Effect of Polyphenolic Compounds of Rosa Canina (L.) Against The Acetylcholinesterase Activity of Rhopalosiphum Padi (L.) (Homoptera: Aphididae)

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Abstract

Rhopalosiphum padi (L.) is among the most aggressive cereal pests worldwide. The pest causes economically heavy crop loss. Chemical insecticides were used for the control of multiple insects. However, the harmful consequences of these chemical products are well known. Seeking more ecological alternatives, respect to the environment is, therefore, a necessity. The phytochemicals are known for their various biological activities of pharmaceutical and agri-food interest. Several plant species have been found to have effective bioinsecticide properties against a variety of insects. In this study, the plant Rosa canina (L.) has made the objective of an in-silico research using molecular docking by screening the inhibitory potential of its polyphenolic compounds against the enzyme acetylcholinesterase of R. padi (L.). The enzyme 3D structure was first modeled, then its stereoechemical quality was validated. The result of molecular docking allowed the selection of seven phytochemicals (Ellagic acid, Dihydroquercetin, Bilobalide A, Luteolin 5-methyl ether, Rosmarinic acid, Kaempferol, and Quercetin) with binding energy lower than that of the commercial insecticide Malathion. These components showed intense links with the catalytic site key residues of the enzyme, indicating their high inhibitor potential. The environmental and health safety of these components and their bio-availability were also validated by the verification of several pharmacokinetic and ADMET criteria, suggesting the interest of the plant R. canina (L.) as promising bioinsecticide material against the pest R. padi (L.).

1. Introduction

Pesticides and their related products are undoubtedly the most widely used chemicals in our environment. The use of these plant protection products helps to take preventive measures against crop pests and to improve crop yield. However, the importance of reducing the exposure of plants, animals, and humans to hazardous chemicals has become increasingly clear. Indeed, pesticides can travel for a considerable distance, and some of them last a long period in the environment [1]. Pesticides are found in different forms around us (air, soil, food, ground, surface, and even drinking water) [2, 3], and they can also have impacts on human health, by exposing it chronically to many toxic substances. These chemical substances also give rise to health impacts that are difficult to predict, which should make them one of the major issues in research and hazard assessment [4].

In addition to the risks to the environment and human health, the continued use of pesticides encourages the growth of insect populations that are resistant to them, necessitating the creation of new pesticides [5]. In recent years, many scientific research initiatives have been taken to develop alternative approaches which call into question the use of synthetic pesticides, to replace them with biological and degradable substances. These methods consist in using molecules called biopesticides. Biopesticides comprise living organisms or their derivatives natural molecules. They are biodegradable, with specific pests’ activity and without side effects on the environment and health [6].

The aphid Rhopalosiphum padi is among the most devastating pests of cereal crops. It is a small green globular aphid, of the class of Hemiptera insects. R. padi is a serious pest of cereals and it carries a virus causing dwarf yellowing of wheat [7, 8]. This insect causes agricultural loss of 19 to 31% [9]. The damage caused by this insect has led to extensive use of chemical insecticides in cereal crops. But this spectacular use of chemical insecticides has led to harmful consequences such as the persistence of pesticide residues on consumable crops and the loss of quality and weight of cereal grains. Aside from these negative effects on crops, aphids have developed remarkable resistance to insecticides, making their control by conventional pesticides more difficult [10]. The development of resistance in target insects to conventional chemical insecticides and the desire to preserve the environment has favored the rapid development of biopesticides.
Several studies have demonstrated the success of plants in terms of bioinsecticide activity [11]. Phytochemicals are known for their low toxicity to mammals, rapid biodegradability in the environment, and targeted effect against harmful parasites [12]. Plants are thus a fertile material rich in bioactive products with bioinsecticide potential, which deserves to be exploited.

One of the most widely used approaches today for utilizing biopesticide activity in plants, computational methods that have proved to be a very good approach in the field of agriculture, where it has shown great efficiency in the creation of new biopesticides [13]. Molecular docking is one of these strategies, and it involves stimulating the interactions between ligands and receptors to determine the best affinity, which is represented by the binding energy. The best conformation of the ligand in the receptor catalytic pocket is then predicted and the various interactions established between the key amino acids are identified. The search for new biopesticides consists of exploring the inhibitory capacity of natural compounds against key pest enzymes [14].

