INTRODUCTION

Anti-oxidants are substances that are capable of counteracting the damaging but normal effects of the physiological process of oxidation in animal tissue. Anti-oxidants are nutrients (vitamins and minerals) as well as enzymes (proteins in your body that assist in chemical reactions) [1]. They are believed to play a role in preventing the development of chronic diseases such as cancer, heart disease, stroke, Alzheimer’s disease, rheumatoid arthritis, and cataracts [2]. Anti-oxidants block the process of oxidation by neutralizing free radicals. In doing so, the anti-oxidants themselves become oxidized [2] and that is why there is a constant need to replenish our anti-oxidant compounds [3].

The compounds which passed the PBPK studies were eligible to become a drug. Of the 10 compounds investigated, eugenol, gingerol, zingerone, and geraniol were found to have higher fraction of absorption to become a drug. Out of these compounds, the compounds gingerol and eugenol have shown the best factor of absorption, and hence, have a better probability of becoming a drug.

PBPK modeling and simulation is a tool that can help predict the pharmacokinetics of drugs in humans and evaluate the effects of intrinsic (e.g., organ dysfunction, age, and genetics) and extrinsic (e.g., drug-drug interactions) factors, alone or in combinations on drug exposure. The use of this tool is increasing at all stages of the drug development process. This report reviews the recent instances of the use of PBPK in decision-making during regulatory review [5]. The objectives of PBPK studies were to develop a risk assessment methodology for chemical mixtures that accounts for pharmacokinetic interactions among components and to apply this methodology to assess the health risk [6]. These PBPK studies have helped the scientists and researchers to identify different toxicity and risk factors when a drug is administered into the human body. Based on the clinical trials conducted on rats, these studies have been found to be of great use [7]. They also help the researchers using the in silico tools for different properties. PBPK studies make the compound enter in vitro research, which then gets formulated into drug. This aids in knowing the adverse effects of the drugs beforehand [8].

Mostly, the animal models suggest the drug candidate which is often considered for clinical trials. Distinctive oral delivery models have been used in the pharmacological research for increasing the patient’s compliance, safety and convenience. So far the interest is often provided to identify the PBPK model for oral delivery, which follows the advanced compartmental and transit (ACAT) model. ACAT model was parameterized to capture distinct properties such as fluid volume, absorptive surface area, and bile concentrations [9-11].

MATERIALS AND METHODS

Materials

10 anti-oxidant compounds were obtained from the in silico literature studies. The compounds’ SMILE structures were obtained using PUBCHEM [12]. These SMILE structures were used in the tool called molinspiration [13] (cheminformatics software tool) to find their absorption, distribution, metabolism, excretion and toxicity (ADMET) properties based on the Lipinski’s rule. The literature studies based on GastroPlus were obtained to show the solubility, dosage, and fraction of absorption of the compound [14].

ABSTRACT

Objective: A pharmacokinetic study is a cumbersome process in clinical research. It is very important in target validation and in shifting a lead compound into a drug. Our major objective was to reveal the most important physiochemical characters of the plant-based anti-oxidants in align with human physiology. The in silico studies can preferably be the best solution to identify the physiologically-based pharmacokinetic (PBPK) behavior of the anti-oxidants.

Methods: Anti-oxidants are found in many foods including fruits and vegetables. Few of the important anti-oxidants, i.e. around 10 plant-based anti-oxidant compounds were taken for this research. These compounds were evaluated based on their pharmacokinetic parameters. The properties such as Lipinski’s rule of 5, absorption, distribution, metabolism, excretion, and toxicity (ADMET) of the compounds were screened thoroughly with the help of tools such as molinspiration and gastroplus.

Results: The physiological studies of these compounds had shown different compartmental absorption so the compound in the human gastrointestinal tract. Certain compounds were found to pass the physiological barriers and had the ability to become a drug. The compounds were filtered using the risk and toxicity factors. These risk factors caused the compounds to fail in the process of becoming a drug.

Conclusion: The compounds which passed the PBPK studies were eligible to become a drug. Of the 10 compounds investigated, eugenol, gingerol, zingerone, and geraniol were found to have higher fraction of absorption to become a drug. Out of these compounds, the compounds gingerol and eugenol have shown the best factor of absorption, and hence, have a better probability of becoming a drug.

