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Aromatherapy and Appetite Suppression: Molecular Mechanism by System Biology

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ABSTRACT

Objective: Obesity is a complex chronic metabolic disorder and a major global health concern, serving as a significant risk factor for insulin resistance, type 2 diabetes, cardiovascular disease, and certain cancers, while also imposing severe psychological impacts such as depression, anxiety, and low self-esteem. Conventional treatments often have limited efficacy and tolerability due to severe side effects. This study aimed to investigate the molecular mechanisms of five essential oils—bergamot, orange, lemon, peppermint, and ginger—in the treatment of obesity using a systems biology approach.

Methods: A systems biology framework was employed to analyze the multi-target molecular interactions and signaling pathways modulated by the selected essential oils, focusing on their potential roles in metabolic regulation and obesity-related pathophysiology.

Results: The systems biology analysis revealed that these essential oils interact with multiple overlapping biological pathways involved in lipid metabolism, adipogenesis, and inflammatory responses. The integrative network modeling highlighted key regulatory nodes that may mediate their anti-obesity effects, providing a mechanistic basis for their previously observed efficacy in weight management.

Conclusion: These findings suggest that aromatherapy using bergamot, orange, lemon, peppermint, and ginger essential oils represents a potentially safe, multi-targeted adjunctive strategy for obesity prevention and treatment. The identified molecular pathways offer promising targets for future experimental validation and clinical translation, though the computational nature of this study necessitates further in vivo and in vitro confirmation.

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Introduction

Obesity is a condition characterized by an excessive accumulation of body fat resulting from genetic, psychological, and socio-environmental factors that leads to an imbalance between calorie intake and energy expenditure in favor to the former (Wright 2012). As established by the World Health Organization (WHO), the term "obesity" is used when the value of the Body Mass Index (BMI, calculated by dividing the weight expressed in kilograms by the square of the height expressed in meters) is greater than 30 (Seidell & Halberstadt 2015). Obesity is one of the main problems concerning public health due to its constant increase, particularly in Western countries (Wang et al. 2012). Obesity is, in fact, a known risk factor for serious chronic diseases such as type 2 diabetes, cardiovascular and respiratory diseases, tumors, and psychological disorders (Apovian 2016).

According to the World Health Organization (WHO), the number of overweight (BMI $\geq$ 25) and obese (BMI $\geq$ 30) individuals is constantly growing. In 2016, these numbers reached 1.9 billion (38% of the worldwide population) and 650 million (13% of the worldwide population), respectively. Hunger and appetite are closely related terms that are often confused. While hunger is an organism's response to maintain homeostasis (e.g., a calorie deficit), appetite, also known as hedonic hunger, is a psychological need for food consumption. This is often a food craving stimulated by a constant food-filled environment, even without a calorie deficit (Lowe & Butryn, 2007; Andermann & Lowell, 2017). The problem of cravings may be caused by a disturbed activity of AGPR neurons, which are responsible for signaling the body's need for calories. This activity can be suppressed by food delivery. Additionally, sensory stimuli related to food intake should be able to induce a similar suppression of neuron activity (Betley et al., 2015). Sensory stimulants, such as food, texture, taste, visual aspects, and smell, can reduce the activity of APGR (Agouti-related protein) neurons. The last two can be used without actual food intake, which is crucial for both stimulating and reducing appetite (Yin et al., 2017; McCrickerd & Forde, 2016).

Although various medications have been used to treat patients with abnormal appetites and eating disorders, their widespread use has been limited due to adverse side effects. One potential solution for regulating appetite is the use of essential oils. These oils are a combination of secondary metabolites from aromatic and medicinal plants, typically obtained through steam distillation or hydro distillation (Liang et al. 2023). Recent studies, conducted both in vivo and in vitro, have shown that essential oils (EOs) have a wide range of therapeutic benefits for obesity and related diseases (Leherbauer & Stappen 2020; Rashed et al., 2016).