*Rosa canina* (L.) species is a plant of the Rosaceae family, found in the temperate regions. By its exceptional phenolic composition, *R. canina* presents a great interest for the research of biological activity in the pharmaceutical and agriculture sector. The polyphenolic composition of this plant has shown several activities as antioxidant, cytotoxic, antimicrobial, and antiviral [15].

In the light of this context, this present study aims at an in-silico screening of the bioinsecticide potential of the Algerian plant *Rosa canina*‘s polyphenolic compounds known for their various pharmaceutical virtues. For this, the acetylcholinesterase enzyme of *R. padi* was chosen as a potential target to identify the phytochemicals capable of inhibiting this crucial enzyme.

2. Material and Methods

2.1. Homology modeling of *Rhopalosiphum padi* acetylcholinesterase

The 3D structure of the enzyme acetylcholinesterase of *R. padi* is not available on the PBD database, therefore, it was first modeled using Modeller 10.1 program [16]. The protein sequence of the enzyme (ID: AII01418.1) has a length of 672 aa was chosen. The best homologous targets were identified using pBLAST. The target templates were chosen based on their high identity percentage, high query sequence converge percentage, and low E-value. The PDB formats of the first four targets were then used as templates for the prediction of the three-dimensional structure of the *R. padi* acetylcholinesterase. The best model was chosen based on the DOPE score given by the Modeller program [17].

2.2. Validation of the homology model

Several computational tools were used in order to assess the quality of the predicted model. The RMSD value between the model and the best template was calculated after the superposition of their 3D structures by the Pymol program. VERIFY3D [18], PROCHECK [19], and ERRAT [20] programs of the SAVES package, as well as PROSA [21], were used to calculate different parameters necessary for the evaluation of the stereochemical quality of the model.

2.3. Molecular docking study

The predicted 3D structure has undergone an optimization and a minimization of its energy by the addition of a hydrogen atom using the UCSF Chimera 1.13 program. The optimized structure was finally saved in (mol2) format. A number of 30 polyphenolic compounds of the Algerian species *R. canina* (L.) were obtained from the literature [22]. The co-crystallized inhibitor Difluoromethyl ketone and the commercial insecticide Malathion is known for its inhibitory effect against the enzyme acetylcholinesterase were used as reference molecules. The canonical smiles of these molecules were then obtained from the PubChem database and used for the construction of their 3D structures by the Chimera program. All these molecules are energetically minimized and saved in (mol2) format.

AutoDock Vina algorithm embedded in the Chimera package was used for molecular docking. Molecular docking of the polyphenolic compounds was carried out within the catalytic site of the predicted model that was identified after the alignment of the model and the best template 3D structures. Co-crystallized Difluoromethyl ketone and Malathion were the first ligands to be docked and their binding energies were taken as a reference. In this docking process, the ligands were considered as flexible molecules, while the receptor is kept rigid. Discovery Studio package was used for the visualization of the established interactions between ligands and the residues of the enzyme catalytic site. The best phytochemicals were those with binding energy equal or lower than that of the reference molecules.

2.4. Drug-likeness activity and ADMET study

The ligands given promising results from the docking step were subjected to an in-silico analysis of their ADMET property to confirm their bioavailability and non-environmental toxicity. This study was carried out by the Swiss-ADME and admetSAR
programs. The pharmacokinetic properties analyzed were those of the Lipinski [23], Veber [24], and Ghose [25] rules. On the other hand, the carcinogenic, cardiotoxic, mutagenic, and hepatotoxic properties of the selected compounds were verified.

3. Results and Discussion

3.1. Model assessment and validation

The modelled structure of the enzyme acetylcholinesterase of *R. padi* is illustrated in Figure 1(a). Chain A of the template 5YDJ of the acetylcholinesterase protein from the insect Anopheles gambiae was identified as the closest homologous protein to the query by the BLASTp algorithm. The percentage identity of this template with the query was 63.22%, the coverage of the query was 82% and the E value was 0. This protein was taken as the best template by the Modeller program. Figure 1(b) shows the superposition of the two 3D structures of the model and the best template. The RMSD value of this alignment was 0.120 with 514 alpha carbon atoms aligned.