Keywords: Anti-oxidants, Lipinski, Absorption, Distribution, Metabolism, Excretion and toxicity, Physiological properties, GastroPlus, In silico.
Methods

Lead compound screening

A set of 10 phytochemical compounds that possess anti-oxidant properties were taken for the study. The compounds taken for this study were aloesin, eugenol, cyanidin, gingerol, zingeron, paradol, geraniol, corilagin, and Asiaticoside. These compounds were obtained from the literature studies, which were already conducted. Using PubChem, the SMILES formats were obtained for these 10 compounds for knowing the ADMET parameters and measuring the GastroPlus model [15].

Lipinski’s rule of study

Identification of drug molecules is one of the major challenges in the field of drug discovery. Existing approach like Lipinski’s rule of 5 plays an important role in the screening of compounds. Thus, there is a need to develop a computational method that can predict the drug-likeness of a molecule with precision [16]. The compounds with their SMILE formats were evaluated based on the Lipinski’s rule. The rule consists of 4 parameters as follows:

- No more than 5 hydrogen bond donors
- No more than 10 hydrogen bond acceptors
- Molecular mass less than 500 Da
- Log P not greater than 5.

Apart from these rules, the rotational bonds and TPSA values were also calculated. Under these conditions, only the compounds were proved to have good pharmacokinetic properties.

ADMET risk factors

ADMET prediction is an extremely challenging area because many of the properties that we tried to predict were as a result of multiple physiological processes. The compounds based on the properties such as hydrogen donor and acceptors, the charges, log p octanol, permeability, and solubility were validated [17,18]. While such models are not sufficiently accurate to act as a replacement for in vivo or in vitro methods, in silico methods nevertheless can help us to understand the underlying physicochemical dependencies of different ADMET properties, and thus, can give us inspiration on how to optimize them [19]. The compounds which violate these properties are considered to be in risk zone. The threshold values of the risk and toxicity factors are given in Tables 1-3 [20].

PBPK studies

PBPK studies are frequently used for pharmacokinetic (PK) analysis when only blood or plasma data is available. The body and model are represented as actual blood and tissue (usually total body weight) volumes, fractions (f d) of cardiac output and systemic or intrinsic clearance [21,22]. Analyzing only blood or plasma concentrations versus time, the minimal-PBPK models parsimoniously generate physiologically-relevant PK parameters [22]. The intake and dosage of these compounds have been formulated by using the tool GastroPlus. The fraction of absorption was found in each compartment of gastrointestinal tract. The compounds violating these factors have a huge risk of toxicity [23].

RESULTS

The various risk factors and their contributions have been shown in Tables 4-9 along with Figures 1-2

DISCUSSION

This study was pursued on a list of anti-oxidant phytocompounds from various plant sources and identifies the PBPK model which could...
help us in understanding the distinctive properties for defining an effective drug candidate. PBPK model is often derived to study about the influencing parameters for oral absorption which mostly has drawbacks with respect to the risks during and after absorption in the gastrointestinal tract.

Based on the above in silico studies, certain drugs had drawbacks with respect to the risk involved in the absorption, distribution, toxicity, and metabolism. On the evaluation of compounds SMILES format, data are studied based on the physiological parameters obtained from GastroPlus simulation tool which had guided the data to evaluate for the drug candidate. Various parameters tell us about the dosage levels, different compartmental models, and C_{max} and T_{max} values of each compound in detail [24]. This type of software minimizes the time taken for validation of so many compounds. Gastroplus data mainly highlight the risk involved and it is illustrated by the risk codes (Tables 1-3) based on which they explain the physiological parameters under which they are affected. However, compounds such as gingerol, eugenol, zingerone, and paradol had no risks involved with the Lipinski’s rule (Table 4). The Lipinski’s risk codes such as log p value and molecular weights are the major drawbacks for the other compounds due to which they have lower absorption rate as well as low hydrophilic nature (Table 4) [25]. Although many of the 10 compounds were approved in this rule, they may cause a dilemma in the bio-availability by having less clearance value and may cause toxicity in future [26,27]. Hence, the toxicity studies were performed to predict which compound had the least toxicity. Research results had shown effectively that there are toxic factors for previously screened compound such as under absorption risk factors (Tables 5 and 6). The toxicity factors did not affect any of the four compounds such as gingerol, geraniol, eugenol, and zingerone. However, the other compounds such as gallotannin, aloesin, and asiasadose had toxicity and mutation factors such as mutation in strains, elevated enzyme levels and high concentration of alkaline phosphates, and caused mutation in rats. Once the compounds were out of toxicity zone, studies were conducted for metabolic risk factors (Table 7). This illustrates better binding ability with the enzymes and hence proven as the better substrate to the few of the important metabolizing enzymes by which they may be metabolized.

