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First Study on Anti-diabetic Effect of Rosemary and Salvia by Using Molecular Docking

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Authors' contributions

This work was carried out in collaboration between all authors. Author BS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AH and GS managed the analyses of the study and the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Nowadays use of herbs as medicines is important research subject over the world attracting researchers from different research filed to look for less use of synthetic drugs because of their side effects on human health. In this paper we use molecular modeling and molecular docking as tools for valorization of natural's plants in medicinal use. Computational chemistry permits a significant gain of time and money in studying medicinal plants role by prediction of molecules inhibition actions of enzymes. *Rosemary* and *Salvia* have been the subject of many classic studies for therapeutic use (antioxidant, antiseptic...) but never studied for their anti-diabetic activity only with molecular docking (especially *Salvia*). In our study we predict interaction of main terpenoids from *Rosemary and Salvia* by investigating inhibition process of DPP-4 enzyme using Molecular Operating Environment software (MOE). Obtained results show and describe capacity of natural's molecules from *Rosemary* and *Salvia* in inhibition of DPP-4. The molecules from *Rosemary and Salvia* which are the best inhibitors of DPP-4 have been identified.

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Keywords: Diabetes type 2; Rosemary; Salvia; DPP4 enzyme; molecular modeling; medicinal plants.

1. INTRODUCTION

Use of Herbs as medicines (phytotherapy) for diseases treatment is subject interested by researchers in many fields. Computational and theoretical chemistry (molecular modeling and molecular docking) allow saving time and money in discovering of new therapeutic molecules and also contribute to better comprehension of medicinal plants action against diseases. Computational chemistry is being important and necessary to wet laboratory experiment, permitting studying structures and functions of biomolecules. Several drugs and drug candidate were developed by molecular docking. Actually natural's terpenoids from medicinal plants as *Rosemary* and *Salvia* (Lamiaceae) are widely investigated for their therapeutic effect (e.g. inflammatory pain) [1,2]. Most investigated terpenoids are carnosic acid and carnosol and many recent researches show efficacy of carnosic acid and carnosol against many illnesses (Table 1). Other recent researches show presence of diterpenoids and triterpenoids (Fig. 1) similar to carnosic acid and carnosol that may have positive effect on human health [3,4]. *Salvia* spices is distributed all around the word, it is also consumed as tea and food in some Mediterranean region. Many *Salvia* and *Rosemary* spices are accepted as medicinal by Pharmacopeias (European Pharmacopeia and British Pharmacopeia) [4]. *Rosemary* extracts were classified as food additives by the European Commission under E393 code [3]. Researches interest to carnosic acid and carnosol increase since U.S food Drug Administration and European food safety approved their use as food additive [5, 6, and 7]. *Rosemary* and *Salvia* are known in traditional and popular Algerian medicine for their interest in treatment of inflammations, pain, regulation of intestinal transit and asthma.

Among investigated disease by computational chemistry we find Type 2 Diabetes mellitus (T2DM). T2DM is a metabolic disease which cause hyperglycaemia with pathophysiological factors and may bring about other health damage. [17]. Main important enzyme responsible of mellitus T2DM is Dipeptidyl-Peptidase (DPP-4), which is also known as CD26 or 5TB4. The importance of DPP-4 for researchers raised since the approval of DPP-4 inhibitors for the treatment of type 2 diabetes mellitus (T2DM) [18].

In best of our knowledge no studies have been done on effect of *Rosemary* and *Salvia* on Type 2 diabetes by studying inhibition of DPP-4 by extracted oils from *Rosemary* and *Salvia* using only molecular modeling by MOE software. In this work we are going to study the anti-diabetic effect of essential terpenoids from *Rosemary* and *Salvia* by inhibition of DPP-4 using molecular modeling and molecular docking, verification of Lipinski rules is also checked. The Molecular Environment Operating software is used [19].

Table 1. Carnosic acid and carsonol effects

Diseases / Pains	References
Antioxidant	[8,9]
antimicrobial	[10,11]
Antitumor	[12,13]
Anti-inflammatory	[14,15]
Anti-obesity	[16,17]
Anticancer,	[7,16]
Anti-proliferative	[7]
Anti-invasive	[7]

