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IN SILICO EVALUATION OF MOST USED DRUGS ON THE TREATMENT OF SLIGHT AND MILD COVID-19 CASES IN BRAZIL

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ABSTRACT

Nowadays, *in silico* tests are one of the primary and most studied analyses. These tests generate pharmacokinetic and toxicology results for new or existing drugs. It is possible to predict some results that will help future steps in vitro and in vivo. In Brazil, the use of medications free of charge available at SUS is widely used, and there is a constant search to find medicines that can help in the treatment of slight and mild cases of COVID-19. This study searched for the most used drugs at this disease stage and made an *in silico* assessment of all parameters. All drugs were investigated in previous literature so that the work sought to find an analysis of individual drugs on their characteristics. It was possible to notice that some drugs generate interaction and interfere with each other's metabolism. It is important to note that this interference or inhibition of metabolism can cause side effects and even toxic effects in the human body. Thus, a more careful analysis is needed to choose the treatment to be more effective to the patient. *In silico* results indicate the need to avoid the use of nitazoxanide due to its drug interaction.

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INTRODUCTION

Every day, new forms of study are sought to minimize costs and speed up achieving results. The search for new reliable tools brings a new study model known as *in silico*. This study aims to optimize the time and costs spent in the laboratory with *in vitro* research. *In silico*assays can predict values through approximations and probabilities, with already published values present in the literature, and analyzing the molecule structure. This analysis is essential to assess drug interactions, a clinical event between drug-drug or drug-food. It is characterized by the interference of a drug or food in the absorption, action, or elimination of another drug (CEMED, 2021). It is possible to evaluate the absorption, distribution, metabolism, excretion, and toxicityof a compound of interest via *silico* assays. Analyze the absorption of a compound in the human bodyis crucial to evaluate the lipophilicity (LogP), water solubility (LogS), human intestinal absorption (HIA), human oral bioavailability (HOB), and Caco-2 permeability. The HIA is a process where drugs administered orally are absorbed from the gastrointestinal system into the bloodstreampassively (DrugBank, 2021). The Caco-2 cells are used to analyze how a molecule permeates it. This analysis is an*in vitro* assay to mimic the gastrointestinal lumen. The *insilico* results are from previous studies.

HOB is the fraction of a drug administeredvia oral that reaches the systemic circulation and the therapeutic site of action (Kim *et al*., 2014). Drug distribution is evaluatedby some parameterssuch as plasma protein binding (PPB), P-glycoprotein substrate or inhibitor, and blood-brain barrier penetration (BBB). PPB estimates the effectiveness of a drug is affected by how it binds to proteins in blood plasma. The less binding the drug is, the more efficiently it can cross cell membranes or diffuse (Croom, E., 2012). The BBB shows theability of the drug to passively cross the blood-brain barrier, influencing the central nervous system.P-glycoprotein (PGP) is responsible for drug transport in many organs. In the intestine, for example, PGP pumps drugs back into the lumen, slowing their absorption. Drugs that induce PGP are substrates that can reduce the bioavailability of other drugs, while inhibitors increase the bioavailability (Finch, A. andPillans, P., 2014). The metabolism of a drug can be analyzed by its interaction with the enzymes from the cytochrome P450 (CYP) superfamily. CYPs from this superfamily are responsible for metabolizing 90% of the drugs available nowadays (Lynch, T. and Price, A., 2007). CYPs are responsible for several drug interactions. If the drug is not activated, it cannot act appropriately in the body, so the patient does not benefit from the treatment. When the drug is not inactivated, the patient is more likely to develop side effects and become intoxicated. Some of the most critical CYPs are analyzed *in silico* assays, like CYP1A2, CYP3A4, CYP2C9, CYP2C19, and CYP2D6. Each one of these CYPs has an