![Figure 1](image)

**Figure 1.** (a) Predicted 3D structure of acetylcholinesterase of *R. padi* modelled through homology modelling using Modeller and visualized by the Discovery Studio tool (b) The superimposed structure of the *R. padi* acetylcholinesterase (red) and the best homologous template chain A of 5YDJ (blue).

The overall quality of the modelled protein was interpreted by the Z-score value given by the computational tool PROSA, indicating a score of -10.09 (Figure 2(a)), which is considered as an excellent score, because the more negative is the value, the better is the quality. The black dot represented in figure 2(a) indicates that the modelled structure is contained in the field of the PDB native proteins, which have sizes similar to the model. The green graph located in the negative zone indicates a good local quality of the model. This graph represents the energy of all the amino acids throughout the modelled structure.

PROCHECK is another tool that has been used to determine the stereochemical reliability of the predicted model. This tool generated a Ramachandran graph which revealed that 88.4, 10.8, 0.5, and 0.2% of the residues were located in the most favorable, additionally allowed, generously allowed, and disallowed regions, respectively (Figure 2(b)). With such percentages of residue distributions, the quality of the model is considered sufficiently reliable. The Verify3D tool showed that the predicted model has 97.51% of residues that have averaged 3D-1D score≥ 0 (Figure 2(c)), which can be explained by an excellent local quality of the modelled protein [18]. ERRAT gave an overview of the overall quality of the model by calculating a statistical measure reflecting the unbound interactions within the protein. The result given for the predicted model was 92.516, which is a good value confirming once again the stability of the modelled enzyme (Figure 2(d)).

Based on these findings, the modelled protein acetylcholinesterase of *R. padi* was shown to have a stable and appropriate structure, as well as being good enough and reliable to be exploited in silico as a target for bioinsecticide.
3.2. Molecular Docking and interaction analysis

A molecular docking study of 30 polyphenolic compounds from the plant *R. canina* (L.) was conducted within the catalytic site of the insect *R. padi*’s acetylcholinesterase. The exact location of the active site within the modelled enzyme was determined by its alignment with the 5YDJ template. The catalytic pocket localization is confirmed by an initial docking step of the co-crystallized inhibitor Difluoromethyl ketone with the modelled protein, which gave binding energy of -6.5 Kcal/mol. The superposition of the docked ligand with the co-crystallized one ensured the reliability of the docking process as well as the identification of the key residues’ catalytic site involved in the receptor-ligand interaction. In addition to the co-crystallized molecule, the commercial insecticide Malathion was also docked to the active site of the modelled enzyme, resulting in the binding energy of -7.0 Kcal/mol. The result of the phytocompounds docking showed that 13 molecules gave a score above or close to that of the reference inhibitor Difluoromethyl ketone and the commercial insecticide Malathion, indicating a probable potential for inhibiting the activity of the acetylcholinesterase. The top seven ligands that showed remarkably superior binding energies are in order: Ellagic acid (-8.7 Kcal/mol), Dihydroquercetin (-8.3 Kcal/mol), Bilobalide A (-7.4 kcal/mol), Luteolin 5-methyl ether (-7.3 Kcal/mol), Rosmarinic acid (-7.2 Kcal/mol), Kaempferol (-7.1kcal/mol), and Quercetin (-7.1Kcal/mol) (Table 1).

With 22 different interactions with the residue’s active site, Luteolin 5-methyl ether is the ligand that interacts the most with the receptor, establishing 3 hydrogen bonds, 03 hydrophobic bonds, and 15 Van der Walls interactions. Followed by Quercetin, with a number of 19 bonds that are similar to the reference molecules, including 3 hydrogens, one hydrophobic, and 15 Van der Walls interactions. The ligands Ellagic acid, Dihydroquercetin, Rosmarinic acid, and Quercetin all showed 18 different interactions with the residues of the enzyme catalytic pocket. With 15 interactions, Bilobalide A is the ligand with the least interaction number (Table 1, Figure 3).

