BJPS

Brazilian Journal of Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902017000300061

Article

In silico pharmacodynamics, toxicity profile and biological activities of the Saharan medicinal plant *Limoniastrum feei*

Ouahab Ammar*

Department of Pharmacy, Faculty of Medical Sciences, University of Batna 2, Algeria

In-silico study was performed to find the pharmacodynamics, toxicity profiles and biological activities of three phytochemicals isolated from *Limoniastrum feei* (Plumbagenaceae). Online pharmacokinetic tools were used to estimate the potential of Quercetin, kaempferol-3-*O*-β-D-glucopyranoside (astragalin) and quercitin-7-*O*-β-D-glucopyranoside as specific drugs. Then the prediction of potential targets of these compounds were investigated using PharmMapper. Auto-Dock 4.0 software was used to investigate the different interactions of these compounds with the targets predicted earlier. The permeability of quercetin was found within the range stated by Lipinski ′s rule of five. Hematopoietic prostaglandin (PG) D synthase (HPGDS), farnesyl diphosphate synthetase (FPPS) and the deoxycytidine kinase (DCK) were potential targets for quercetin, astragalin and quercetin 7, respectively. Quercetin showed antiallergic and anti-inflammatory activity, while astragalin and quercetin 7 were predicted to have anticancer activities. The activity of Astragalin appeared to be mediated by FPPS inhibition. The inhibition of DCK was predicted as the anticancer mechanisms of quercetin 7. The compounds showed interesting interactions and satisfactory binding energies when docked into their targets. These compounds are proposed to have activities against a variety of human aliments such as allergy, tumors, muscular dystrophy, and diabetic cataracts.

Keywords: *Limoniastrum feei*/pharmacokinetics. *Limoniastrum feei*/biological activity. Quercetin. Astragalin. Quercetin 7. Medicinal plants. Molecular docking.

INTRODUCTION

Nowadays, the world of pharmaceutical industry is inclining towards finding new chemical entities of natural source with biological activities (Neamati, Barchi, 2002). Therefore, the identification of different lead compounds follow many approaches (Sams-Dodd, 2006), recently, the utilization of in silico approach was found cost and time effective especially that several regulations and standardizations are under way (Pakomwit *et al.,* 2015). The proper pharmacokinetics and toxicity profile along with efficacy are the major determinants for successful drug development. Hence, the poor ADMET profile and the risk of toxicity are the major cause of late costly failure of drug development. Therefore, these fundamental criteria have to be studied carefully at the beginning of the chain of drug discovery (Chuai, 2017; Van de Waterbeemd, Gifford, 2003). In an aim to achieve reliable results, a number of tools were developed (Moroy *et al.*, 2012; Gabrielle *et al.*, 2014). The high cost and lengthy time needed to conduct these in vitro screens have called for the development of in silico approaches. Computational docking as a means to prioritize small molecules in drug discovery projects remains a highly popular in silico screening approach. Contemporary docking approaches without experimental parametrization can reliably differentiate active and inactive chemo types in a protein binding site (Pakomwit *et al.*, 2015, Van de Waterbeemd, Gifford, 2003). The diversity of content in natural plants and the presumably safe chemical nature of most of them placed their research in the core of drug discovery process. Many plants have their ethno medical uses, however many other curative potentials of those same plants remain unraveled. Herein, the medicinal plant Limoniastrum feei (plumbagenaceae) is not an exception. It is a Saharan medicinal plant, used in Saharan ethnopharmacopeae to treat gastric tract, hepatic disorder and cough (Rahmani *et al.*, 2012). Being involved in drug discovery from natural resources, a team

***Correspondence:** O. Ammar. Department of Pharmacy. Faculty of Medical Sciences. Université de Batna 2. Route de Tazoult – 05000. Batna – Algeria. Tel: +213-667479052. E-mail: ouahab.am@gmail.com.

of researchers from Algeria has recently isolated and identified three antimicrobial phytochemicals namely, quercetin 1, kaempferol-3-*O*-β-D-glucopyranoside 2 (astragalin) and quercetin-7-*O*-β-D-glucopyranoside 3 (quercetin 7) (Ziane *et al.*, 2015). Their chemical structures are displayed in Figure 1. To further estimate the drug ability of these phytochemicals, we herein report their ADMET profiles and potential biological activities using several in silico approaches.

