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Computational chemistry contribution in study of Terpenoid's from *Rosemary* and *Salvia* on diabetes type 2 treatment

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Abstract
Nowadays phytotherapy is important research subject over the world attracting researchers for less use of synthesized drugs because of their secondary effects. In this paper we use molecular modeling and molecular docking as tools for valorization of natural's plants in medicinal use which permit saving time and money in studying medicinal plants actions. We study anti-diabetic effect of main molecules from *Rosemary* and *Salvia* by investigating inhibition process of DPP-4 enzyme using Molecular Operating Environment software. Obtained results show importance of natural molecules from *Rosemary* and *Salvia* in diabetes type 2 treatment comparing to synthesized molecules used as drugs that have many secondary undesirables' effects.

Keywords: Diabetes type 2- phototherapy- DPP4 –Molecular modeling- medicinal plants

1. Introduction
Use of medicinal plants (phytotherapy) for diseases treatment is subject interesting researchers in many fields. Computational and theoretical chemistry (molecular modeling and molecular docking) allow saving time and money in drug discovering and conception and also contribute de better comprehension of medicinal plants action against diseases. Nowadays natural's terpenoids from medicinal plants as *Rosemary* and *Salvia* (Lamiaceae family) are widely investigated for their therapeutic effect (e.g. inflammatory pain) [1]. Most investigated terpenoids are Carsonic acid and Carnosol and many recent researches show efficacy of Carsonic acid and Carnosol against many illnesses (Table 1). Other recent researches show presence of diterpenoids and triterpenoids (figure 1) similar to carsonic acid and carnosol that may have positive effect on human health [2, 3]. *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) [3]. *Rosemary* extracts were classified as food additives by the European Commission under E393 code [2]. Researches interest to carsonic acid and carnosol increase since U.S food Drug Administration and European food safety approved their use as food additive [4, 5, 6]. Analytical method showed high extraction yields for the determination of this compound in a complex matrix such as tissue.

Table 1: Carsonic acid and Carsonol effects

Diseases / Pains	References
Antioxidant	11-13 A2
antimicrobial	14-17 A2
Antitumor	20-21 A2
Anti-inflammatory	22-24 A2
Anti-obesity	25-26 A2
Anticancer,	A 2 et petiwala
Anti-proliferative	A2
Anti-invasive	A2

Among investigated disease by computational chemistry we find Diabetes type 2. Type 2 diabetes (T2DM) is a metabolic disease which cause hyperglycaemia with pathophysiological factors and may bring about other health damage [7].

Main important enzyme responsible of type 2 Diabetes 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) [25 article clove].