By examining the catalytic site residues involved with the co-crystallized inhibitor, the commercial insecticide Malathion, as well as the various phytochemical compounds of the plant *Rosa canina* L., we can notice that there were residues that participate in all complexes by establishing hydrogen, hydrophobic, or Van der Walls bonds. These essential residues for the activity of the enzyme are Tyr332, Gly123, Glu202, His443, Trp88, Tyr125, Phe292, Ser203, Gly121, and Cys290 (Table 1, Figure 3). By occupying these crucial residues, the enzyme becomes inactive and cannot establish its normal biological function, consisting in the cleavage of the neurotransmitter acetylcholine, which allows the neuron to return to the rest state.
Blocking this reaction leads to paralysis and the death of the insect. Thus, the polyphenolic compounds of the plant *Rosa canina* L. can be considered as potential bioinsecticides.

**Table 1.** Docking result of the reference and the top-seven ligands within the active site of the modelled enzyme acetylcholinesterase of *R. padi*

| Compound                  | code | Binding energy (Kcal/mol) | Hydrogen interactions | Hydrophobic interactions | Van der Waals | Other interactions |
|---------------------------|------|---------------------------|-----------------------|--------------------------|---------------|-------------------|
| Difluoromethylene ketone (reference) | R1   | -6.5                      | Gly<sup>123</sup>, Ty<sup>132</sup> | Glu<sup>202</sup>, His<sup>443</sup>, Trp<sup>88</sup>, Tyr<sup>125</sup>, Phe<sup>202</sup>, His<sup>443</sup>, Tyr<sup>332</sup> | Phe<sup>403</sup>, Ser<sup>203</sup>, Gly<sup>444</sup>, Ile<sup>447</sup>, Gly<sup>202</sup>, Ala<sup>120</sup>, His<sup>443</sup>, Gly<sup>121</sup> | Glu<sup>202</sup>, His<sup>443</sup> |
| Malathion (reference)      | R2   | -7.0                      | Ser<sup>203</sup>, Tyr<sup>125</sup>, His<sup>443</sup>, Tyr<sup>332</sup> | Phe<sup>202</sup>, Tyr<sup>125</sup>, Gly<sup>121</sup>, Phe<sup>403</sup> | Tyr<sup>134</sup>, Gly<sup>121</sup>, Tyr<sup>125</sup>, Ser<sup>126</sup>, Gly<sup>124</sup>, Gly<sup>126</sup>, Ser<sup>126</sup>, Gly<sup>444</sup>, Ser<sup>333</sup>, Phe<sup>292</sup>, Cys<sup>290</sup>, Phe<sup>403</sup>, His<sup>123</sup> | Ser<sup>126</sup>, Ser<sup>333</sup>, Phe<sup>292</sup>, Cys<sup>290</sup>, Phe<sup>403</sup>, His<sup>123</sup> |
| Ellargic acid              | 1    | -8.7                      | Tyr<sup>125</sup>     | Tyr<sup>332</sup>, Tyr<sup>125</sup>, Gly<sup>121</sup>, Trp<sup>88</sup> |  | |
| Dihydroquercetin           | 2    | -8.3                      | Trp<sup>88</sup>, Glu<sup>202</sup> | Trp<sup>88</sup>, Tyr<sup>332</sup> |  | |
| Bilobalide A               | 3    | -7.4                      | Cys<sup>203</sup>, Ser<sup>203</sup>, Tyr<sup>332</sup> |  |  | |
| Quercetin                  | 4    | -7.3                      | Glu<sup>202</sup>, Tyr<sup>124</sup>, Gly<sup>121</sup> | Tyr<sup>332</sup> |  | |
| Luteolin 5-methyl ether    | 5    | -7.3                      | Ser<sup>203</sup>, Tyr<sup>125</sup>, Gly<sup>121</sup> | Phe<sup>202</sup>, Tyr<sup>332</sup>, Tyr<sup>125</sup> |  | |
| Rosamiric acid             | 6    | -7.1                      | Glu<sup>202</sup>, Tyr<sup>332</sup>, Cys<sup>290</sup> | Phe<sup>202</sup>, Tyr<sup>332</sup>, Tyr<sup>125</sup>, Gly<sup>121</sup> |  | |
| Kaempferol                 | 7    | -7.1                      | His<sup>443</sup>, Ser<sup>203</sup> | Trp<sup>236</sup>, Phe<sup>292</sup>, Tyr<sup>123</sup>, Tyr<sup>332</sup>, Gly<sup>121</sup> | Ser<sup>333</sup>, Phe<sup>403</sup>, Gln<sup>402</sup>, Tyr<sup>25</sup>, Glu<sup>202</sup>, Ala<sup>120</sup>, His<sup>443</sup>, Gly<sup>121</sup> | Cys<sup>290</sup>, His<sup>443</sup> |
Figure 3. 3D and 2D illustrations showing the interactions between the reference and the top-seven ligands and the modelled acetylcholinesterase of *R. padi*.
3.3. Drug-likeness activity and ADMET study