essential role in the metabolism of the drug. CYP1A2metabolizes polyunsaturated fatty acids, xenobiotics, caffeine, acetaminophen, numerous antidepressants and antipsychotics, and many other commonly prescribed medications (The Medical Biochemistry Page, 2020). CYP3A4 is inducible by glucocorticoids and is an essential hepatic enzyme responsible for the biotransformation of almost 60% of all available drugs (The Medical Biochemistry Page, 2020).CYP2C9 and CYP2C19 provide instructions for making an enzyme involved in protein processing and transport. The CYP2C9 metabolizes compounds, such as steroid hormones and fatty acids, and aids in the metabolism of drugs that reduce inflammation. The CYP2C19 process or metabolize at least 10% of commonly prescribed drugs. Both CYPs play an essential role in drug degradation, preventingblood clots from forming (MedlinePlus Genetics, 2020). CYP2D6 is responsible for the metabolism of diverse neuroleptics, tricyclic antidepressants, selective serotonin reuptake inhibitors, and B-blockers. This enzyme works both activating and inactivating medications (Genomika, 2020).

To evaluate the excretion of a compound is necessary to consider the half time ($T_{1/2}$) and the clearance (CL) of it. $T_{1/2}$is the time taken for the concentration of the drug, or the total amount in the body, to be reduced by 50%, i.e.,the drug concentration in the body will be half of the starting dose (Golan, D.E., *et al*., 2014). CL is the ability of the kidney or liver to eliminate substances derived from the metabolism of compounds from the blood (Oxford Languages, 2021). The toxicity of the drugs is commonly evaluated by *in vitro* assays, but *in silico* tests can be used as an alternative to pre-assessment. This type of assessment is vital to predicting some values, providing security for performing steps *in vivo*. In these tests, it is possible to evaluate organ and genomic toxicity. Interactions with human organs, it is possible to evaluate eye injury and corrosion,skin sensibility, skin permeation (Log *K*p), an inhibitor of the human Ether-à-go-go-Related Gene (hERG)best known for its contribution to the heart electrical activity, human hepatoxicity (H-HT), and drug-induced liver injury (DILI). It is also possible to predict acute toxicity by the maximum dosage of a drugand the lethal dose (LD_{50}) necessaryto kill 50% of a test population. H-HTlinks to damage to hepatocytes caused by chemicals called hepatotoxins. DILI is related to adverse effects, or a clinical condition developed from drugs' use (acute or chronic).

Genetic evaluation counts with three analyses: AMES, carcinogenesis, and micronucleus.The Ames testis a mutagenicity assay that can detect if a compound can produce genetic damage that leads to gene mutations (Mortelmans, K. and Zeiger, E., 2000). Carcinogenesis is the formation process of the tumor. The prevision of carcinogenesis shows if a compound can cause or stimulate the appearance of cancer in an organism (Sung, H., *et al*., 2019). The micronucleus assay can predict whether a compound is mutagenic by evaluating chromosomal damage (Cik, M. andJurzak, M.R., 2007). Coronavirus is an infectious disease caused by the virus Sars-CoV-2. Some people infected with this virus will experience mild to moderate respiratory illness and will recover withtreatment. Still, they do not necessarily need to go to the hospital or require intubation.Older people and those with medical problems (diabetes, chronic respiratory disease, cardiovascular disease, and cancer) are more likely to develop severe illness, going through intubation. COVID-19 can spread through droplets of saliva or discharge from the nose when an infected person coughs or sneezes (WHO, 2021). In June of 2021, Brazil has registered the mark of half a million people killed by COVID-19 (DATASUS, 2021). This scenario is worrying. Today the best alternative is to take vaccines, but unfortunately, vaccinate all the population is not the reality. In this way, all the health systems (public and private) searchfor a treatment that can reduce deaths. Brazil has chosen a treatment to avoid the evolution of some COVID-19 cases.