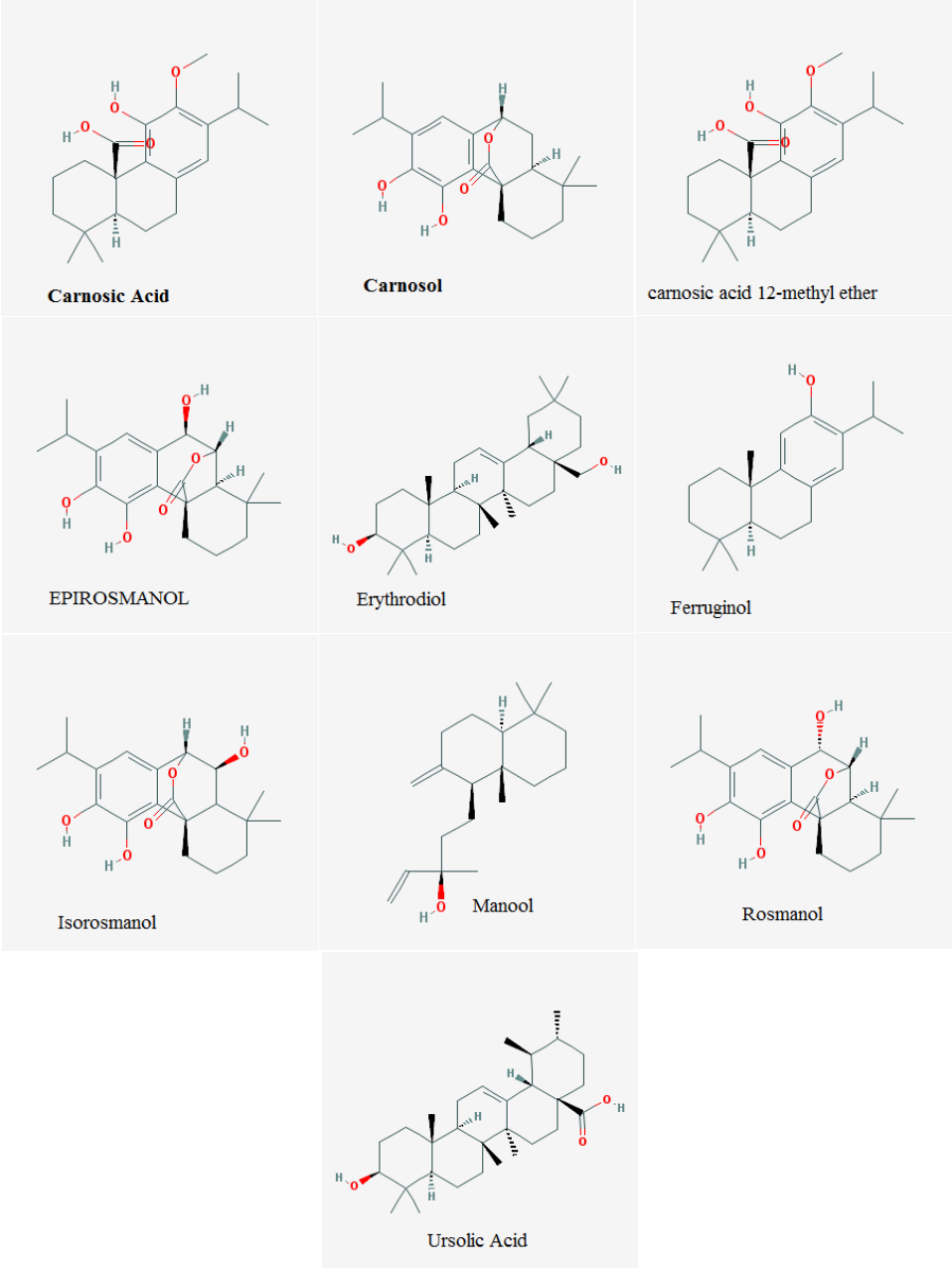

Fig 1: Terpenoids structures from *Rosemary* and *Salvia*

In best of our knowledge no studies have been done on inhibition of DPP-4 by extracted oils from *Rosemary* and *Salvia*. In this work we are going to study the anti-diabetic effect of some terpenoids from *Rosemary* and *Salvia* in inhibition of DPP-4 using molecular modeling and molecular docking. The Molecular Environment Operating software is used [8].

2. Materials and Methods

According to recent researches terpenoids from *Rosemary* and *Salvia* were identified [6], and their structures were downloading from PubChem Data Base (Figure 1]. The structure of Dipeptidyl-peptidase (DPP-4) (Figure 2) was downloading from PROTEIN DATA BANK (code 5T4B) with three-dimensional structure obtained by X-ray diffraction (resolution 1.76 Å).

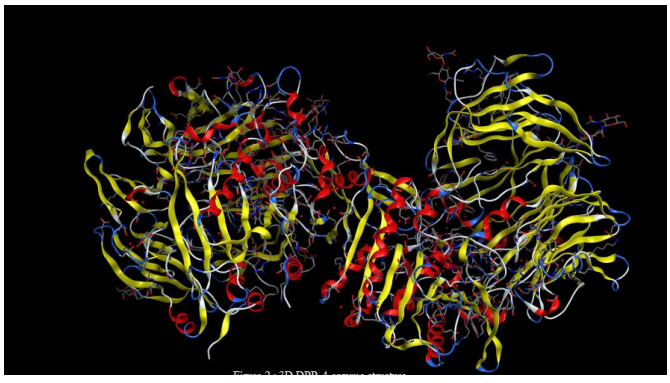

Fig 2: 3D DPP-4 structure

2.2. 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. 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 (Molecular Operating Environment). The second important step is isolation of the enzyme active site identification of general protein distribution (figure 3 and figure 4). The active site was performed using MOE site finder (according to MOE protocols). Main molecules from *Rosemary* and *Salvia* (figure 1) were downloading from PubChem Data base. Optimization of molecules was done under the same conditions of enzyme optimization.