MATERIALAND METHODS

Generation of the chemical structures

To estimate the *in silico* pharmacokinetic parameters of each one of the compounds, some web based in silico pharmacokinetic tools were used by submitting the chemical structure in the form of canonical simplified molecular input line entry system (SMILE).

1. Quercetin: C1=CC(=C(C=C1C2=C(C(=O)C3=C(-C=C(C=C3O2)O)O)O)O)O
2. Kaempferol-3-*O*-β-D-glucopyranoside (astragalin): C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=-C3O2)O)O)OC4C(C(C(C(O4)CO)O)O)O)O
3. Quercetin-7-*O*-β-D-glucopyranoside: C1=CC(=C(-C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)OC4C(-C(C(C(O4)CO)O)O)O)O)O)O)O

Molecular parameters

The estimation of the molecular parameters of the three lead compounds was performed using Molinspiration online server (http://www.molinspiration.com/). The estimated molecular properties were LogP, Topological polar surface area (TPSA), the number of hydrogen bond donors (HBD) and hydrogen bond acceptors (HBA). Drug likeliness property of the tested molecules was investigated as Gprotein coupled receptor (GPCR) ligands, ion channel modulators (ICM), kinase inhibitors (KI), nuclear receptor ligands (NRL), protease inhibitors (PI) and enzyme inhibitors (EI).

Admet properties

The ADMET profiles of the lead Chemicals were predicted using Admet SAR online server (http://lmmd.ecust.edu.cn:8000/) (Cheng *et al.*, 2012).

Metabolic transformations

The metabolic transformations of the three compounds were obtained using MetaPrint2D online server (http://www-metaprint2d.ch. cam.ac.uk/) (Carlsson *et al.*, 2010).

Pharmacological activities

The sdf formats of the lead compounds were submitted to PASS online tool (http://www.pharmaexpert.ru/passonline/) (Poroikov *et al.*, 2003), and then their probable pharmacological activities and toxicities were predicted.

Ligand preparation

The chemical structure of the compounds was drawn using ACD/ChemSketch v.12.0 software, and the obtained MDL format was converted into PDB format using Open Bable software (O'Boyle *et al.*, 2011).

Pharmmapper calculations

For each lead compound, the PharmMapper server (http:// 59.78.96.61/pharmmapper/) (Liu *et al.*, 2010) was used to identify its potential target based on its fit score. The lead compounds were submitted in MDL. sdf format, the target set was limited to human targets, and all other parameters were kept as default.

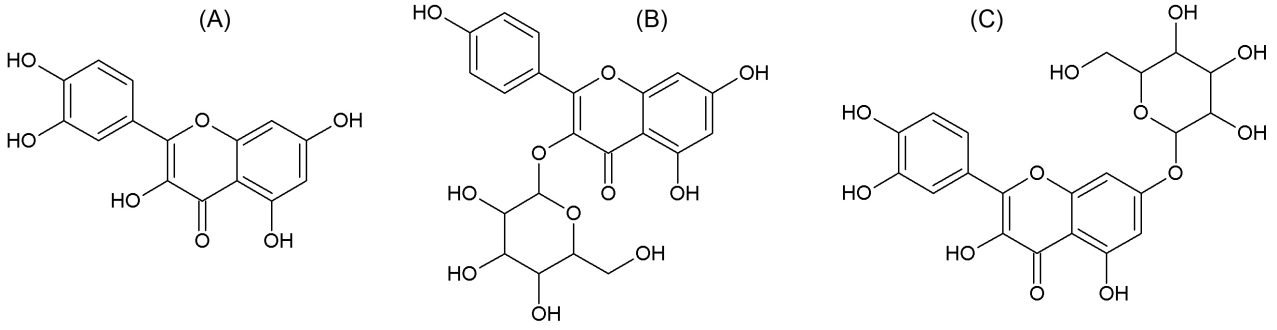

FIGURE 1 - Chemical structures of (1A) quercetin, (1B) astragalin and (1C) quercetin 7.