Brazil had a free public access program for health services, called SUS (translated from Portuguese: Health Unic System), created in 1988. It is considered one of the world's largest and best public health systems (FIOCRUZ, 2021). All used drugs are available atSUS. This work evaluated the five most used drugs to treat slight and mild COVID-19 cases in Brazil via *silico* assays. The drugs analyzed were: Ivermectin (CAS: 70288-86-7), Nitazoxanide (CAS: 55981-09-4), Azithromycin (CAS: 83905-01-5), Dexamethasone (CAS: 50-02-2), and Acetaminophen (CAS: 103-90-2). Ivermectin is an anti-parasite medication used to treat head lice, onchocerciasis, strongyloidiasis, ascariasis, trichuriasis, and enterobiasis. Nitazoxanide is used to treat infections by protozoa, helminths, anaerobic bacteria, microaerophilic bacteria, and viruses.These drugs can be used to decrease the viral load, being an alternative for the treatment already used in Brazil (Zaidi, A. K.andDehgani-Mobaraki, P., 2021). The doctor chooses one of them for the treatment. Azithromycin is an antibiotic used to treat bacterial infections.Once the COVID-19 already weakens the body, it becomes necessary to use it as lung infections begin. Dexamethasone is a glucocorticoid and can be administrated in various modes. It can beused to treat inflammatory conditions and endocrine and rheumatic disorders due to the successful results obtained (The RECOVERY Collaborative Group, 2021). Acetaminophen is an analgesic drug used for pain management and an antipyretic agent, which fights fever by lowering body temperature. In Brazil, the dosage used for this compound in COVID-19 treatment is 750mg due to its better performance in this scenario. This work aims to evaluate, through *in silico* trials, the most used drugs in Brazil to treat mild and moderate cases of COVID-19. The tests aim to assess each compound's ADMET concepts (absorption, distribution, metabolism, excretion, and toxicity) individually.

MATERIAL AND METHODS

The drugs are available at PubChem and DrugBank, where it was possible to obtain the canonical SMILES of each compoundanalyzed and the experimentalvalues, or in some cases the predicted values,of some properties to compare with the ones obtained *in silico*. The software used were SwissADME, ADMETlab, and admetSAR. All software used are free to use. *In silico* results were grouped in tables for easy visualization and understanding.

RESULTS

The values of LogP and LogS (Table 1) must show a balance. If LogP is too negative, the compound is hydrophilic, which hinders absorption, as it has low permeability through lipid membranes.On the other hand, if the LogP values are very positive, the compound is hydrophobic. The drug's distribution throughout the body will be hampered, as the drug's dissolution in the gastrointestinal tract fluid and blood circulation will be impeded.With LogS, it is necessary to note that the values fit within scales, where values smaller than -10are considered insoluble, smaller than -6 are poorly soluble, smaller than -4 are moderately soluble, smaller than -2 are very soluble, and smaller than 0 are highly soluble (Lipinski, C. A., 2000).

Table 1. *In silico* values of LogP and LogS

SwissADME			
Drugs	LogP	LogS	Solubility (mg/mL)
Ivermectin	4,35	-9,7	0,000000174
Nitazoxanide	1,16	-4,66	0,00676
Azithromycin	2,13	-7,5	0,0000234
Dexamethasone	2,14	-3,56	0,109
Acetaminophen	0,93	-1,06	13,0

The HIA, HOB, and Caco-2 are measured only as positive and negative (Table 2). HIA and Caco-2 show if the drug can be passively absorbed in the intestine. HOB shows two parameters, F20%, and F30%. Suppose the result is positive for both means that the compound is bioavailable in the human body up to 20%. If it is negative means, it is not bioavailable neither in 30% nor in 20%.Results positive for F30% mean a high oral bioavailability, and negative for F20% means a low oral bioavailability. It is possible to obtain 100% of bioavailability, F1, only by administration parenteral (intravenous) (Kumar, R. *et al*., 2011). It is possible to note that

Azithromycin and Ivermectinare negative for HIA, meaning both drugs are not absorbed passivelyby the intestine's membranes. The other threedrugs are absorbed. In Caco-2 evaluation, Ivermectin and Nitazoxanide are negative, showing a difficulty to permeate the cells in this *in vitro* assay. In HOB, Ivermectin and Azithromycin are negative for F20%, and only ivermectin is negative for F30%.