2. MATERIALS AND METHODS

According to recent researches terpenoids from *Rosemary* and *Salvia* were identified [6], and their structures were drawn by ChemDraw software (Fig. 1). **(a) Carnosic acid 12-methyl ether**: (4aR,10aS)-5-hydroxy-7-isopropyl-6-methoxy-1,1-dimethyl-1,3,4,9,10,10a-hexahydrophenanthrene-4a(2H)-carboxylic acid; **(b)carnosic acid**: (4aR,10aS)-5,6-dihydroxy-1,1-dimethyl-7-propan-2-yl-2,3,4,9,10,10a-hexahydrophenanthrene-4a-carboxylic acid; **(c)carnosol**: (9S)-5,6-dihydroxy-7-isopropyl-1,1-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-9-yl propionate; **(d)Epirosmanol**: methyl((9S,10R)-3,4,10-trihydroxy-2-isopropyl-8,8-dimethyl-4b,5,6,7,8,8a,9,10-octahydrophenanthren-9-yl)-l4-oxidanone ;**(e)Erythrodiol**: (3S,4aR,6aR,6bS,8aS,12aS,14aR,14bR)-8a-(hydroxymethyl)-4,4,6a,6b,11,11,14b-heptamethyl-1,2,3,4a,5,6,7,8,9,10,12,12a,14,14a-tetradecahydropicen-3-ol; **(f)Ferruginol**:(4bS,8aS)-4b,8,8-trimethyl-2-propan-2-yl-5,6,7,8a,9,10-hexahydrophenanthren-3-ol; **(g)Isorsmanol**: (9R,10S)-5,6,10-trihydroxy-7-isopropyl-1,1-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-9-yl propionate; **(h)Manool**: (3R)-5-[(1S,4aS,8aS)-5,5,8a-

trimethyl-2-methylidene-3,4,4a,6,7,8-hexahydro-1H-naphthalen-1-yl]-3-methylpent-1-en-3-ol

(i)Rosmanol: (4bR,8aS,9S,10S)-3,4,10-Trihydroxy-2-isopropyl-8,8-dimethyl-6,7,8,8a,9,10-hexahydro-5H-9,4b-(epoxymethano)phenanthren-12-one;