Aromatherapy is a complementary and alternative medicine (CAM) method that utilizes highly concentrated essential oils or essences distilled from plants (Tillett & Ames, 2010). It is a non-invasive procedure that is widely used due to its ease of use (Zor et al., 2021). These essential oils can be applied topically, ingested, or inhaled, and they have a direct impact on the central nervous system by reaching the neocortex of the brain through the limbic system. This release of blocked energy, which is known in CAM as balancing the body's natural energy flow, can result in relaxation, calmness, or arousal. By promoting a balanced flow of energy, aromatherapy supports healing and enhances both physical and mental well-being (Ozer et al., 2025).

The primary routes for fragrance absorption include olfaction, dermal absorption into subcutaneous layers, ingestion, and efficient absorption through the mucous membranes of the

lungs and respiratory tract. The process of olfactory absorption follows a specific sequence: from the nose, to the olfactory nerve, to the olfactory bulb, to the translational system, to the cerebral cortex, to the hypothalamus, to the pituitary gland, to the hormones, and finally to the autonomic nervous system. Dermal absorption occurs when fragrance spreads through bodily fluids from the epidermis to the dermis, and then through the lymphatic system to the bloodstream. Respiratory absorption follows a similar path: from the nose, to the nasal cavity, to the pharynx, to the larynx, to the trachea, to the bronchi, to the alveoli, and finally to the blood vessels throughout the body (Song et al., 2024).

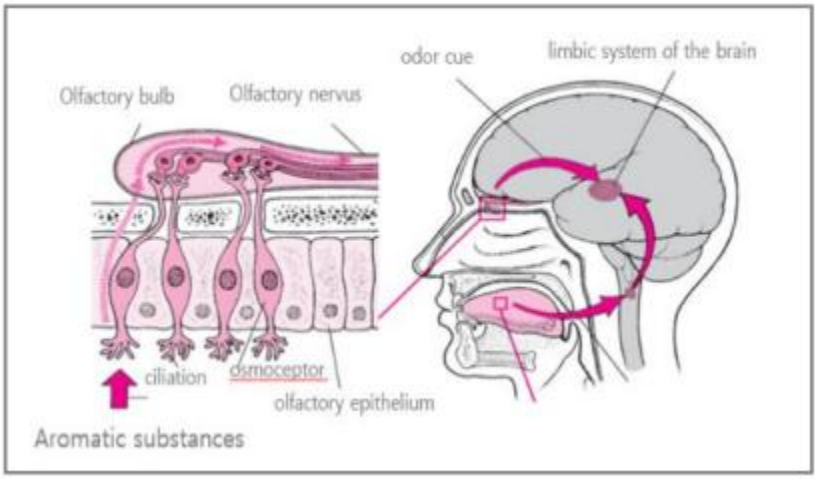


Figure 1. Olfactory sense (Song et al., 2024)

In this study, we utilized a systems biology approach to elucidate the mechanism of action of herbal compounds in treating obesity. Specifically, we examined the effects of compounds found in orange, lemon, bergamot, peppermint, and ginger on the genes involved in obesity suppression at the molecular level.

Material & Methods

- Obesity gene targets

  Obesity involved genes were identified by GeneCards database (https://www.genecards.org/) the searched key word was “obesity”. According to GeneCards database11177 genes are recognized to act in obesity disease (Stelzer et al., 2016).

- Active compounds of herbs

  Compounds from ginger (*Zingiber officinale*), bergamot (*Citrus bergamia*), peppermint (*Mentha piperita*), orange (*Citrus sinensis*), and lemon (*Citrus limon*) were obtained from the Traditional Chinese Medicine System Pharmacology (TCMSP) database (Ru et al., 2014). The selection process focused on identifying bioactive and druggable compounds, taking into consideration factors such as absorption, distribution, metabolism, and excretion (ADME), as well as oral bioavailability (OB) and drug-likeness (DL). Compounds with an

OB > 30% and a DL > 0.18 were considered bioactive. The targets of each compound were identified using the Analysis Tool for Molecular Mechanism of Traditional Chinese Medicine (BATMAN-TCM) database (http://bionet.ncpsb.org/batman-tcm/) (Liu et al., 2016).