Table 2. *In silico* parameters of absorption

ADMETlab				
Drugs	HIA	Caco-2	HOB	
			F20%	F30%
Ivermectin	-	-	-	-
Nitazoxanide	+	-	+	+
Azithromycin	-	+	-	+
Dexamethasone	+	+	+	+
Acetaminophen	+	+	+	+

Drug distribution was evaluated by BBB, PGP substrate and inhibitor, and PPB (Table 3). Nitazoxanide, dexamethasone, and acetaminophen may be able to cross the blood-brain barrier passively. Ivermectin and azithromycin are PGP inhibitors and substrates, and dexamethasone is a PGP substrate. Nitazoxanide and acetaminophen are not a substrate or even inhibitors of PGP. To have a good PPB is suggested a value above 90%. In this way, only ivermectin and nitazoxanide have a good binding.

Table 3. Distribution values

ADMETlab				
Drugs	BBB	PGP		PPB
		Inhibitor	Substrate	(%)
Ivermectin	-	+	+	91,72
Nitazoxanide	+	-	-	95,64
Azithromycin	-	+	+	46,14
Dexamethasone	+	-	+	67,74
Acetaminophen	+	-	-	24,02

Table 4 shows the excretion predicted values for the desired compounds. The renal clearance is high when the value is >15mg/mL/kg, moderate when between 15 and 5, and low when <5. The range to measure the $T_{1/2}$ is >8 hours is considered high, between 8 and 3 is moderate, and <3 is low. Suggested good half-life time is above 0,5h.

Table 4. Excretion values

ADMETlab		
Drugs	CL (mg/mL/kg)	$T_{1/2}$ (h)
Ivermectin	1,036	2,43
Nitazoxanide	0,755	0,71
Azithromycin	1,212	1,22
Dexamethasone	1,413	1,27
Acetaminophen	1,669	0,9

It was evaluated if the drugs are inhibitors of the CYP1A2, CYP3A4, CYP2C9, CYP2C19, and CYP2D6 (Table 5).

Table 5. Metabolism and CYPs inhibitors

ADMETlab, admetSAR and SwissADME					
Drugs	CYP inhibitor				
	1A2	3A4	2C9	2C19	2D6
Ivermectin	-	-	-	-	-
Nitazoxanide	-	-	+	-	-
Azithromycin	-	-	-	-	-
Dexamethasone	-	-	-	-	-
Acetaminophen	-	-	-	-	-

Ideally, no compound should inhibit any CYP. All the other compounds evaluated do not inhibit any CYPs, except for nitazoxanide which inhibits CYP2C9. Table 6 evaluates the drug toxicity prediction. Ivermectin is the only drug capable of blocking the hERG. It is possible to not the presence of hepatotoxicityin ivermectin, nitazoxanide, and acetaminophen. The skin sensibility was noted only in nitazoxanide and acetaminophen. It was also possible to note that these drugs have the smallest log*K*p value, which implies the lesser permeability of the skin among the analyzed drugs. None of themedicines cause eye corrosion, but eye irritation could be caused by acetaminophen.

Table 6. Organ and genetic toxicity prevision

admetSAR and ADMETlab					
	Ivermectin	Nitazoxanide	Azithromycin	Dexamethasone	Acetaminophen
hERG	+	-	-	-	-
H-HT	+	+	-	-	+
DILI	-	+	-	-	-
SkinSen	-	+	-	-	+
LogK_P(cm/s)	-7,14	-6,73	-8,01	-7,32	-6,9
Eye corrosion	-	-	-	-	-
Eye irritation	-	-	-	-	+
LD_{50} (mg/kg)	182,42	1590,54	940,76	223,77	1680,55
Acute toxicity	high	low	low	high	low
AMES	-	+	-	-	-
Carcinogenesis	-	-	-	-	-
Micronucleus	-	+	+	-	+

The LD_{50} has a suggested value to be considered good when >500mg/kg when values are between 1 and 50, it isdeemed to behigh toxicity, between 51 to 500 is toxicity, and between 501 and 5000, it is low toxicity. The acute toxicity demonstrated a low dosage to be toxic for nitazoxanide, dexamethasone, and acetaminophen. Only nitazoxanide showed a mutagenic profile by AMES, none of the drugs are carcinogenic, and nitazoxanide, dexamethasone, and acetaminophen showed a shape that could be mutagenic.