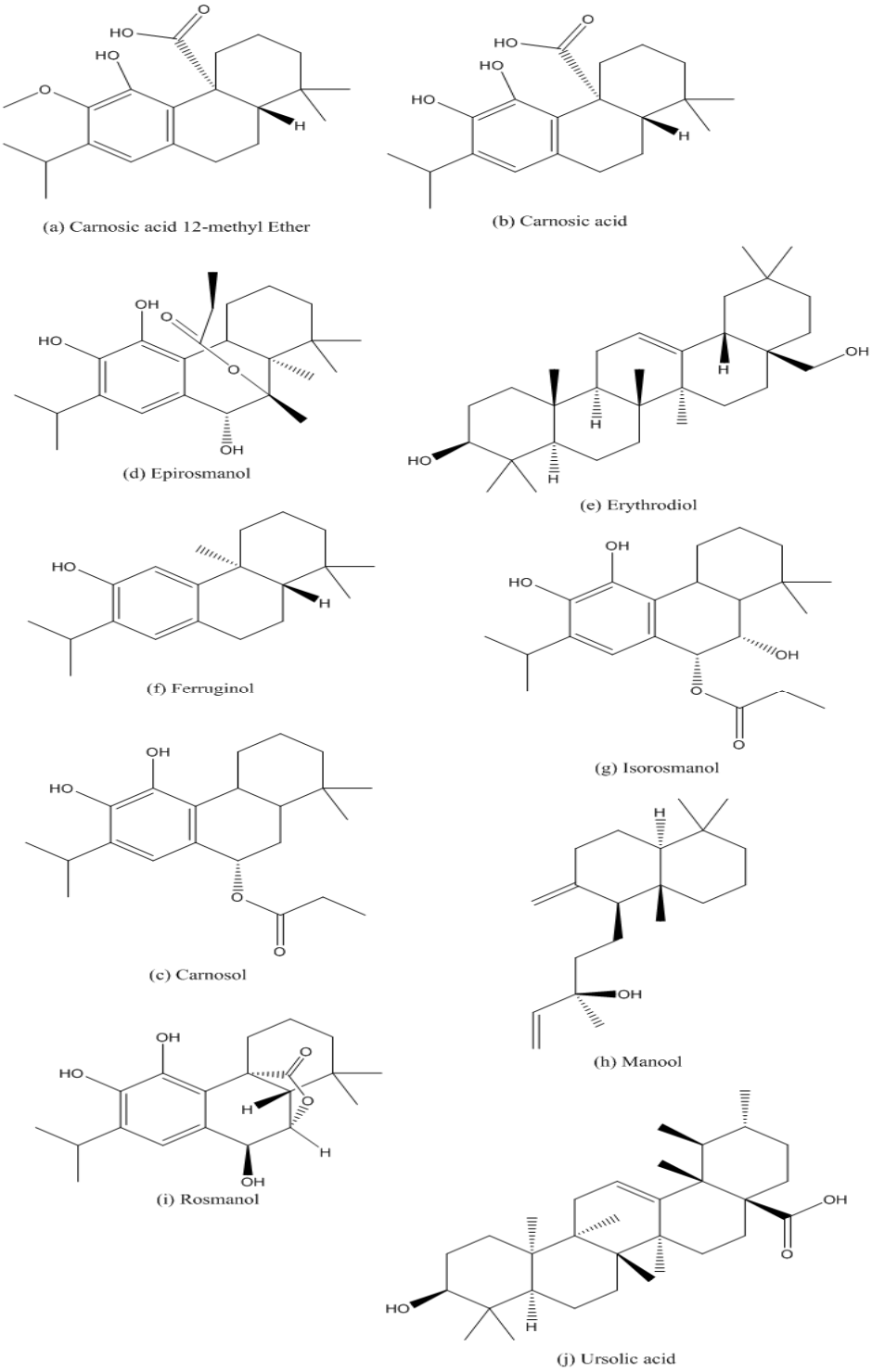

Fig. 1. Terpenoids structures from *Rosemary* and *Salvia*

(j)Ursolic Acid: (1S,2R,4aS,6aS,6bR,8aR,10S,12aR,12bR,14bS) -10-hydroxy-1,2,6a,6b,9,9,12a,12b,14b-nonamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14 b-octadecahydropicene-4a(2H)-carboxylic acid

Physicochemical parameters of terpenoid's ligand are reported in Table 2. " Rule-of-five " (RO5) or Lipinski's rule is famous filter for drug-likeness concept proposed by medicinal and computational chemists, which is valuable tool to select more promising lead candidates by predicting (or) evaluating drug-likeness property in the early stage of drug discovery and development. The four simple physicochemical parameter ranges (MWT ≤ 500, log P ≤ 5, H-bond donor's ≤ 5, H-bond acceptors ≤10). These physicochemical parameters are associated with acceptable aqueous solubility and intestinal permeability (logS ≤ -4). [20,21]. RO5 has been expanded to other parameters for prediction of drug- likeness, (*e.g;* Polar surface area: TPSA) [22].

The structure of Dipeptidyl-peptidase (DPP-4) (Fig. 2) was downloaded from PROTEIN DATA BANK (code 5T4B) with three-dimensional structure obtained by X-ray diffraction (resolution 1.76 Å).

Table 2. Molecular descriptors analysis of 10 ligands using MOE software

Ligand	MW	TPSA	LogP	LogS	H- bonds donors	H- bonds acceptors	Toxicity	Violations
Compound (a)	346.47	66.76	4.62	-6.06	2	4	No	0
Compound (b)	332.44	77.76	4.32	-5.65	3	4	No	0
Compound (c)	330.42	66.76	4.38	-5.52	2	3	No	0
Compound (d)	346.42	86.99	3.35	-4.80	3	4	No	0
Compound (e)	442.73	40.46	7.14	-8.74	2	2	No	1
Compound (f)	286.46	20.23	5.55	-7.59	1	1	No	1
Compound (g)	346.42	86.99	3.35	-4.80	3	4	No	0
Compound (h)	290.49	20.23	5.50	-6.90	1	1	No	1
Compound (i)	346.42	86.99	3.35	-4.80	3	5	No	0
Compound (j)	456.71	57.53	7.09	-8.62	2	3	No	1

MW: Molecular weight (g/mol), TPSA: Polar surface area (Å^2), logP: Octanol-water partition coefficient, logS : aqueous solubility, H- bonds donors : Number of H- bonds donors, H- bonds acceptors: Number of H- bonds acceptors, Violations: number of rule of 5 violations