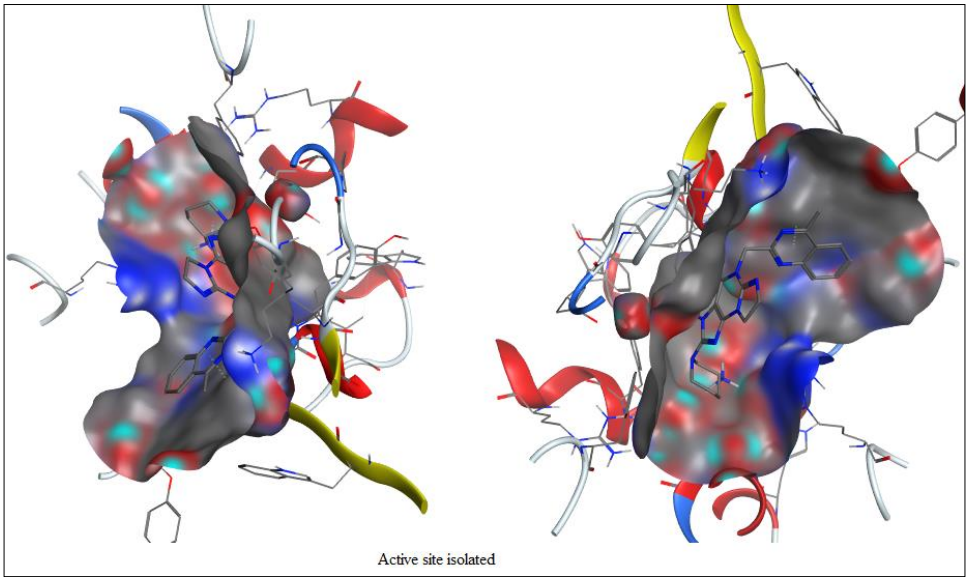

Fig 3: Active site enzyme isolated

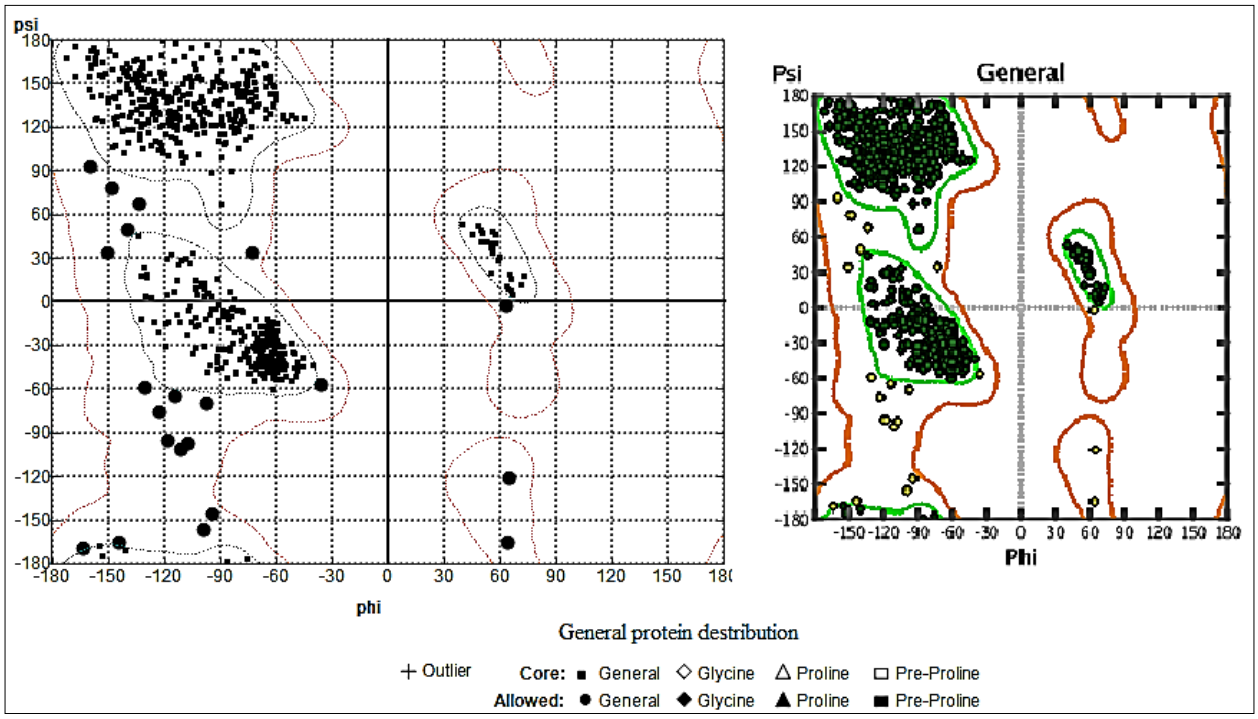

Fig 4: General Protein distribution

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) with MOE software (Molecular operating environment) [8]. 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. The site finder implemented in MOE used for prediction a nearby pocket or active site able to anchor molecule. Figure 5 shows Interaction potential in the optimized enzyme. Each level slider controls a contour graphic that shows the locations in space at which the probe has an 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.