Preparation of the target protein

The pdb files of the identified top targets were obtained from protein databank (http://www.rcsb.org/pdb/home/home.do). Then, the protein files were prepared by removal of all water molecules and hetero groups except metals. The structures of the target molecules were optimized and the energy was minimized using Swiss PDB viewer V.4.1.0 software (Guex, Peitsch, 1997). Metapocket 2.0 online server (http://projects.biotec.tu-dresden.de/metapocket/index.php) was then used to predict the best active pocket and residues of the target proteins. MetaPocket 2.0 is a meta server to identify ligand binding sites on protein surface, metaPocket is a consensus method, in which the predicted binding sites from eight methods: LIGSITEcs, PASS, Q-SiteFinder, SURFNET, Fpocket, GHECOM, ConCavity and POCASA are combined together to improve the prediction success rate (Zengming *et al.*, 2011; Bingding, 2009)

In silico molecular docking

Molecular docking was performed using Autodock 4.0 software (Michel, 1999), based on Lamarckian Genetic Algorithm; which combines energy evaluation through grids of affinity potential to find the suitable binding position for a ligand on a given protein (Morris *et al.*, 1998). Polar hydrogen atoms were added to the protein targets and Kollman united atomic charges were computed. All hydrogen atoms were added to the ligands before the Gastiger partial charges were assigned. The cocrystal ligand was removed, and the bond orders were checked. The target's grid map was calculated and set with appropriate grid spacing to include the whole protein. The grid box was then allocated properly in the target to include the active residue in the center. The default docking algorithms were set in accordance with standard docking protocol. Finally, ten independent docking runs were carried out for each ligand, and results were retrieved as binding energies. Poses that showed lowest binding energies were visualized using MGL tools 1.5.6.

RESULTS AND DISCUSSION

Molecular parameters

According to 'Lipinski's rule of five', the lead compounds with poor absorption or permeation are known when there are more than 10 HBA, 5 HBD, the molecular weight is greater than 500 Da and the calculated LogP (CLogP) is greater than 5 (or MilogP>4.15) (Lipinski *et al.*, 2001). Moreover, good bioavailability is more likely for compounds with rotatable bonds≤10 (nrotb) and total polar surface area (TPSA) of ≤140 Å (Veber *et al.*, 2002). In this study; only Quercetin was predicted to have a high probability for good oral bioavailability where the calculated LogP values agreed with Lipinski's rule of five. Furthermore, TPSA, total hydrogen bond count and the number of rotatable bonds felt within the limit ranges (Table I). In addition, the number of hydrogen bond acceptors (HBA) and hydrogen bond donors (HBD) for Quercetin was found to be within Lipinski's limit range of 7 HBA and 5 HBD. Drug molecules of molecular weight less than 500 Da are easily transported, diffuse and absorbed as compared to heavy molecules (Srimai *et al.*, 2013). Case in point, Quercetin has a molecular weight (MW) of 302.24. Astragalin and Quercetin 7 displayed poor bioavailability according to Lipinski's rule of five, however, that does not prevent from applying other methods to enhance their bioavailability given that they show great therapeutic benefit.