The results of the drug-likeness and ADMET analysis of the top-seven phytocompounds are summarized in tables 2 and 3. This study aims to assess the pharmacokinetic availability of these molecules as effective bioinsecticides, and on the other hand, confirmed their environmental safety and non-toxicity.

Lipinski established a range of features based on four physicochemical parameters to evaluate a compound’s bioavailability. To be effectively efficient, a drug substance has to have a molecular weight of less than 500 g/mol, a maximum of 5 hydrogen bond donors, 10 hydrogen bond acceptors, and a lipophilicity coefficient (LogP) of less than 5. Other rules (Ghose, Veber, Egan, and Muegge) based on multiple variables, defining the possible pharmacokinetic quality were also studied to identify the drug-likeness of the various compounds. The top seven polyphenolic compounds have respected most of the studied rules, especially the Lipinski one, therefore verifying their biological availability by being soluble, and easily distributed in the biological fluids.

Other important measurements have been successfully verified for most of the phytocomponents studied, in particular the criterion of atom molar refractivity or AMR, which should normally be between 40 and 130, and the topological polar surface area (TPSA), which must be less than 140 Å², as well as the number of rotational bonds which must be less than 10. The solubility measurements expressed by LogS are satisfactory for all the seven ligands, indicating good to excellent solubilities. Verification of these biochemical criteria is a strong indicator of the bioavailability and therefore of the effectiveness of the studied compounds.

Blood-Brain Barrier permeability test results are negative for all the components, which removes the risk of their access to the central nervous system. The HIA criterion confirms that the seven components are permeable through the intestinal membrane. Concerning the assessment of the toxicity risk of these phytocomponents, the results illustrated in table 3 show that with the exception of Quercetin, which inhibits the cytochromes CYP1A2 and CYP1A4, and Kaempferol, which inhibits the cytochrome CYP1A2, the other components do not present any risk of inhibition for all cytochrome families. In addition, the seven polyphenolic compounds do not present any danger of carcinogenicity and cardiotoxicity (represented by the blockage of the Ether-a-go-go-Related Gene potassium channel). Only Dihydroquercetin and Kaempferol can have mutagenic potential. While a possible risk of hepatotoxicity is attributed to Quercetin and Kaempferol. The other components are considered completely safe in every aspect.

### Table 2. Drug-likeness properties of the top-seven ligand.

| Code | MW (g/mol) | logP | Log S | HBA | HBD | TPSA (Å²) | AMR | nRB | Lipinski | Ghose | Veber | Egan | Muegge |
|------|------------|------|-------|-----|-----|-----------|-----|-----|----------|-------|-------|------|--------|
| 1    | 302.19     | 1.00 | -2.94 | 8   | 4   | 141.34    | 75.31 | 0   | yes      | yes   | no    | no   | yes    |
| 2    | 304.25     | 0.63 | -2.66 | 7   | 5   | 127.45    | 74.76 | 1   | yes      | yes   | yes   | yes   | yes    |
| 3    | 326.30     | 0.06 | -1.63 | 8   | 2   | 119.36    | 71.20 | 1   | yes      | no    | yes   | yes   | yes    |
| 4    | 302.24     | 1.23 | -3.16 | 7   | 5   | 131.36    | 78.03 | 1   | yes      | yes   | yes   | yes   | yes    |
| 5    | 300.26     | 1.89 | -3.56 | 6   | 3   | 100.13    | 80.48 | 2   | yes      | yes   | yes   | yes   | yes    |
| 6    | 360.31     | 1.52 | -3.44 | 8   | 5   | 144.52    | 91.40 | 7   | yes      | yes   | no    | no    | yes    |
| 7    | 286.24     | 1.58 | -3.33 | 6   | 4   | 11.13     | 76.01 | 1   | yes      | yes   | yes   | yes   | yes    |