- Intersection between herb's compound targets and targets of obesity

All the bioactive compound targets of ginger, bergamot, peppermint, orange, and lemon were intersected with obesity genes by using Venny 2.1 (http://bioinfogp.cnb.csic.es/tools/venny/) (Chen et al., 2021).

- PPI network and hub genes selection

The PPI network which demonstrates the interactions among proteins was constructed by using String database (Szklarczyk et al., 2017). Later by using Cytoscape software (version 3.10.2)140 hub genes were selected as the most probable targets for obesity (Shannon et al., 2003).

- Compound-target network

To identify the most active compounds in the mentioned herbs, a compound-target diagram was constructed using Cystoscope software (Xu et al., 2018).

- GO and KEGG pathway analyses

The Gene Ontology (GO) knowledgebase provides information on the functions of genes, including biological processes (BPs), cellular components (CCs), and molecular functions (MFs) (Primmer et al. 2013). In order to identify the functions of genes related to obesity, gene ontology (GO) was applied to the hub genes. The top 20 biological processes (BPs), cellular components (CCs), and molecular functions (MFs) were selected based on their high count and significance ($P<0.05$) (Zhou et al., 2019). The Kyoto Encyclopedia of Genes and Genomes (KEGG) is a database resource for understanding high-level gene functions and genomic information (Kanehisa et al., 2017). By utilizing KEGG, we were able to identify the most involved pathways in obesity.

Results

According to GeneCards, 11,177 genes are associated with obesity. To evaluate the therapeutic potential of ginger, peppermint, orange, lemon, and bergamot against obesity, all predicted targets of the bioactive compounds present in these herbs were collected and compared with obesity-related genes. A total of 229 overlapping targets were identified between the herbs and obesity-

related genes, indicating potential interactions between the selected herbal compounds and obesity-associated molecular targets (Figure 2).

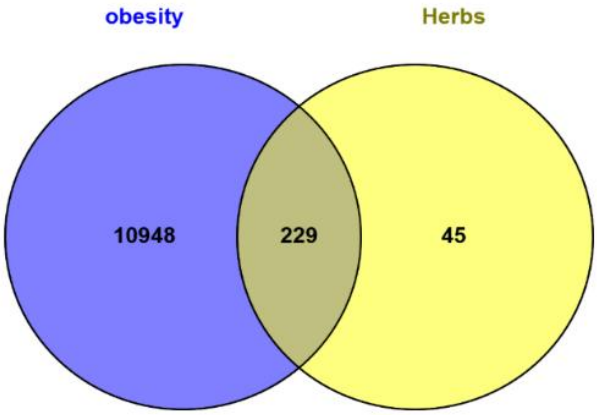


Figure 2. Venn diagram of the herb's compound targets and obesity constructed by linking the overlapped targets (between targets of selected herbs and obesity related targets)

Among the selected herbs, ginger possessed 36 predicted targets, of which 32 overlapped with obesity-related proteins. The major bioactive compounds responsible for these interactions were 10-gingerol, dibutyl phthalate, and galanthamine.

Bergamot exhibited five obesity-related targets, with bergapten identified as the principal bioactive compound contributing to these interactions.

Peppermint contained 38 predicted targets, including 34 common targets with obesity. The major active compounds involved were L-menthol, eucalyptol, and β-bourbonene.

Lemon showed 76 predicted targets, of which 56 overlapped with obesity-related genes. The principal compounds involved in these interactions included fisetin, naringin, ferulic acid, caffeic acid, butein, diosmin, esculetin, and hesperidin.

Among all investigated herbs, orange exhibited the highest number of common targets with obesity. A total of 156 obesity-related targets were associated with orange, mainly through naringenin, citric acid, limonene, chlorogenic acid, and α-terpineol.