TABLE I - Physicochemical parameters of the three lead compounds

Lead	miLogP	TPSA	MW	HBA	HBD	nrotb
Quercetin	1.68	131.35	302.24	7	5	1
Astragalin	0.12	190.28	448.38	11	7	4
Quercetin 7	-0.1	210.50	464.38	12	8	4

Drug ability likeliness property of quercetin, astragalin and quercetin 7 as GPCR ligands, ion channel modulators (ICM), kinase inhibitors (KI), nuclear receptor ligands (NRL), protease inhibitors (PI) and enzyme inhibitors (EI) were studied, and results were obtained as bioactivity scores. In this context, scores>0.00 indicate high activity, while scores between 0.00 to −0.5 indicate moderate activity and scores <−0.5 indicate inactivity (Paramashivam *et al.*, 2015). The results of the present study demonstrated that the three leads showed high bioactivity scores as KI, NRL and EIs (score>0.00) with Astragalin and Quercetin 7 being the most active as EIs (0.41 and 0.42, respectively) and Quercetin being the most active as KI and NRL (Table II). Nuclear receptors (NRs) are important pharmaceutical targets because they are key regulators of many metabolic and inflammatory diseases, including diabetes, dyslipidemia, cirrhosis and fibrosis (Yang, Li, Li, 2014). Based on our results, quercetin, qstragalin and quercetin 7 could be envisioned as potential ligands for NRs representing interesting and promising therapeutic alternatives to cure relevant disorders. Considerable

bioactivity against GPCR was revealed by astragalin and quercetin 7 (0.05 and 0.04 respectively); Quercetin, on the other hand, produced moderate activity (−0.06). All three compounds exhibited moderate activities as ion channel modulators (−0.19, −0.05 and −0.10, respectively). Moderate protease inhibition was also predicted for all three of them. Quercetin, astragalin and quercetin 7 were found active as kinase inhibitors (0.28, 0.10 and 0.15, respectively), and they could be used to treat diseases due to hyperactive protein kinases, including mutant or overexpressed kinases in cancer, or to modulate cell functions to overcome other disease drivers (Adam, Laszlo, David, 2016). In fact, a previous study proved that even a low concentration of quercetin decreased the activity of 16 kinases by more than 80%. Quantitative video microscopy analyses revealed that quercetin displayed strong anti-mitotic activity, leading to cell death (Boly *et al.*, 2011). In another study, quercetin 7 was found to possess anti-inflammatory activity, inhibiting expression of inducible nitric oxide synthase and release of nitric oxide by lipopolysaccharide-stimulated RAW 264.7 macrophages in a dose-dependent manner. Quercetin 7 also inhibited overexpression of cyclooxygenase-2 and granulocyte macrophage-colony-stimulating factor (Legault *et al.*, 2011).

Admet properties

The ADMET properties of the studied leads were calculated using admetSAR. Blood-Brain Barrier (BBB) penetration, Human Intestinal Absorption (HIA), Caco-2 cell permeability and Ames test were calculated. The results obtained for BBB penetrability greatly agreed with structures of the studied compounds. It was also found that all tested compounds could be absorbed by the human intestine, but they cannot penetrate to Caco-2 (Table III). Nevertheless, the tested compounds proved to be potential substrates for Pglycoprotein (P-gp) which effluxes drugs and various compounds to undergo further metabolism and clearance (Amin, 2013) resulting in therapeutic failure because the drug concentration would be lower than expected (Levin, 2012). Many of the human microsomal P450s aromatase catalyze the metabolism of a wide variety of compounds including xenobiotic and drugs (Ghosh *et al.*, 2012). Thus, inhibition of cytochrome P450 isoforms might cause drug-drug interactions in which co-administered drugs fail to be metabolized and accumulate to toxic levels (Lynch, Price, 2007). Notwithstanding, some of the cytochrome P450 isoforms could be inhibited by one or more of the tested compounds. Fortunately, Quercetin did not show any acute toxicity and mutagenic effect with respect to the Ames test data. Surprisingly, astragalin and quercetin 7 were found mutagenic (Mortelmans, Zeiger, 2000) and they need to be administered cautiously. The different Chemical compounds were classified into four categories based on the criterion of WHO (WHO, 2010). Category I contains compounds with LD50 values less than or equal to 50 mg/kg. Category II contains compounds with LD50 values greater than 50mg/kg but less than 500mg/kg. Category III includes compounds with LD50 values greater than 500mg/kg but less than 5000mg/kg. Category IV consisted of compounds with LD50 values greater than 5000mg/kg. Hence, quercetin is slightly hazardous while astragalin and quercetin 7 are unlikely to present acute hazard.

