliver novel drugs. As per the literature survey, these plants were found to have anticancer and antiviral activities. These plants have almost 74 compounds possessing anticancer and antiviral activities. This *in-silico* study helps to screen the compounds and lead to development against various diseases.

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