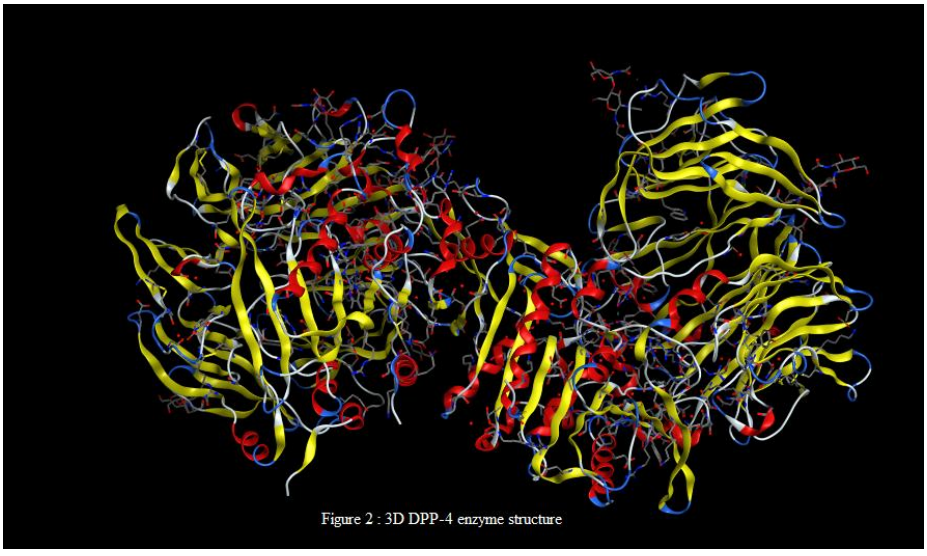

Fig. 2. 3D DPP-4 structure

2.1 Preparation and Optimization of Both Enzyme and Terpenoids from Rosemary and Salvia

The preparation of DPP-4 enzyme consists of elimination of one chain from the enzyme, than protonation and hiding hydrogen's of the second chain. Hydrogen's are hidden to minimize the size of file. As an necessary step, all water molecules were removed from the surface of the protein, that they will not mask the protein surface from the ligand. Also energy minimizing of the enzyme and the geometry was performed using the field strengths in the MMFF94x and Hamiltonian AM1 implanted in MOE Software. The second important step is isolation of the enzyme active site and identification of general protein distribution (Figs. 3,4) The Protein Geometry distribution provides a variety of stereochemical measurements for inspection of the structural quality in a given protein. The atomic structures of protein molecules provide a

