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Research Article

The investigation of the interaction of gastric cancer receptors and natural drug ligands in *origanum bilgeri*

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ABSTRACT

Plants have been used for medicinal purposes since ancient times. They include bioactive compounds, constitute the basis of the pharmaceutical industry. *Origanum bilgeri* includes bioactive compounds, display the significant biological activities. The present study includes the active ingredients used to stop the proliferation of gastric cancer and to prevent its spread with the effect of metastasis. In this study, the interaction of bioactive compounds found in *Origanum bilgeri* such as rosmarinic acid, trans-cinnamic acid, and resveratrol with gastric cancer receptors has been investigated by using docking, a chemical calculation method. Stomach cancer is a common disease among cancer types. The cause of this cancer is various factors, dietary habits and the foods taken are the leading ones. The interaction points will be determined by comparing the interaction of the active bioligands in these plants with the gastric cancer receptors with the foods taken, both as spices and as supplements. As a result of this study, it has been determined that the inhibitory effect of linalool (8-hydroxydihydro), Cinnamic acid, Resveratrol, Rosmarinic acid ligands in the Origanum medicine plant on gastric cancer receptors is quite high.

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INTRODUCTION

The main natural products obtained from plants (Juniperus excelsa (1), Althaea officinalis L. (2), Allium vineale (3), Echinacea pallida (4), Mentha dumetorum (5), Teucrium chamaedrys (6) are used for drug development due to their bioactivities. Plays an important role in the process. *Origanum* genus belonging to the Lamiaceae family have been used for traditional medicine for treatment of various diseases such as cold, digestive disorders, cough [7]. These species are known for their antimicrobial and antioxidant activities [8]. The antimicrobial activity attributes to their high concentration of essential oils [9]. Moreover, these essential oil constituents contribute to the flavour and aroma [10]. Phytochemical studies on

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Origanum species revealed the isolation and identification bioactive compounds such as flavonoids, phenolic acids [11]. The phenolic compounds possess various biological activities such as anti-inflammatory, antidiabetic, cytotoxic, antiviral, antiulcer [12].

Quantitative analysis of phenolic compounds in *Origanum bilgeri* resulted in the determination of rosmarinic acid, trans-cinnamic acid and resveratrol as well as other compounds [13]. Rosmarinic acid was found as a major product in *Origanum* species [14]. *Origanum* species are well known with their essential oils used for food, cosmetic and medicinal industries [15]. Gastric cancer is an aggressive malignancy caused by metastatic lesions with a high mortality rate and poor prognosis [16].

Gastric cancer is one of the most common types of cancer in both sexes and is the third leading cause of cancer death [17]. Peritoneal metastases are most common in gastric cancers, and cancer-associated fibroblasts (CAFs) play a critical role in this process [18]. Extracts developed for therapy (BE) prevent gastric cancer by inhibiting the MAPK signaling pathway and NF-κB downstream signaling [19]. Gastric cancer is the third leading cause of cancer-related death worldwide and the most common malignancy of the digestive tract [20]. Celastrol has a role in the proliferation of cisplatin-resistant gastric cancer cells and the reduction of drug resistance [21].

In this study, the interaction of the main active substances in Origanum sage as ligand with gastric cancer receptors, that is, the inhibition effect, has been determined by chemical calculation method and to guide experimental and clinical studies by preventing time and substance loss.

MATERIALS AND METHODS

In this study, the interaction energy values, possible bonds and interaction points of the main effective ligands in oregano species with gastric cancer receptors will be determined by using chemical calculation methods [22, 23]. The major effective receptors [24] in gastric cancer are 3OCB, 1UOM, 5P21, 1M17, 1BG1, 4JT6 and 4GT3.

RESULTS AND DISCUSSION

The inhibition effect of the important active ingredients in Origanum sage on the receptors in gastric cancer cells is given in Table 1 [22.23].

As shown in Table 1; The binding energy values of Cinnamic acid, Resveratrol and Rosmarinic acid, which are among the active ingredients in Origanum sage, are quite low, so they interact with gastric cancer receptors as ligands. In other words, the inhibitory effect of these receptors on the gastric cancer cells receptors is good. In the following sections, this interaction will be indicated by Tables (2-9) and Figures (1-8). Some important active ingredients in this Oils of Oregano are Carvacrol, Thymol, Linalool, B-myrcene and B-caryophyllene [30].