Metabolic transformations

MetaPrint2D predictions revealed that the red colored hydroxyl groups for the three compounds represented good sites for metabolism (Figure 2). Metabolic transformations (Glucuronidation, Sulfation, Methylation, Dehydroxylation, Glucosidation, Hydroxylation, Acylation, and Phosphorylation) were predicted for the hydroxyl groups. Dealkylation, on the other hand, was proposed for the ether group.

The color highlighting an atom indicates its Normalized Occurrence Ratio (NOR). A high NOR indicates a more frequently reported site of metabolism in the metabolite database. Atoms are colored according to the likelihood of a metabolic site; High: red, Medium: orange, Low: green, very low is not colored, and No data: grey.

PASS online server

The chemical structure is described in PASS by original descriptors called Multilevel Neighborhoods

TABLE II - Estimation of drug ability of the three lead compounds

Lead	GPCR	ICM	KI	NRL	PI	EI
Quercitin1	-0.06	-0.19	0.28	0.36	-0.25	0.28
Astragalin	0.05	-0.05	0.10	0.20	-0.05	0.41
Quercitin7	0.04	-0.10	0.15	0.23	-0.06	0.42

TABLE III - ADMET properties of the three lead compounds

Model	**Lead compound**		
Absorption	**Quercetin**	**Astragalin**	**Quercetin 7**
Blood-Brain Barrier	BBB-	BBB-	BBB-
Human Intestinal Absorption	HIA+	HIA+	HIA+
Caco-2 Permeability	Caco2-	Caco2-	Caco2-
P-glycoprotein Substrate	Substrate	Substrate	Substrate
P-glycoprotein Inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor
	Non-inhibitor	Non-inhibitor	Non-inhibitor
Renal Organic Cation Transporter	Non-inhibitor	Non-inhibitor	Non-inhibitor
Distribution and Metabolism			
CYP450 2C9 Substrate	Non-substrate	Non-substrate	Non-substrate
CYP450 2D6 Substrate	Non-substrate	Non-substrate	Non-substrate
CYP450 3A4 Substrate	Non-substrate	Non-substrate	Non-substrate
CYP450 1A2 Inhibitor	Inhibitor	Non-inhibitor	Non-inhibitor
CYP450 2C9 Inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor
CYP450 2D6 Inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor
CYP450 2C19 Inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor
CYP450 3A4 Inhibitor	Inhibitor	Non-inhibitor	Non-inhibitor
CYP Inhibitory Promiscuity	High CYP Inhibitory Promiscuity	Low CYP Inhibitory Promiscuity	Low CYP Inhibitory Promiscuity
Excretion and Toxicity			
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	Weak inhibitor	Weak inhibitor
	Non-inhibitor	Non-inhibitor	Non-inhibitor
AMES Toxicity	Non AMES toxic	AMES toxic	AMES toxic
Carcinogens	Non-carcinogens	Non-carcinogens	Non-carcinogens
Fish Toxicity	High FHMT	High FHMT	High FHMT
Tetrahymena Pyriformis Toxicity	High TPT	High TPT	High TPT
Honey Bee Toxicity	High HBT	High HBT	High HBT
Biodegradation	Not ready biodegradable	Not ready biodegradable	Not ready biodegradable
Acute Oral Toxicity	II	III	III
Carcinogenicity (Three-class)	Non-required	Non-required	Non-required
ADMET Predicted Profile (Regression)			
Absorption			
Aqueous solubility (LogS)	-2.9994	-2.4489	-2.4489
Caco-2 Permeability (LogPapp, cm/s)	0.2245	-0.8582	-0.8582
Toxicity			
Rat Acute Toxicity (LD50, mol/kg)	3.0200	2.3869	2.3869
Fish Toxicity (pLC50, mg/L)	0.4787	1.0156	1.0156
Tetrahymena Pyriformis Toxicity (pIGC50, ug/L)	0.6854	0.3284	0.3284