As seen above, the compounds gingerol and geraniol had good binding with the enzyme sites although there was one risk factor for eugenol

| Rules                        | Values                                                                                      |
|------------------------------|---------------------------------------------------------------------------------------------|
| hE: hERG liability           | Qualitative estimation of the likelihood of hERG potassium channel inhibition in human;   |
|                              | Simulations Plus                                                                          |
| ra: Acute toxicity in rats   | TOX_hERG > 6                                                                              |
| Xr: Carcinogenicity in chronic rat studies | TOX_RAT < 300                                                                      |
| Xm: Carcinogenicity in chronic mouse studies | TOX_BRM_Rat > 4                                                                   |
| Hp: Hepatotoxicity           | TOX_BRM_Mouse < 25                                                                      |
| SG: SGOT and SGPT elevation | (TOX_AlkPhos = Toxic OR TOX_GGT = Toxic OR TOX_LDH = Toxic ) AND                           |
|                              | (TOX_SGOT = Toxic OR TOX_SGPT = Toxic )                                                   |
| Mu:                          | TOX_MUT_Risk > 2                                                                          |

| TOX_hERG                     | Qualitative estimation of the likelihood of hERG potassium channel inhibition in human;   |
|                              | Simulations Plus                                                                          |
| TOX_RAT                     | [mg/kg] (LD50 for lethal rat acute toxicity, all mechanisms; Simulations Plus)            |
| TOX_BRM_Rat                 | [mg/kg/day] (TD50, which is defined as the oral dose of a compound required to induce tumors |
| TOX_BRM_Mouse               | in 50 percent of rat population after exposure over a standard lifetime; Simulations Plus) |
| TOX_AlkPhos                 | [mg/kg/day] (TD50, as above, but for mouse; Simulations Plus)                             |
| TOX_GGT                     | Human liver adverse effect as the likelihood of causing elevation in the levels of alkaline |
|                              | phosphatase enzyme; Simulations Plus                                                      |
| TOX_SGOT                    | Human liver adverse effect as the likelihood of causing elevation in the levels of SGPT enzyme; Simulations Plus |
| TOX_SGPT                    | Human liver adverse effect as the likelihood of causing elevation in the levels of SGPT enzyme; Simulations Plus |
| TOX_MUT_Risk                | ADMET Risk and ADMET Code for mutagenicity in S. typhimurium – a computational filter     |
|                             | developed by Simulations Plus summarizing the output of TOX_MUT* models)                   |
| TOX_MUT.97+1537             | Qualitative assessment of mutagenicity of the pure compound in TA97 and/or TA1537 strains of S. typhimurium; Simulations Plus |
| TOX_MUT.m97+1537            | Qualitative assessment of mutagenicity of the compound and its microsomal rat liver metabolites in TA97 and/or TA1537 strains of S. typhimurium; Simulations Plus |
| TOX_MUT.98                  | Qualitative assessment of mutagenicity of the pure compound in TA98 strain of S. typhimurium; Simulations Plus |
| TOX_MUT.m98                 | Qualitative assessment of mutagenicity of the compound and its microsomal rat liver metabolites in TA98 strain of S. typhimurium; Simulations Plus |
| TOX_MUT.100                 | Qualitative assessment of mutagenicity of the pure compound in TA100 strain of S. typhimurium; Simulations Plus |
| TOX_MUT.m100                | Assessment of mutagenicity of the compound and its microsomal rat liver metabolites in TA100 strain of S. typhimurium; Simulations Plus |
| TOX_MUT.102+wp2             | Qualitative assessment of mutagenicity of the pure compound in TA102 strain of S. typhimurium and/or WP2 uvrA strain of E. coli; Simulations Plus |
| TOX_MUT.m102+wp2            | Qualitative assessment of mutagenicity of the compound and its microsomal rat liver metabolites in TA102 strain of S. typhimurium and/or WP2 uvrA strain of E. coli; Simulations Plus |
| TOX_MUT.1535                | Qualitative assessment of mutagenicity of the pure compound in TA1535 strain of S. typhimurium; Simulations Plus |
| TOX_MUT.m1535               | Qualitative assessment of mutagenicity of the compound and its microsomal rat liver metabolites in TA1535 strain of S. typhimurium; Simulations Plus |