DISCUSSION

All experimental values obtained via DrugBank are similar to the *in silico* results. Thus, it is possible to affirm that the data obtained in this study are safe. Absorption in the gastrointestinal lumen is observed in all drugs, except ivermectin; this is related to their LogP and LogS values. The results LogP show all the compounds have a lipophilic character. That is, they are hydrophobic. Lipophilic drugs undergo biliary clearance in the liver. For having this character and tending to penetrate through the gastrointestinal membranes, so it is known that its absorption by the human body will be more excellent.The value of LogP cannot be very positive, as it makes it difficult to dissolve in the liquid in the gastrointestinal tract and the bloodstream. In this way, its distribution throughout the body is hampered. It is possible to classify drug solubility by analyzing the LogS scale where ivermectin and azithromycin are insoluble, nitazoxanide is poorly soluble, and dexamethasone is, and acetaminophen is very soluble. Corroborating the results obtained from LogP. The more soluble the drug, the better its transportation through the body. All data obtained from the PPB are reconciled with the data from LogP, where drugs with lower solubility have a much higher binding to plasma proteins showing less efficiency in crossing cell membranes or diffusing due to its transport through the body being impaired (Croom, E., 2012). In COVID-19 cases, the transport of the drugsthrough the nervous system is not desirable once none of the analyzed drugs are supposed to act in this system. Only ivermectin and azithromycin do not pass the BBB passively, showing proper behavior.

The oral bioavailability of nitazoxanide, dexamethasone, and acetaminophen is up to 20%. Ivermectin is not bioavailable neither in 30% nor 20% azithromycin has a high oral bioavailability. P-

glycoprotein is a transmembrane receptor, and the drug can act as a substrate or interact in some allosteric site, causing a conformational change that blocks the channel. Ivermectin, azithromycin, and dexamethasone act as substrates, lowering the bioavailability. Ivermectin and azithromycin act as PGP inhibitors, raising the bioavailability. Absorption and distribution affect each other. If the human body does not easily absorb a drug, it will distribute poorly. The absorption is responsible for making available the medicine for the body, and the distribution is responsible for delivering it to the active site. (Golan, D.E., *et al*., 2014). It is considered a good half-life time ($T_{1/2}$) value above 0,5 h. All drugs have a $T_{1/2}$ low once all values are below 3,0 h, indicating a reasonable rate of drug removal from the human body. The CL of the analyzed drugs is below 5mL/min/kg, which means a low renal clearance rate.These parameters are interlinked since the slower the CL, the longer the $T_{1/2}$. Ivermectin has the most extended half-life among all drugs analyzed, and nitazoxanide has the shortest.

The metabolism of drugs can changequickly, causing drug neutralization and inefficiency, or in some cases, toxicity. It is possible that the patient suffers from an over-concentration of the drug or even toxic effects since the metabolism of the drug can be affected. There will be changes in Clearance and half-life time. The substrates induce the activity of a CYP enzyme, and the inhibitors will act like a CYP blockers. Any of the drugs administered together must not interfere with the metabolism of each other, that is, that they are not inhibitors of CYP that act on the metabolism of another drug.Analyzing the five drugs studied, it is possible to note that only nitazoxanide is an inhibitor of CYP2C9. This enzyme is responsible for metabolizing dexamethasone, which in turn is accountable for inducing CYP3A4.The CYP3A4 enzyme is essential for drug metabolism in the liver, such as nitazoxanide and ivermectin.All other medicines do not affect the studied CYPs. Therefore, they will not have drug interactions. It is possible to make a relationship between the absorption, excretion, and metabolism of a drug. If absorption is lacking, the drug will not be available to the body in the amount needed for action. If absorption is ideal, the body will metabolize and then excrete. If the excretion rates are too long, the metabolism of this drug will be slow as it will be available in the body for a longer time. The body will be metabolizing this drug until its complete elimination (Golan, D.E., *et al*., 2014). LD_{50} measures acute toxicity, where nitazoxanide, azithromycin, and acetaminophen are toxicwith a low dosage, while ivermectin and dexamethasone need a higher dosage harmful. Noted skin sensibility only in nitazoxanide, and it can cause dermatitis if used topically. Skin permeation is easier in azithromycin, dexamethasone, and ivermectin. None of the drugs cause eye irritation, but acetaminophen can cause eye irritability. A critical factor that needs to evaluate is the hERG, a channel responsible for control the heartbeat. Once this channel is affected, it can cause arrhythmia. Only ivermectin shows to be able to modify the hERG. H-HT and DILI are two different predictors related but not necessarily will lead to the same result. The chemical space of the H-HT predictor is more expansive than DILI. Through these predictors, it is possible to have an early notion of the problems that may be faced in the future and, thus, anticipate and overcome them with other analyses.Nitazoxanide, ivermectin, and acetaminophen can damage hepatocytes. DILI, on the other hand, can only be caused by excessive use of nitazoxanide. An important parameter to consider is the ability of a drug to be mutagenic. None of the analyzed medicine is carcinogenic. Nitazoxanide is the only drug positive for AMES, and it shows that it can cause gene mutations. Azithromycin, nitazoxanide, and acetaminophen may cause chromosomal damage, being mutagenic by the micronucleus assay(Mortelmans, K. and Zeiger, E., 2000; Cik, M. andJurzak, M.R., 2007).