When we look at the Table 1:

According to AKT1 receptor, the inhibition effect of ligands from high to low; Linalool > B-caryophyllene> Rosmarinic acid > Cinnamic acid > B-myrcene > Thymol > Carvacrol > Resveratrol

According to ESR1 receptor, the inhibition effect of ligands from high to low; B-caryophyllene > Rosmarinic acid > Resveratrol > Linalool > Carvacrol > Thymol > B-myrcene > Cinnamic acid

According to H-Ras receptor, the inhibition effect of ligands from high to low; Rosmarinic acid> B-caryophyllene > Linalool > Resveratrol > Carvacrol > B-myrcene > Cinnamic acid >Thymol

According to EGFR receptor, the inhibition effect of ligands from high to low;Linalool>B-caryophyllene > Resveratrol > Cinnamic acid > B-myrcene > Thymol > Carvacrol > Rosmarinic acid

According to STAT3 receptor, the inhibition effect of ligands from high to low; Rosmarinic acid> B-caryophyllene > Linalool > B-myrcene > Thymol > Carvacrol > Resveratrol > Cinnamic acid

According to MTOR receptor, the inhibition effect of ligands from high to low; Rosmarinic acid> B-caryophyllene > Resveratrol > Linalool > Carvacrol > B-myrcene > Thymol > Cinnamic acid

Table 1. The inhibition effect of the important active ingredients in Origanum sage on the receptors in gastric cancer cells

Docking score (kcal/mol) Receptörs/Ligands	Carvacrol	Thymol	Linalool	B-myrcene	B-caryophyllene	Cinnamic acid	Resveratrol	Rosmarinic acid
AKT1 (3OCB)	-2.76	-3.36	-5.20	-3.44	-4.30	-4.09	-2.50	-4.17
ESR1 (1UOM)	-4.90	-4.89	-5.19	-4.85	-7.19	-4.32	-5.69	-5.90
H-Ras (5P21)	-4.46	-4.18	-6.05	-4.52	-6.26	-4.37	-5.19	-6.63
EGFR (1M17)	-4.02	-4.33	-5.97	-4.39	-5.96	-4.57	-5.49	-1.51
STAT3 (1BG1)	-2.83	-2.94	-3.65	-3.05	-3.90	-2.20	-2.76	-4.09
MTOR (4JT6)	-5.59	-5.41	-5.92	-5.48	-6.69	-5.01	-6.67	-8.33
MAPK1 (4GT3)	-3.70	-3.73	-4.45	-4.09	-5.08	-3.70	-3.89	-5.30

According to MAPK1 receptor, the inhibition effect of ligands from high to low; Rosmarinic acid> B-caryophyllene > Linalool > B-myrcene > Resveratrol > Thymol > Carvacrol = Cinnamic acid.

The interaction points of linalool (8-hydroxydihydro) ligand and the 5p21 – Oncogeneprotein receptor; 17: SER18: ALA29: VAL30: ASP32: TYR85: ASN117: LYS120: LEU.

The bonds of linalool (8-hydroxydihydro) ligand and the 5p21 – Oncogeneprotein receptor in gastric cancer cells is given in Table 2 [22.23].

The interaction points of trans-Cinnamic acid ligand and the 5p21 – Oncogene protein receptor;

15: GLY16: LYS17: SER29: VAL

The bonds of trans-Cinnamic acid ligand and the 5p21 – Oncogeneprotein receptor in gastric cancer cells is given in Table 3 [22.23].

The interaction points of Resveratrol to 1m17 receptor are 694: LEU702: VAL719: ALA721: LYS738: GLU742: MET764: LEU766: THR769: MET820: LEU830: THR.

The bonds of Resveratrol ligand to 1m17 receptor in gastric cancer cells is given in Table 4 [22.23] .

The interaction points of Rosmarinic acid to 1m17 receptor are 773: CYS776: ASP813: ASP817: ARG818: ASN820: LEU831: ASP834: LEU

The bonds of Rosmarinic acid ligand to 1m17 receptor is given in Table 5[22.23].

The interaction points of Rosmarinic acid ligand to 3ocb receptor are 273: ARG297: LYS300: ILE306: MET307: LYS309: PHE.

Table 2. The bonds of linalool (8-hydroxydihydro) ligand and the 5p21 – Oncogeneprotein receptor in gastric cancer cells

Hydrogen bonds	Polar	Hydrophobic	Other
ASN85 (-0.2564)	LYS117 (-1.2517)	VAL29 (-0.2253)	TYR32 (-1.386)
	ASP30 (-0.9059)	ALA18 (-0.1851)	SER17 (-0.5455)
		LEU120 (-0.0711)	

Table 3. The bonds of trans-Cinnamic acid ligand and the 5p21 – Oncogeneprotein receptor in gastric cancer cells

Hydrogen bonds	Hydrophobic	Other
LYS16 (-1.2731)	VAL29 (-0.0833)	SER17 (-0.5629)
GLY15 (-0.6486)		

Table 4. The bonds of resveratrol ligand to 1m17 receptor in gastric cancer cells

Hydrogen bonds	Polar	Hydrophobic	Other
THR766 (-0.6972)	LYS721 (-1.1453)	LEU820 (-0.8283)	LEU764 (-0.4614)
	THR830 (-0.4525)	VAL702 (-0.6502)	
	GLU738 (-0.2004)	LEU694 (-0.5559)	
		MET769 (-0.4628)	
		ALA719 (-0.4382)	
		MET742 (-0.2394)	