Figure 3 illustrates the compound-target interaction network. As shown, naringenin, caffeic acid, naringin, hesperidin, ferulic acid, menthol, and fisetin interacted with a greater number of target proteins than the other compounds, indicating that these compounds may represent the major bioactive constituents involved in obesity treatment.

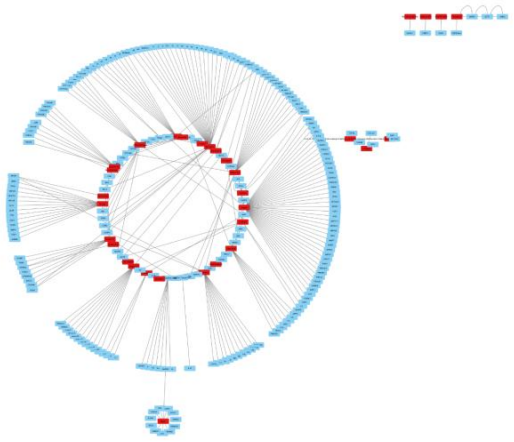


Figure 3. Compound-target network of bergamot, peppermint, orange, lemon, and ginger. Blue rectangles represent the targets, and red rectangles represent the herb's bioactive compounds

To identify the key obesity-related proteins, a protein-protein interaction (PPI) network was constructed using the 229 common target genes (Figure 4).

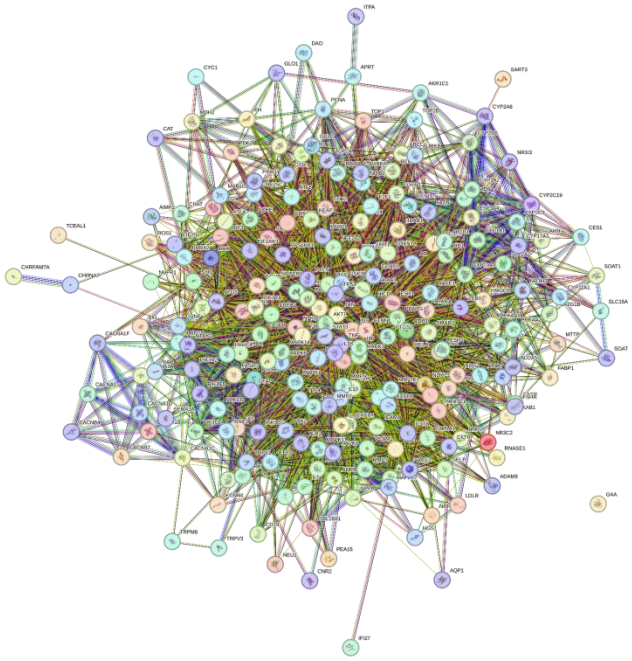


Figure 4. Common target protein interaction network of 229 target genes of herbs

Subsequently, Cytoscape analysis identified 140 hub genes according to closeness and betweenness centrality indices. The ten highest-ranked hub genes were AKT1, IL6, TNF, TP53, INS, CASP3, JUN, BCL2, IL1B, and STAT3 (Table 1).

Table 1. PPI network interactions of top 10 hub genes of obesity

Target name	Closeness Centrality	Betweenness centrality
AKT1	0.965277778	1.914386287
IL6	0.939189189	1.724020678
TNF	0.932885906	1.67934266
TP53	0.920529801	1.465796356
INS	0.908496732	1.497190007
CASP3	0.902597403	1.257249426
JUN	0.896774194	1.2545468
BCL2	0.896774194	1.323693959
IL1B	0.885350318	1.302597433
STAT3	0.874213836	0.978278101

To further investigate the biological significance of these hub genes, KEGG pathway enrichment analysis was performed. The top 20 enriched pathways are presented in Table 2. Among them, Pathways in cancer (hsa05200), Hepatitis B (hsa05161), and Human cytomegalovirus infection (hsa05163) exhibited the highest enrichment significance.

Gene Ontology (GO) enrichment analysis was also conducted to characterize the biological functions of the hub genes. The enriched GO terms were classified into biological process (BP), cellular component (CC), and molecular function (MF). Cellular process, cellular anatomical entity, and binding represented the most significantly enriched categories within BP, CC, and MF, respectively (Table 3).