S. typhimurium: Salmonella typhimurium, E. coli: Escherichia coli. ADMET: Absorption, distribution, metabolism, excretion, and toxicity
CONCLUSION

Pharmacokinetics plays an important role in the validation of a lead compound. Many a time the compounds obtained from plant sources are left without being taken to the next level of becoming an appropriate drug. These studies have taken our compound of interest to the various PBPK models which helped our research to identify the best anti-oxidant compound. The PBPK models were illustrated with four the various PBPK models which helped our research to identify the best appropriate drug. These studies have taken our compound of interest to the next level of becoming an drug in future.

Our study has given us the scope to carry on further in vitro and ex vivo [29] studies to test these compounds for a better drug molecule or therapeutic compound. The future prospective of this study will be to

and zingerone (Fig. 1): this is because they did not have good binding with the enzyme C9 (Fig. 1); whereas, the other compounds had shown drawbacks by being non-substrate to many of the enzymes (Table 7). In this study, we even evaluated the physiological factors. The compounds were taken as immediate release tablets with a dosage of 100 mg and were observed with a time period of 24 hrs. The compounds were absorbed into different compartments of the human intestinal tract. Based on the total fraction of absorption and the C\textsubscript{max}-T\textsubscript{max} values, it was found that the previously screened compounds such as eugenol, gingerol, zingerone, and geraniol had a better rate of absorption rather than the other compounds (Table 7). Here, the other compounds faced a disadvantage of having very less absorption fraction along with the high T\textsubscript{max} values with Asiaticoside being the least satisfying compound. The four compounds have been shown with the maximum fraction of absorption in the human intestinal compartment, out of which gingerol and eugenol have comparatively highest with risk factors as well (Fig. 2). The entire compartment model that occurred in the PBPK was literally suggested to have better fraction of absorption for the very few eugenol and gingerol, zingerone, and geraniol had better ADME and pharmacological properties (Figs. 1 and 2) although one or two risk factors might cause certain negligible side effects. Since eugenol and gingerol have higher factor of absorption, there is more probability of these two therapeutic compounds as an appropriate drug.

Our study has given us the scope to carry on further in vitro and ex vivo [29] studies to test these compounds for a better drug molecule or therapeutic compound. The future prospective of this study will be to
Table 4: Absorption risk factors

| Name      | Molwt  | N_Aatoms | Mol_vol | N_Bonds | Hdbdh | Hdbch | Hba   | Hbach  | Npa_Absq | T_Psa  | S+Logg | S+Logd | Mlogg | Mdpck | S+Sw  | S+Peff | Mdck | S+Prunbd | S+Vd  | Risk Codes | Number of risk codes |
|-----------|--------|----------|---------|---------|--------|--------|-------|--------|----------|--------|--------|--------|-------|-------|-------|--------|------|----------|-------|------------|----------------------|
| Aloesin   | 394.38 | 29       | 329     | 30      | 5      | 2.39   | 9     | -5.88  | 17.37    | 158    | -0.79  | -0.79  | -1.14 | 0.01  | 10887 | 7.73E+00 | 24.64 | 1.07      | HD, CH, Pf           | 3                     |
| Eugenol   | 164.21 | 12       | 168     | 12      | 3      | 1      | 0.46  | 2.12   | 6.6      | 2.95E+01| 2.53   | 2.52   | 2.62  | 7.8   | 63281 | 9.15E-01 | 44.1  | 1.26      | 0                    | 0                     |
| Cinnamaldehid | 287.25 | 21       | 203     | 23      | 0      | 5.29   | 6     | -3.47  | 11.39    | 1.14E+02| 0.93   | 0.11   | 0.6   | 0.46  | 20.58 | 2.06E+01 | 8.48  | 0.14      | hv                  | 2                     |
| Gingerol  | 294.39 | 21       | 322     | 21      | 10     | 2      | 0.91  | 2.94   | 14.25    | 66.8   | 2.99   | 2.99   | 2.03  | 3.19  | 3573  | 1.24E+01 | 26.96 | 1.23      | 0                    | 0                     |
| Zingerone | 194.23 | 14       | 189     | 14      | 4      | 1      | 0.46  | 3.16   | 8.72     | 46.54  | 1.6    | 1.6    | 2.08  | 6.22  | 50711 | 1.64E+00 | 47.45 | 0.98      | 0                    | 0                     |
| Paradol   | 278.39 | 20       | 315     | 20      | 10     | 1      | 0.45  | 1.68   | 13.52    | 46.54  | 4.54   | 4.53   | 3.64  | 7.62  | 4573  | 1.49E-02 | 24.21 | 1.46      | ow                  | 1                     |
| Geraniol  | 154.25 | 11       | 217     | 10      | 4      | 1      | 0.45  | 0.76   | 8.17     | 2.02E+01| 2.59   | 2.59   | 2.64  | 4.89  | 40823 | 1.46E+00 | 43.21 | 1.45      | 0                    | 0                     |
| Gallotannin | 636.48 | 45       | 455     | 48      | 7      | 1      | 5.32  | -11.5  | 27.23    | 3.11E+02| -0.04  | -1.51  | -4.01 | 0.27  | 14.24 | 3.28E+00 | 1.57  | 0.18      | S1, H, H, HA, S1, Ch, Pf, Fu | 6                     |