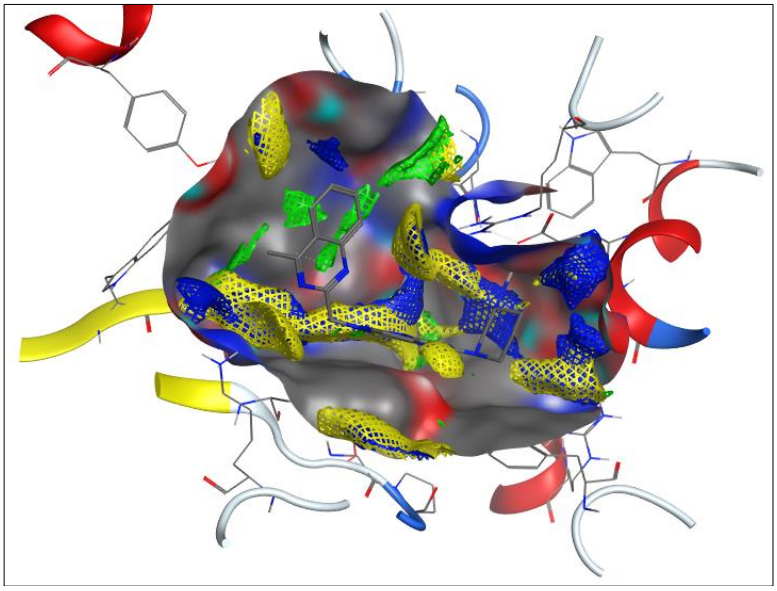

Fig 5: Interaction Potential; *N: Yellow, OH2: blue, DRY: Green*

Table 2: 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

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 Kcal/mol).

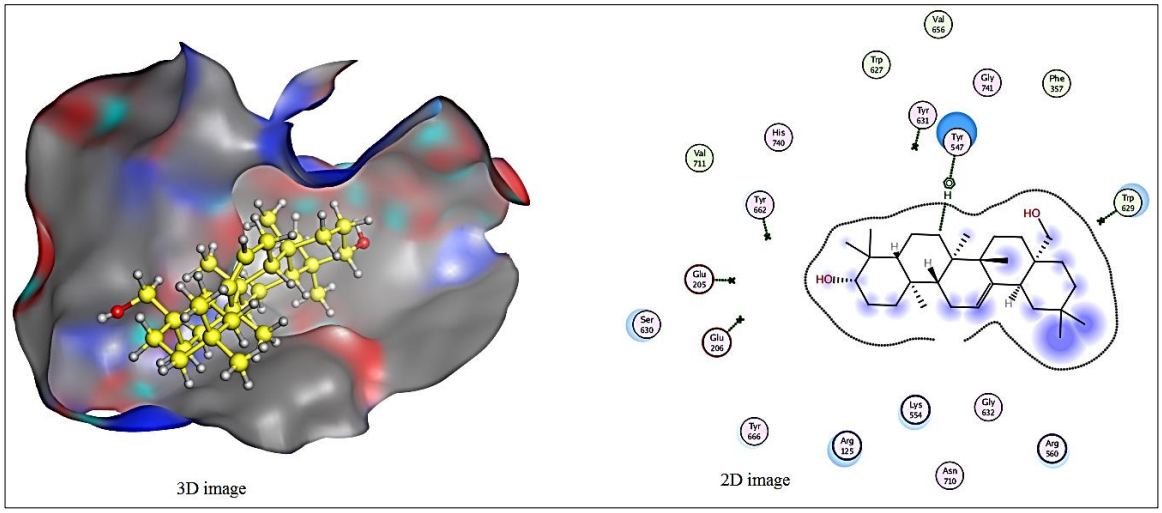

Fig 6: Diagram interaction of Erythrodiol with DPP-4 enzyme

According to obtained results complex formed with Erythrodiol is the most stable (Figure 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 (figure 7).