Table 5. The bonds of Rosmarinic acid ligand to 1m17 receptor in gastric cancer cells

Hydrogen bonds	Polar	Hydrophobic	Other
CYS773 (3.1615)	ASN818 (-1.4403)	LEU820 (-0.0851)	LEU834 (5.5878)
	ARG817 (-1.116)		
	ASP813 (-0.9951)		
	ASP776 (-0.2969)		
	ASP831 (4.1302)		

Table 6. The bonds of Rosmarinic acid ligand to 3ocb receptor in gastric cancer cells

Hydrogen bonds	Hydrophobic	Other
ARG273 (-0.5481)	MET306 (-0.8258)	LYS307 (-1.7678)
		LYS297 (-1.0333)
		ILE300 (-0.3239)
		PHE309 (-0.0696)

Table 7. The bonds of Rosmarinic acid ligand to 4gt3 in gastric cancer cells

Hydrogen bonds	Polar	Other
TYR314 (-1.236)	HIS123 (-0.6693)	TYR126 (-1.0843)
	GLU107 (1.9429)	LEU113 (-0.5173)
		PHE127 (-0.4539)

Table 8. The bonds of Rosmarinic acid ligand to 4jt6 in gastric cancer cells

Hydrogen bonds	Polar	Cation-pi	Hydrophobic	Other
TYR222 (-1.192)	ASP219 (-0.6474)	TRP223 (-0.6581)	ILE235 (-1.821)	ASP235 (-1.2774)
	GLU219 (-0.2339)		ILE223 (-0.701)	MET234 (-0.2943)
			LEU218 (-0.5936)	
			LEU219 (-0.4548)	

Table 9. The bonds of Rosmarinic acid to 5p21 - Oncogene Protein in gastric cancer cells

Hydrogen bonds	Polar	Hydrophobic	Other
LYS147 (-0.8106)	ASP30 (-0.1551)	PHE28 (-1.3414)	LYS117 (-2.0459)
SER145 (-0.3589)	ASP119 (-0.1367)	TYR32 (-1.0474)	ASN116 (-0.4148)
		ALA146 (-0.3723)	

The bonds of Rosmarinic acid ligand to 3ocb receptor is given in Table 6 [22.23].

The interaction points of Rosmarinic acid ligand to 4gt3 are 107: GLU113: LEU123: HIS126: TYR127: PHE314: TYR.

The bonds of Rosmarinic acid ligand to 4gt3 is given in Table 7 [22.23] .

The interaction points of Rosmarinic acid ligand to 4jt6 receptorare 2185: LEU2190: GLU2192: LEU2195: ASP2225: TYR2237: ILE2239: TRP2345: MET2356: ILE2357: ASP

The bonds of Rosmarinic acid ligand to 4jt6 receptor is given in Table 8 [22.23] .

The interaction points of Rosmarinic acid to 5p21 - Oncogene Protein receptor are 28: PHE30: ASP32: TYR116: ASN117: LYS119: ASP145: SER146: ALA147: LYS.

The bonds of Rosmarinic acid to 5p21 - Oncogene Protein is given in Table 9 [22.23] .

As shown in Tables (2-9) above, the interactions between ligand and receptors occur with many intermolecular bonds. The studies on this [25-28] confirm the accuracy of the method. It can be stated that a molecule can form strong intermolecular interactions between the hydrogen bond donor site and the hydrogen bond acceptor site [29]. In methods that provide chemical calculation, many factors such as the activation energy of molecules [31], the solvents they are in, their stability and reactivity depending on their tendency to donate and accept electrons [32,33] can be examined, but in this study, the chemical calculation method reveals the interaction of the effective compounds selected as ligands with the receptors in the gastric cancer pathway. It was researched using docking.

CONCLUSION

The inhibitory effect of Linalool (8-hydroxydihydro), Cinnamic acid, Resveratrol and Rosmarinic acid ligands, mainly found in Origanum, on gastric cancer receptors is quite

high. This ability to inhibit can be explained by the formation of cation-pi, polar, hydrophobic and other bonds, especially hydrogen bonds. These active substances can be used to stop the proliferation of stomach cancer and prevent its spread through metastasis, but experimental and clinical studies need to be conducted on them. The data obtained from this research is important in terms of guiding experimental and clinical studies by preventing loss of time and materials.

AUTHORSHIP CONTRIBUTIONS

Authors equally contributed to this work.

DATA AVAILABILITY STATEMENT

The authors confirm that the data that supports the findings of this study are available within the article. Raw data that support the finding of this study are available from the corresponding author, upon reasonable request.

CONFLICT OF INTEREST

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ETHICS

There are no ethical issues with the publication of this manuscript.

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