*The highlighted values represent the various absorption risk factors of anti-oxidants which exceed the threshold values based on Table 1

Table 5: Mutation risks factor

| Name      | Tox_Mut_97+ | Tox_Mut_M97+ | Tox_Mut_98 | Tox_Mut_M98 | Tox_Mut_100 | Tox_Mut_M100 | Tox_Mut_102+ | Tox_Mut_M102+ | Tox_Mut_1535 | Tox_Mut_M1535 | Tox_Mut_Risk | Tox_Mut_Code |
|-----------|-------------|--------------|------------|-------------|-------------|-------------|--------------|--------------|--------------|---------------|--------------|---------------|
| Aloesin   | Undecided   | Toxic        | Nontoxic   | Nontoxic    | Nontoxic    | Nontoxic    | Undecided    | Nontoxic    | Nontoxic    | Nontoxic     | 1.5 m1, SU   |
| Eugenol   | Nontoxic    | Toxic        | Nontoxic   | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic     | 0 m1, S4      |
| Cinnamaldehid | Nontoxic | Nontoxic    | Nontoxic   | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic     | 0             |
| Gingerol  | Nontoxic    | Toxic        | Nontoxic   | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic     | 0             |
| Zingerone | Nontoxic    | Nontoxic    | Nontoxic   | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic     | 0             |
| Paradol   | Nontoxic    | Nontoxic    | Nontoxic   | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic     | 0             |
| Geraniol  | Nontoxic    | Nontoxic    | Nontoxic   | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic     | 0             |
| Gallotannin | Nontoxic | Nontoxic    | Nontoxic   | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic     | 0             |
| Corilagin | Toxic       | Nontoxic    | Nontoxic   | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic     | 1 s1          |
| Asiaticoside | Nontoxic | Nontoxic    | Nontoxic   | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic    | Nontoxic     | 0             |

Table 6: Toxicity risks factor

| Name      | Tox_Herg | Tox_Rat | Tox_Brm_Rat | Tox_Brm_Mouse | Tox_Alkphos | Tox_Sgpt | Tox_Ggt | Tox_Ldh | Tox_Sgot | Tox_Code | Tox_Risk |
|-----------|----------|---------|-------------|---------------|-------------|---------|--------|--------|--------|---------|---------|
| Aloesin   | 3.6      | 901.75  | 113.04      | 1516.75       | Nontoxic    | Nontoxic | Nontoxic | Nontoxic | Nontoxic | 0       | 0       |
| Eugenol   | 3.96     | 1299.83 | 141.96      | 679.33        | Nontoxic    | Nontoxic | Nontoxic | Nontoxic | Nontoxic | 0       | 0       |
| Cinnamaldehid | 4.43   | 1699.22 | 393.09      | 519.84        | Nontoxic    | Nontoxic | Nontoxic | Nontoxic | Nontoxic | 0       | hp, SG  |
| Gingerol  | 4.97     | 3516.66 | 109.78      | 1212.79       | Nontoxic    | Nontoxic | Nontoxic | Nontoxic | Nontoxic | 0       | 0       |
| Zingerone | 4.32     | 2194.53 | 149.15      | 999.92        | Nontoxic    | Nontoxic | Nontoxic | Nontoxic | Nontoxic | 0       | 0       |
| Paradol   | 5.29     | 3440.73 | 121.01      | 1191.51       | Nontoxic    | Nontoxic | Nontoxic | Nontoxic | Nontoxic | 0       | 0       |
| Geraniol  | 3.78     | 2350.75 | 101.61      | 267.61        | Nontoxic    | Nontoxic | Nontoxic | Toxic    | Toxic    | Undecided | 0       |
| Gallotannin | 4.52   | 2614.57 | 574.97      | 2167.39       | Nontoxic    | Nontoxic | Nontoxic | Toxic    | Toxic    | Toxic    | 0       |
| Corilagin | 4.24     | 1740.31 | 535.02      | 1174.89       | Nontoxic    | Nontoxic | Nontoxic | Toxic    | Toxic    | hp    | 1       |
| Asiaticoside | 3      | 32.52   | 11.49       | 1559.5        | Nontoxic    | Toxic    | Nontoxic | Nontoxic | Toxic    | ra, SG  | 2       |
### Table 7: Metabolic risk factors