CONCLUSION

It is essential to have a balance between absorption, distribution, metabolism, and excretion. Thus, there will be no accumulation or lack of drug for its action at the site of interest. With the balance between these parameters, it is easier to control toxicity in the body. The drugs evaluated in this study have different functions, except for nitazoxanide and ivermectin. Both have the same purpose: decreasethe viral load. By analyzing all drugsthe parameters, greater attention should be given to thosewho presented unexpected results. As seen, nitazoxanide affects the metabolism of dexamethasone by acting as an inhibitor of CYPs.Nitazoxanide was positive for mutagenicity and skin sensitivity, and it can cause allergic dermatitis. Azithromycin, nitazoxanide, and acetaminophen are toxic in low dosages, while ivermectin and dexamethasone need higher dosages to be toxic. Compared to nitaxozanide, the downsides of ivermectin are the longer half-life time and the fact that it alters the hERG channel. Drugs can damage hepatocytes, but only DILI has a liver damage effect when used in excess. Thus, once the patient already has a liver problem, the drugs tested positive for H-HT (nitazoxanide, ivermectin, and acetaminophen) should be administered cautiously so that future issues do not occur. With nitazoxanide, which was the only positive drug for DILI, it is necessary to be careful with high doses for a long time. It is possible to affirm with the results obtained *in silico* that ivermectin should be the primary option to be administered, excluding the use of nitazoxanide since its adverse effects are more severe, and it is capable of inactivating the metabolism of dexamethasone. All drugs used are easily accessible, free of charge, and are currently used in Brazil to treatsligh and mild cases of COVID-19. Thus, it is ensured through the data obtained *in silico* that all drugs can be administered concomitantly, except for nitazoxanide, which should be avoided since there is another less harmful alternative.

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REFERENCES

CEMED. “O que é interação medicamentosa?”. 2021. Available at: < https://www.farmacia.ufmg.br/o-que-e-interacao-medicamentosa/>. Access on 18th june, 2021.

Cik, M. and M.R. Jurzak, M.R. *Comprehensive Medicinal Chemistry II*. Elsevier Science, 2007, 2 ed.

Croom, E. *Toxicology and Human Environments*. Academic Press, 2012, 1 ed.

DATASUS. Coronavirus Brasil. Available at: < https://covid.saude.gov.br/>. Access on 20th June 2021.

Drug Bank. Acetaminophen. 2021. Available at: <https:// go.drugbank.com/drugs/DB00316>. Access on 10th June 2021.

Drug Bank. Azithromycin. 2021. Available at: <https:// go.drugbank.com/drugs/DB00207>. Access on 10th June 2021.

Drug Bank. Dexamethasone. 2021. Available at: <https:// go.drugbank.com/drugs/DB01234>. Access on 10th June 2021.