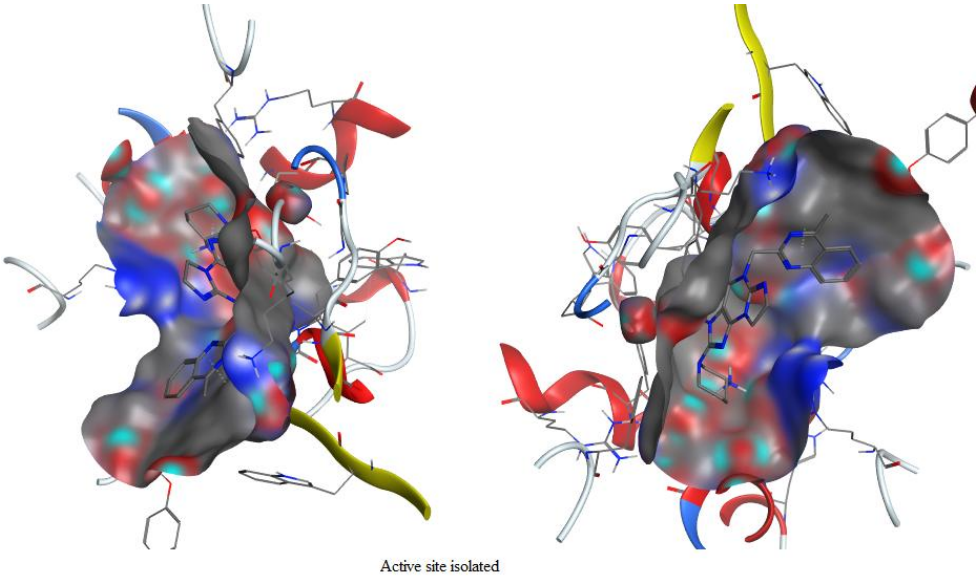

Fig. 3. Active site enzyme isolated

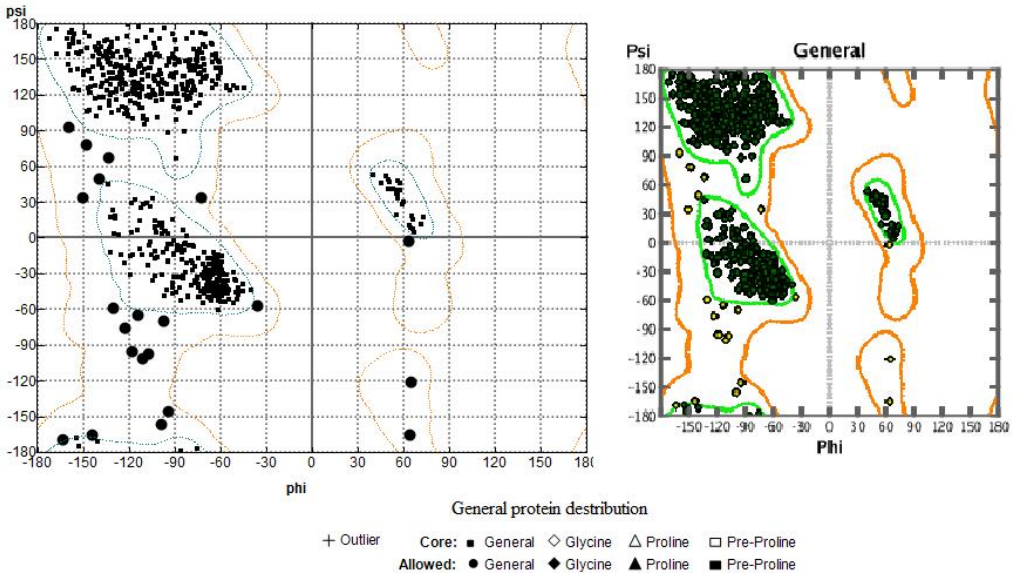

Fig. 4. General protein distribution

wealth of information for understanding the biological roles of proteins. With geometric characterization, we can gain important insight on the structural basis of proteins. By directly estimate the evolutionary pattern of residue substitution for voids or pockets; we can separate selection pressure due to biological role from that due to the need to maintain protein structure and folding stability. The evolutionary pattern can be used to predict and characterize protein functions. It is likely that continued geometric and topological studies of protein structures and their interplay will generate new knowledge and lead to important innovation in computational tools for furthering our understanding of biology. Information's can be used to predict protein function and characterize binding properties of enzymes [22]. The active site was performed using MOE site finder (according to MOE protocols). Optimization of molecules was done under the same conditions of enzyme optimization.

3. DOCKING AND BUILDING COMPLEXES

After optimization of both molecules from *Rosemary* and *Salvia* (ligands) and enzyme, we proceed to positioning of ligands in to active site of the enzyme (5TB4) using Dock module (Molecular Docking) implemented in MOE software [23], and ligplot is implemented in MOE permitting visualization of interactions between enzyme and ligand. The purpose of the Dock application is looking at favorable conformational binding between medium size ligands and a not so soft macromolecular target, which is usually a protein.

Molecular mechanics determine the bending energy between target (host binding site) and the ligand. The site finder implemented in MOE used for prediction a nearby pocket or active site able to anchor molecule. Fig. 5 shows interaction potential in the optimized enzyme which is a map providing graphical representation of where chemical probe has favorable interaction with molecular surface. Each level slider controls a contour graphic that shows the locations in space at which the probe has interaction energy equal to given value (Kcal/mol). Energy balances of complexes are shown in Table 2. In this work we are going to focus our study on interactions in three first complexes giving the best score.

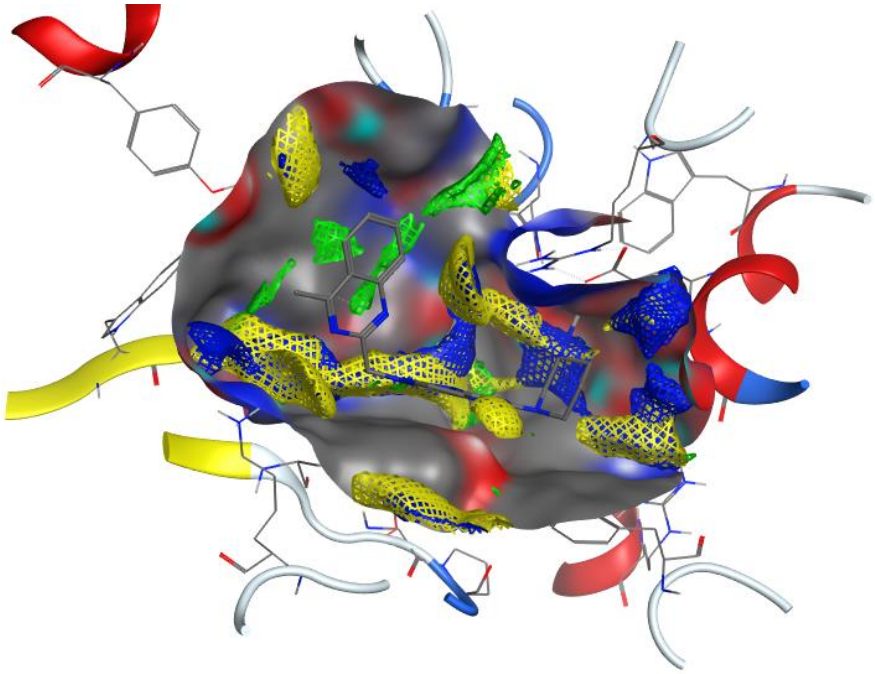

Fig. 5. Interaction potential
N: Yellow, OH2: blue, DRY: Green

Table 3. Energy balance of complexes (Kcal/mol)