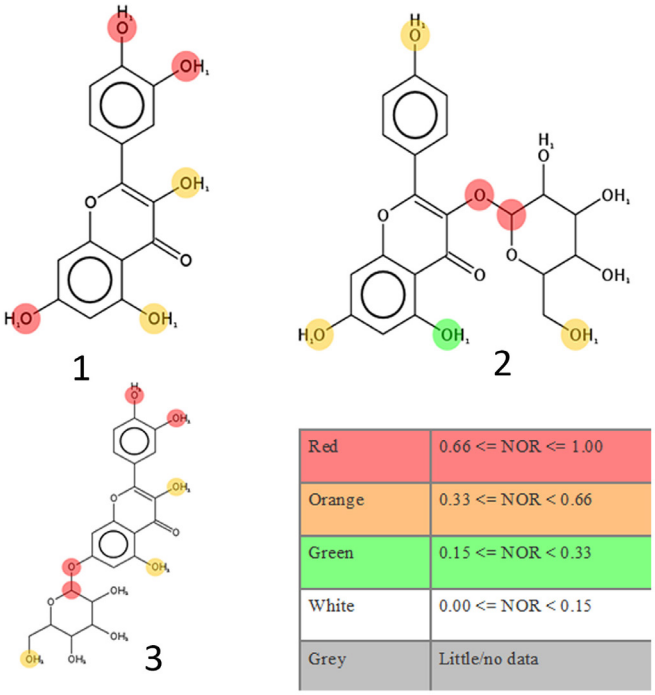

FIGURE 2 - Metabolic transformations of (1) quercetin, (2) astragalin and (3) quercetin 7.

of Atoms (MNA). For each investigated activity, PASS calculates two probabilities, Pa and Pi, based on statistics of MNA descriptors. Pa and Pi values vary from 0.000 to 1.000 indicating the probabilities of the compound to be active or inactive, respectively. Our findings revealed that Quercetin is a potential chlordecone reductase inhibitors (Pa=0.986) (Table IV). The clinically important chlordecone reductase belongs to a family of enzymes known as aldo-ketoreductases. These enzymes are involved in the metabolism of xenobiotics and have been implicated in the pathogenesis of diabetic cataracts and muscular dystrophy (Molowa, Andrew, Shayne, 1986). Nonetheless, chlordecone reductase inhibition could be a drawback in the sense that risk of developing prostate cancer is positively associated with the chlordecone concentration in blood (Multigner *et al.*, 2016). Astragalin showed a higher probability to function as Membrane integrity agonist (Pa = 0.989). Thus playing an important role in the anti-inflammatory mechanism, Case in point, the results of a recent study showed that astragalin suppressed the expression of tumor necrosis factor α, interleukin 6, and nitric oxide in a dose-dependent manner in primary cultured mouse mammary epithelial cells (Li *et al.*, 2014). Quercetin 7 on the other hand was found useful as hemostatic.