| Name             | CYP_1A2_Substr | CYP_1A2_Sites | CYP_1A2_CLint [μl/min/mg microsomal protein] | CYP_2C19_Substr | CYP_2C19_Sites | CYP_2C19_CLint [μl/min/mg microsomal protein] | CYP_2C9_Substr | CYP_2C9_Sites | CYP_2C9_CLint [μl/min/mg microsomal protein] | CYP_2D6_Substr | CYP_2D6_Sites | CYP_2D6_CLint [μl/min/mg microsomal protein] | CYP_3A4_Substr | CYP_3A4_Sites | CYP_3A4_CLint [μl/min/mg microsomal protein] |
|------------------|---------------|--------------|---------------------------------|-----------------|---------------|---------------------------------|----------------|--------------|---------------------------------|---------------|--------------|---------------------------------|---------------|--------------|---------------------------------|
| Aloe              | No            | Non Substrate | 0.15                            | Yes             | C1 (0.959)    | 0.71                            | No             | Non Substrate | 0.14                            | No             | C1 (0.939)    | 0.14                            | No             | C1 (0.939)    | 0.14                            |
| Eugenol          | Yes           | Yes          | 0.59                            | Yes             | C9 (0.904)    | 0.49                            | No             | Non Substrate | 1.49                            | No             | C8 (0.962)    | 0.49                            | No             | C8 (0.962)    | 0.49                            |
| Cynarin          | Yes           | Yes          | 1.49                            | No              | Non Substrate | 0.15                            | Yes            | C1 (0.959)    | 0.203                           | Yes            | C1 (0.959)    | 0.203                           | No             | C1 (0.939)    | 0.203                           |
| Zingerone        | No            | Non Substrate | 0.21                            | Yes             | C1 (0.939)    | 0.203                           | Yes            | C1 (0.959)    | 0.203                           | No             | C1 (0.939)    | 0.203                           | No             | C1 (0.939)    | 0.203                           |
| Panarol          | No            | Non Substrate | 0.15                            | Yes             | C1 (0.959)    | 0.203                           | Yes            | C1 (0.959)    | 0.203                           | No             | C1 (0.939)    | 0.203                           | No             | C1 (0.939)    | 0.203                           |
| Geraniol         | Yes           | Yes          | 0.15                            | Yes             | C1 (0.959)    | 0.203                           | Yes            | C1 (0.959)    | 0.203                           | No             | C1 (0.939)    | 0.203                           | No             | C1 (0.939)    | 0.203                           |
| Galloolarin       | No            | Non Substrate | 0.033                           | No              | Non Substrate | 0.12                            | No             | Non Substrate | 0.12                            | No             | C1 (0.939)    | 0.12                            | No             | C1 (0.939)    | 0.12                            |
| Corilagin        | No            | Non Substrate | 0.033                           | No              | Non Substrate | 0.12                            | No             | Non Substrate | 0.12                            | No             | C1 (0.939)    | 0.12                            | No             | C1 (0.939)    | 0.12                            |
| Asiaticoside     | No            | Non Substrate | 0.033                           | No              | Non Substrate | 0.12                            | No             | Non Substrate | 0.12                            | No             | C1 (0.939)    | 0.12                            | No             | C1 (0.939)    | 0.12                            |

*The highlighted values represent the various metabolic risk factors of anti-oxidants which exceed the threshold values based on Table 3*
facilitate the four compounds to be formulated as a drug with the help of pharmacodynamic studies.

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