Drug Bank. Human Intestinal Absorption. 2021. Available at: <https://dev.drugbank.com/guides/terms/human-intestinal-absorption>. Access on 18th June 2021.

Drug Bank. Ivermectin. 2021. Available at: <https://go.drugbank.com/drugs/DB00602>. Access on 10th June 2021.

Drug Bank. Nitazoxanide. 2021. Available at: <https:// go.drugbank.com/drugs/DB00507>. Access on 10th June 2021.

Finch, A. and Pillans, P. “P-glycoprotein and its role in drug-drug interactions”, in *Australian* Prescriber, vol. 37, 2014, pp. 137–139.

FIOCRUZ. SUS. Available at: <https://pensesus.fiocruz.br/sus>. Access on 20th June 2021.

Genomika. Exame » Estudo Molecular do Polimorfismo *4 do Gene CYP2D6 [CYP2D6]. 2020. Avaible at: < https://www. genomika.com.br/exames/CYP2D6/>. Access on 26th June 2021.

Golan, D. E., *et al*. 2014. *Princípios de Farmacologia.*Guanabara Koogan, 2014, 2 ed.

Kim, M. *et al*. “Critical evaluation of human oral bioavailability for pharmaceutical drugs by using various cheminformatics

approaches", in *Pharmaceutical Research*, vol. 31, 2014, pp. 1002–1014.

Kumar, R. *et al*. "A prediction model for oral bioavailability of drugs using physicochemical properties by support vector machine", in *J Nat Sci Biol Med.*, vol. 2, 2011, pp. 168–173.

Lipinski, C. A. "Drug-like properties and the causes of poor solubility and poor permeability", in *J. Pharmacological and Toxicological Methods*,vol. 44, 2000, pp. 235–249.

Lynch, T. and Price, A."The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects", in *Am Fam Physician*, vol. 76, 2007, pp. 391–396.

MedlinePlus Genetics. CYP2C9 gene. 2020. Available at: <https://medlineplus.gov/genetics/gene/cyp2c9/>. Access on 26th June 2021.

Mortelmans, K. and Zeiger, E."The Ames Salmonella/microsome mutagenicity assay", in *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, vol. 455, 2000, pp. 29–60.

Oxford Languages. Clearance. Available at: < https:// languages. oup.com/google-dictionary-pt/>. Access on 20th June 2021.

PubChem. Acetaminophen. 2021. Available at: <https://pubchem. ncbi.nlm.nih.gov/compound/1983>. Access on 10th June 2021.

PubChem. Azithromycin. 2021. Available at: <https:// pubchem.ncbi. nlm.nih.gov/compound/447043>. Access on 10th June 2021.

PubChem. Dexamethasone. 2021. Available at: <https:/ /pubchem. ncbi.nlm.nih.gov/compound/5743>. Access on 10th June 2021.

PubChem. Ivermectin. 2021. Available at: <https:// pubchem. ncbi.nlm.nih.gov/compound/6321424>. Access on 10th June 2021.

PubChem. Nitazoxanide. 2021. Available at: <https:// pubchem. ncbi.nlm.nih.gov/compound/41684>. Access on 10th June 2021.

Sung, H. *et al*. "Breast cancer subtypes among Eastern-African-born black women and other black women in the United States", in *cancer*, vol. 125, 19, 2019, pp. 1097-0142.

The Medical Biochemistry Page. Cytochrome P450 (CYP) Enzymes. 2020. Available at: < https:// themedicalb iochemist rypage.org/cytochrome-p450-cyp-enzymes/>. Access on 26th June 2021.

The RECOVERY Collaborative Group. "Dexamethasone in Hospitalized Patients with Covid-19", in *The New England Journal of Medicine*, vol. 384, 2021, pp. 693–704.

WHO. Coronavirus. Available at: < https://www.who.int/health-topics/coronavirus#tab=tab_1>. Access on 20th June 2021.

Zaidi, A.K. and Dehgani-Mobaraki, P. "The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article", in *The Journal of Antibiotics*, 2021.

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