In silico molecular docking

PharmMapper server has predicted that hematopoietic prostaglandin (PG) D synthase (HPGDS) (PDB ID: 1V40), Farnesyl diphosphate synthetase (FPPS) (PDB ID: 1YQ7) and the deoxycytidine kinase (DCK) (PDB ID: 1P60) are the best targets, in terms of fit scores (3.596, 3.647 and 6.265), for quercetin, astragalin and quercetin 7, respectively. HPGDS is responsible for the production of PGD (2) as an allergy or inflammation mediator in mast and Th2 cells (Inoue *et al.*, 2004). It has shown promise as a potential target for anti-allergic and anti-inflammatory drugs (Fredrik *et al.*, 2015). Quercetin was successfully docked into HPGDS with a binding energy of -6.28 kcal/mol. Analysis of the binding interactions revealed that quercetin formed a hydrogen bond with the active pocket via two residues namely Arg 412 and Lys 598 (Figure 3A). The above-mentioned interaction of Quercetin with the two amino acids results in a recognizable conformational change in the active pocket. Thus, the active pocket will no longer be complementary with the natural substrate. Being an HPGDS inhibitor, Quercetin can be considered as a potential lead for development of novel drugs for allergy and inflammation. As shown in Figure 3B, Docking of astragalin into FPPS enzyme (binding energy = -2.72 kcal/mol) showed hydrogen bonding with Tyr 363, Arg 74, Asn 73, which are central binding residues for the top active pocket as predicted by Metapocket 2.0. FPPS is a key enzyme in isoprenoid biosynthesis which catalyzes the formation of farnesyl diphosphate (FPP), a precursor for several classes of essential metabolites including sterols, dolichols, carotenoids, and ubiquinones. FPP also serves as substrate for protein farnesylation and geranylgeranylation. Catalyzes the sequential

TABLE IV - Prediction of biological activities of the compounds

Lead compound	Pa	Pi	Activity
Quercetin	0.986	0.001	Chlordecone reductase inhibitor
Astragalin	0.989	0.001	Membrane integrity agonist
Quercetin 7	0.986	0.001	Hemostatic

Pa: Probability of activity. Pi: Probability of inactivity.

condensation of isopentenyl pyrophosphate with the allylic pyrophosphates, dimethylallyl pyrophosphate, and then with the resultant geranylpyrophosphate to the ultimate product farnesyl pyrophosphate (Manoj, Archana, Sanjana, 2013). Recent studies have validated FPPS as a molecular target of bisphosphonates for drug development against tumors as well as human pathogens (Raikkonen *et al.*, 2011; Oldfield, 2010). It appears that Astragalin activity could be mediated through FPPS-inhibition. Quercetin 7 docked nicely within the fourth active pocket of DCK enzyme (binding energy = -4.04 kcal/mol). The hydrogen bonds were formed with Gln 168, Arg 20, Gln 165, and Lys 23 (Figure 3C). It is worth noting that DCK is required for the phosphorylation of several deoxyribonucleosides and their nucleoside analogs. Deficiency of DCK is associated with resistance to antiviral and anticancer chemotherapeutic agents. Conversely, increased deoxycytidine kinase activity is associated with increased activation of these compounds to cytotoxic nucleoside triphosphate derivatives. DCK is clinically important because of its relationship to drug resistance and sensitivity (Hazra *et al.*, 2011). Thus, an anticancer activity is predicted for quercetin 7 through DCK inhibition.