Molecules	Poses	Rmsd_refine	E_conf	E_place	E_refine	Score
Carnosic acid 12-methyl ether	7	2.79107833	41.8281441	-58.2427597	-12.254199	-5.07837057
Carnosic acid	9	2.71786642	19.5741119	-36.2673874	-12.5738926	-4.63349819
Carnosol	8	1.40474367	73.8832932	-43.7374573	-12.466506	-4.5695734
Epirosmanol	8	2.92705584	69.0868988	-40.8612785	-12.6123352	-4.5118165
Erythrodiol	6	3.11756945	147.777985	-44.6511002	-12.8621216	-5.59761238
Ferruginol	6	1.15516746	63.946537	-63.2288437	-12.5733271	-5.3558712
Isorosmanol	9	2.7637105	91.5079956	-54.7710533	-13.3065596	-5.15827656
Manool	8	1.79628408	74.3825684	-47.5340347	-7.755373	-5.38269901
Rosmanol	9	2.84367108	75.288475	-52.3082123	-12.1775198	-4.44419193
Ursolic acid	9	1.84541321	77.215538	-50.3139153	-6.60194302	-5.44997978

rmsd_refine: the mean square deviation between the laying before refinement and after refinement pose, E_conf: energy conformer, E_place: score of the placement phase, E_scor1: score the first step of notation, E_refine: score refinement step and number of conformations generated by ligand, Score: the final score; is the score of the last step.

4. RESULTS AND DISCUSSION

4.1 Docking Procedure Validation

For validation of our MOE-docking protocol, the co-crystallized ligand was removed from the active site of the DPP-4 enzyme and re-docked in the same binding cavity (Fig. 7), the obtained result shown RMSD = 1,5922 (RMSD < 2) which mean that our Docking protocol is valid [24] .

Given results in Table 2 show that complex formed with Erythrodiol gives the best score (-5.59761238 Kcal/mol), that mean the most stable complex. The second stable complex is given with Ursolic acid ligand (-5.44997978 Kcal/mol). The third important score is given by Manool (-5.38269901).

According to obtained results complex formed with Erythrodiol is the most stable (Fig. 6), only one interaction is possible type H-π with distance of 3.74 Å and energy about -0.6 Kcal/mol. In the complex formed with Ursolic acid there are no interactions, only Van der Wals interactions are perceptible (Fig. 7).

Diagram of complex formed with Manool don't show any interactions, only Van Der Wals interactions are perceptible (Fig. 8). Graphical legend of 2D interaction is shown in Fig. 10.