**Table 2.** Drug-likeness properties of the top-seven ligand.

**HBA:** Num. H-bond acceptors  **HBD:** Num. H-bond donors  **nRB:** Num. rotatable bonds  **AMR:** Atom Molar Refractivity

### Table 3. ADMET properties of the top-seven ligands.

| Code | BBB | Caco2 | HIA | P-gp inhibitor | CYP1A2 inhibitor | CYP2C9 inhibitor | CYP2C19 inhibitor | CYP2D6 inhibitor | CYP3A4 inhibitor | Ames | Carcinogenicity | hERG inhibition | H-HT |
|------|-----|-------|-----|----------------|------------------|-------------------|-------------------|-------------------|-------------------|------|---------------|----------------|------|
| 1    | no  | no    | yes | no             | no               | no                | yes               | no                | no                | no   | no            | no             | no   |
| 2    | no  | no    | yes | no             | no               | no                | no                | no                | yes               | no   | no            | no             | no   |
| 3    | no  | no    | yes | no             | no               | no                | no                | no                | no                | no   | no            | no             | no   |
| 4    | no  | no    | yes | no             | yes              | no                | no                | no                | yes               | no   | no            | no             | no   |
| 5    | no  | yes   | yes | yes            | no               | no                | no                | no                | yes               | no   | no            | no             | no   |
| 6    | no  | no    | yes | no             | no               | no                | no                | no                | no                | no   | no            | no             | no   |
| 7    | no  | no    | yes | no             | no               | no                | no                | no                | yes               | yes  | no            | no             | yes  |
BBB, Blood-Brain Barrier. HIA, Human Intestinal Absorption. Caco2, Permeability assay. hERG, human Ether-a-go-go-Related Gene potassium channel. H-HT, Human Hepatotoxicity.

Several studies have shown the bioinsecticidal activity of polyphenols of a wide variety of plant species. Indeed, these bioactive substances can have different modes of pharmacological action on insects [26, 27]. Phenolic compounds are known for their toxic properties against plant pathogens, so they are a natural defense system [28]. In a study carried out on the leaf worm Spodoptera littura, the authors showed that the phenolic compounds of the plant Capsicum annum, had an inhibitory effect on insects of the larval and adult stage [29]. In another study, it was shown that the phenols of the tomato were toxic against the fruitworm, Heliothis zea [30]. In addition, Johnson et al., [31] found that honey bees were negatively affected by the phenolic extract of the plant Aloe veraheades.

Conclusion

The problem of environmental and health toxicity of a large number of conventional chemical insecticides, as well as the appearance of a generation of insects resistant to these chemicals, which is becoming increasingly ineffective for the control of crop pests, pushes researchers to a continuous search for new effective and eco-friendly products. Since the dawn of time, plant extracts have been used by humans as bioinsecticides. Polyphenols, essential oils, and alkaloids of plant origin have proven their insecticidal potential against several species of harmful insects, and are therefore good candidates for the biological control of the crops devastating insects.

In this study, the in silico molecular docking approach was adopted to screen the bioinsecticide activity of the polyphenolic compounds of the Algerian plant R. canina L. against the acetylcholinesterase enzyme of the cereal pest R. padi. As the three-dimensional structure of this enzyme is unavailable in the PDB database, an initial modeling step was performed, followed by an evaluation and validation of the predicted model. The molecular docking of 30 polyphenolic compounds of R.canina L. has highlighted seven important substances based on the result of their binding energies, which were significantly lower than that of the commercial insecticide Malathion known for its effectiveness against aphids. The top seven phenols, Ellagic acid, Dihydroquercetin, Bilobalide A, Luteolin 5-methyl ether, Rosmarinic acid, Kaempferol, and Quercetin showed multiple interactions with the crucial residues of the enzyme active site, therefore inhibiting its biological activity, which can lead to possible paralysis and death of the insect. An in-silico evaluation of the drug likeness and ADMET proprieties of these components showed their biological bioavailability and their safety for human health, suggesting that R. canina's polyphenolic compounds may be good bioinsecticidic candidates against the pest R. padi.

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