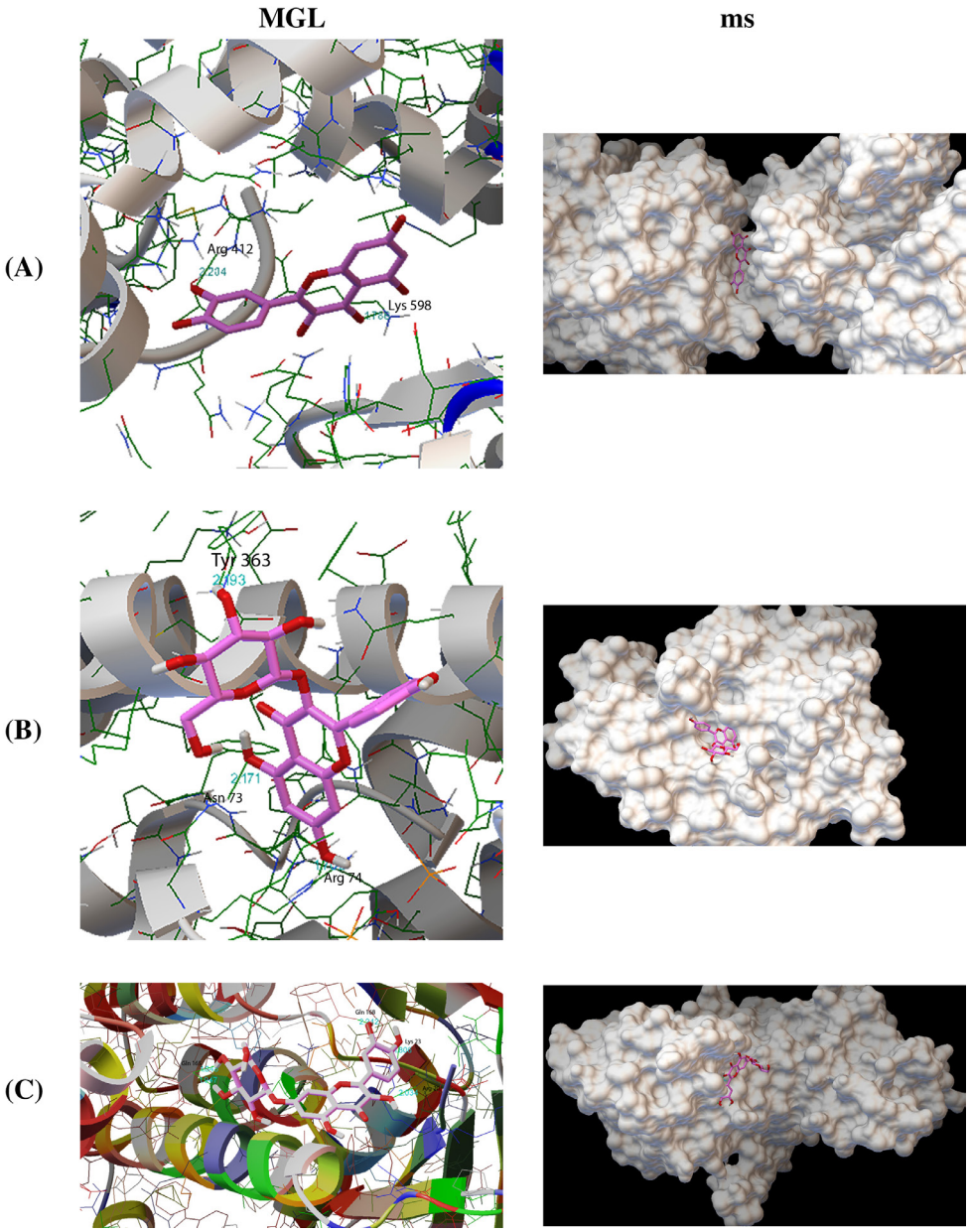

FIGURE 3 - The chemical interaction between the proteins and the ligands visualized using MGL tools and molecular surface (ms), where: (3A) HPGDS and quercetin, (3B) FPPS and astragalin, (3C) DCK and quercetin 7.

CONCLUSION

The ADMET profiles for the lead compounds; quercetin, astragalin and quercetin 7, isolated from *Limoniastrum feei* have been estimated using different web based in silico tools. In addition, their biological activity spectra were also investigated. Quercetin was proposed to have potential antiallergic and anti-inflammatory activity through inhibition of HPGDS and was also proposed to play a role in the treatment of diabetic cataracts and muscular dystrophy through inhibition of chlordecone reductase enzyme. Astragalin was predicted to have anticancer activity mediated by FPPS inhibition. While quercetin 7 was proposed to have an anticancer and antiviral activity through DCK inhibition and hemostatic activity as well.

ACKNOWLEDGMENT

The author acknowledges the members of the Department of Pharmacy, University of Batna 2 in Algeria for support and assistance.

CONFLICT OF INTERESTS

The author declares no conflict of interest.

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Received for publication on 23rd September 2016
Accepted for publication on 31st January 2017