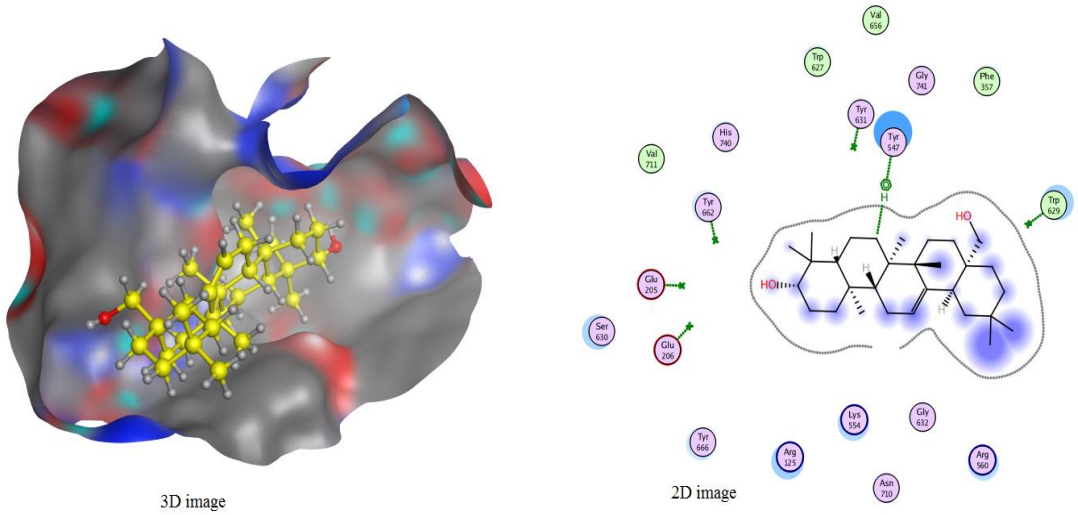

Fig. 6. Diagram interaction of Erythrodiol with DPP-4 enzyme

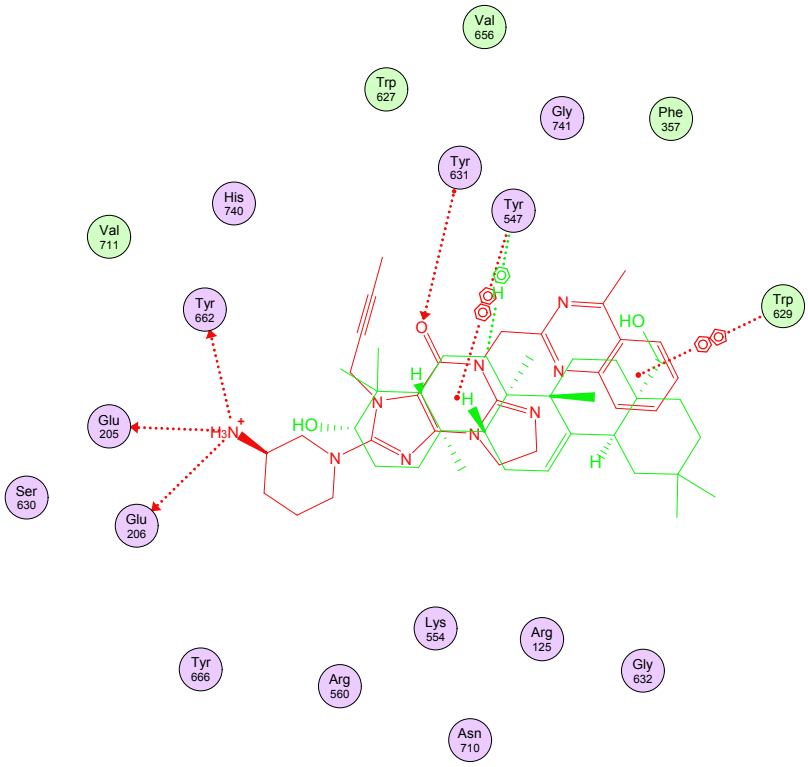

Fig. 7. The two ligands overlay

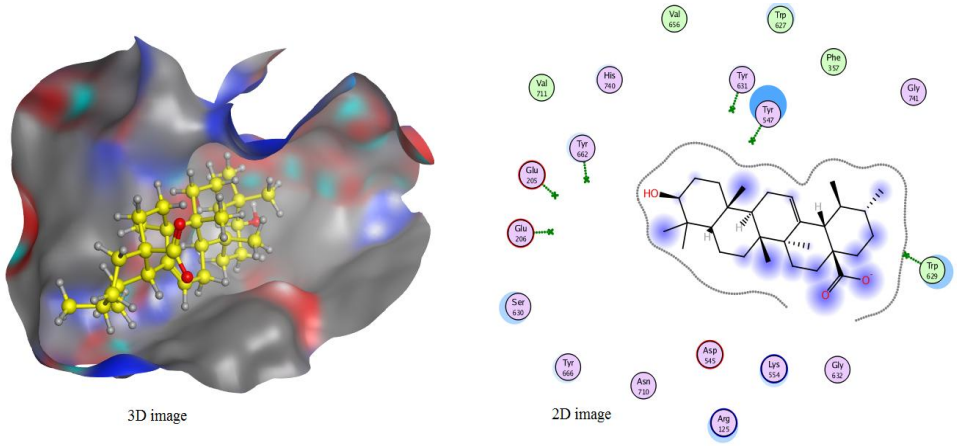

Fig. 8. Diagram interaction of Ursolic acid with DPP-4 enzyme

Comparing to other investigations [25] in the same field of Diabetes research using molecular docking we find that there are synthesized molecules which inhibit DPP-4 enzyme better than molecules contained in *Rosemary and salvia* with score docking results not so higher than score obtained with Terpenoids from *Rosemary* and *Salvia*. The synthesized molecules (Metformine, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin) are used as drug for treatment of diabetes type 2, but those molecules have many side effects as reported by European Medicines Agency [26]. The Table 4 below gives overview about side effect of principals synthesized hypoglycemic cited above.

Table 4. Main side effects of some synthetic hypoglycemic drugs [26]

Synthesized hypoglycemic	Secondary effect
Sitagliptin (Januvia)	• Blood and lymphatic system disorders • Cardiac disorders • Gastro intestinal disorders • Nervous system disorders • Respiratory, thoracic and mediastinal disorders • Renal and urinary disorders • Psychiatric disorders
Linagliptin (Trajenta)	• Cardiac disorders • Gastro intestinal disorders • Hepatobiliary disorders • Metabolism and nutrition disorders • Nervous system disorders • Skin and subcutaneous tissue disorders • Renal and urinary disorders
Metformine (Glucophage)	• Cardiac disorders • Gastro intestinal disorders • General disorder and administration site disorders • Injury, poisoning and procedural complication • Metabolism and nutrition disorders • Nervous system disorders • Renal and urinary disorders • Vascular disorders
Saxagliptin (Onglyza)	• Cardiac disorders • Eye disorders • Gastro intestinal disorders • Infections and infestations • Injury, poisoning and procedural complications • Psychiatric disorders • Muskuloskeletal and connective tissue disorders • Hepatobiliary disorders • Vascular disorders • Renal and urinary disorders
Vildagliptin (Galvus)	• Blood and lymphatic system disorders • Cardiac disorders • Gastro intestinal disorders • Eye disorders • General disorder and administration site disorders • Hepatobiliary disorders • Immune system disorders • Hepatobiliary disorders • Metabolism and nutrition disorders • Psychiatric disorders • Renal and urinary disorders • Respiratory, thoracic and mediastinal disorders • Skin and subcutaneous tissue disorders • Vascular disorders