The complex formed with Manool, there are no interactions only Van Der Wals interactions are perceptible (figure 8).

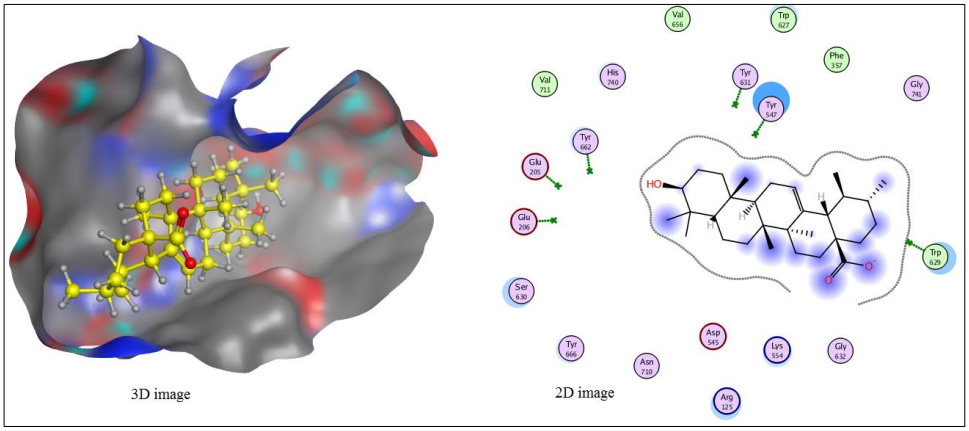

Fig 7: Diagram interaction of Ursolic acid with DPP-4 enzyme

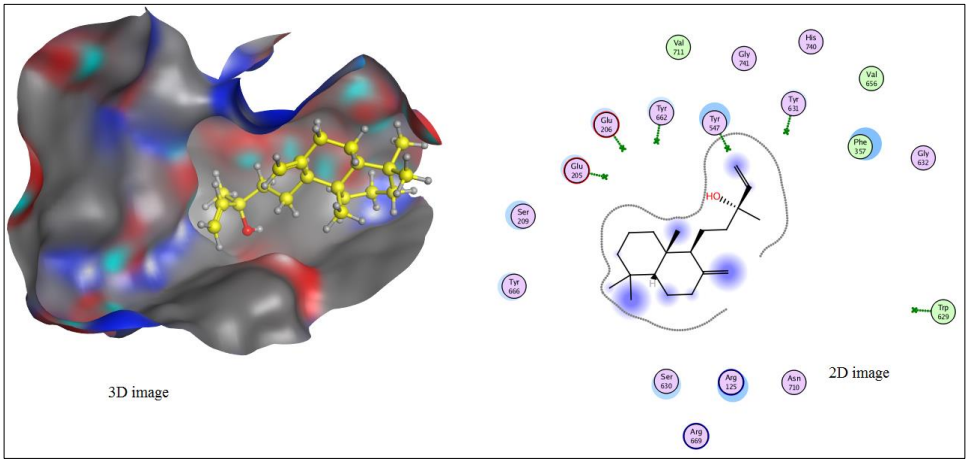

Fig 8: Diagram Interaction of Manool with DPP-4 enzyme

Comparing to other researches [10] in the same field 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 (Metformin, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin) are used as drug for treatment of diabetes type 2, but those molecules have many secondary effects as repotted by European Medicines Agency [11]. The table 3 below gives an overview about secondary effect of principals synthesized hypoglycemic cited above.

Table 3: Main secondary effect of some synthesized hypoglycemic [11]

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
Metformin (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 ▪ Musculoskeletal 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

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 secondary effect on Health. Also we can conclude that molecular modeling and molecular docking methods allow discovering new molecules from plants that may have therapeutic effect. Computational chemistry is very important for phytotherapy research allowing saving time and money permitting identification molecules with therapeutic interest. In this way we encourage investigating *Rosemary* and *Salvia* in diabetes type 2 treatments.

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