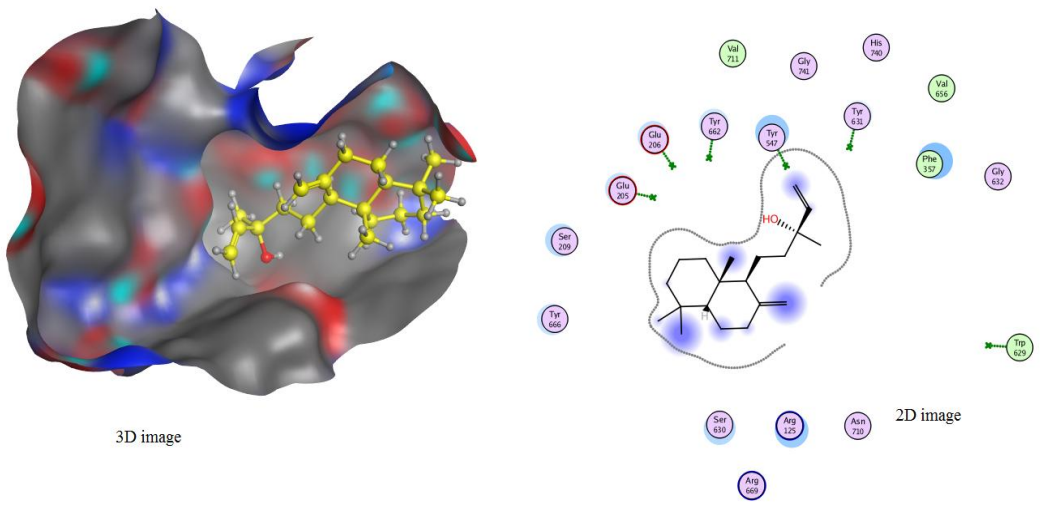

Fig. 9. Diagram Interaction of Manool with DPP-4 enzyme

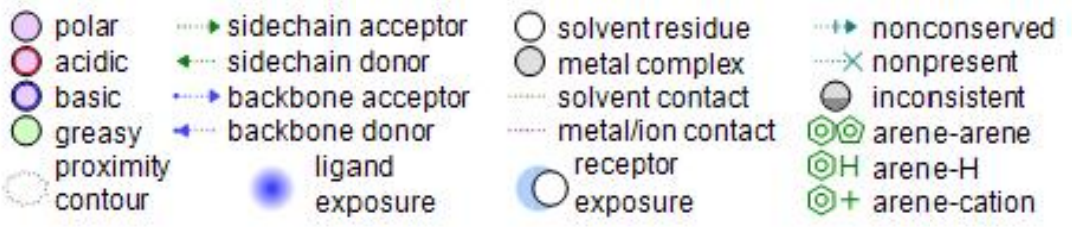

Fig. 10. 2D graphical legend

5. CONCLUSION

Regarding the obtained results we can admit that *Rosemary and Salvia* have significant effect on DPP-4 enzyme inhibition and consequently anti-diabetic effect without mentioned undesirable side effects on health. Regarding Lipniski rules we can conclude that excepting Erythrodiol, Ferruginol, Mannol and Ursolic acid, terpenoids from *Rosemary* and *Salvia* orally administered may have hypoglycemic effect, this latter confirm importance of *Rosemary* and *Salvia* in traditional medicine and as additive food. To our knowledge, we are the first to report the binding of terpenoids from *Rosemary* and *Salvia* with DPP-4 enzyme. Computational chemistry is very important for phytotherapy research allowing saving time and money permitting identification molecules with the best therapeutic interest and the best administration use. In this way we encourage investigating *Rosemary* and *Salvia* in diabetes type 2 treatments. Because of secondary effects of synthetic hypoglycemic molecules, use of medicinal plants is highly recommended. As future investigation we advise studying inhibition of DPP-4 enzyme by association docking of two or three terpenoids from *Rosemary* and *Salvia*. Morever terpenoids need further studies in terms of synthesis, structural relationship activity followed by testing in various *in vitro* and *in vivo* testing.

CONSENT

It is not applicable

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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