Table 2. KEGG pathway enrichment analysis

Pathway	Term	Genes	Count	P value
Pathways in cancer	hsa05200	KEAP1,MAPK1,HMOX1,NFKBIA,MMP2,PIK3R2,RPS6KB1,NFKB1,IL2,CCND1,CDKN1B,IFNG,IL4,IL5,CDK4,CCND2,CDH1,MAP2K2,MAPK3,PIK3CA,STAT3,CDK2,RB1,TP53,EGFR,NOTCH1,PPARG,PIK3CB,BAX,CRK,MAP2K1,PRKCB,FOS,CXCL8,CASP3,BID,NQO1,MMP1,GSK3B,NOS2,CASP9,SMAD3,HSP90AA1,PTK2,ESR2,CTNNB1,E2F1,FAS,CASP8,MTOR,FH,PTGS2,FASLG,CHUK,JUN,PTEN,MMP9,HDAC1,AR,PIK3CD,BMP2,BAD,MAPK8,NFE2L2,BCL2,GSTP1,RELA,CDKN1A,IL6,CXCR4,MAPK9,ESR1,PRKCA,PIK3R1,HIF1A,AKT1,VEGFA,MYC	78	7.33E-61
Hepatitis B	hsa05161	MAPK1,NFKBIA,PIK3R2,NFKB1,MAPK14,TLR2,MAP2K2,MAPK3,PIK3CA,STAT3,CDK2,RB1,TP53,PIK3CB,BAX,MAP2K1,PRKCB,FOS,CXCL8,CASP3,BID,CASP9,SMAD3,MAPK11,ATF4,E2F1,FAS,CASP8,FASLG,CHUK,JUN,MMP9,SRC,TLR4,PIK3CD,PCNA,BAD,MAPK8,BCL2,RELA,CDKN1A,IL6,CREB1,NFATC1,IRAK4,MAPK9,TNF,PRKCA,PIK3R1,AKT1,MYC	51	2.43E-53
Human cytomegalovirus infection	hsa05163	MAPK1,NFKBIA,PIK3R2,RPS6KB1,NFKB1,CCND1,MAPK14,CDK4,MAP2K2,MAPK3,IL1B,PIK3CA,STAT3,RB1,TP53,EGFR,PIK3CB,BAX,CRK,MAP2K1,PRKCB,CXCL8,CASP3,BID,GSK3B,CASP9,MAPK11,ATF4,PTK2,CTNNB1,E2F1,FAS,CASP8,MTOR,PTGS2,FASLG,CHUK,SRC,PIK3CD,RELA,CDKN1A,IL6,CXCR4,CREB1,NFATC1,TNF,PRKCA,PIK3R1,AKT1,VEGFA,MYC	51	2.08E-47

Kaposi sarcoma-associated herpesvirus infection	hsa05167	MAPK1,NFKBIA,PIK3R2,NFKB1,CCND1,MAPK14,CDK4,MAP2K2,MAPK3,PIK3CA,STAT3,ICAM1,RB1,TP53,PIK3CB,BAX,MAP2K1,FOS,CXCL8,CASP3,BID,GSK3B,CASP9,MAPK11,CTNNB1,E2F1,FAS,CASP8,PIK3CG,MTOR,BECN1,PTGS2,CHUK,JUN,SRC,PIK3CD,MAPK8,RELA,CDKN1A,IL6,CREB1,NFATC1,MAPK9,PIK3R1,HIF1A,AKT1,VEGFA,MYC	48	3.15E-46
PI3K-Akt signaling pathway	hsa04151	MAPK1,PIK3R2,RPS6KB1,COL1A1,NFKB1,IL2,CCND1,CDKN1B,IL4,CDK4,TLR2,CCND2,MAP2K2,MAPK3,PIK3CA,CDK2,TP53,EGFR,NTRK2,PIK3CB,MAP2K1,GSK3B,CASP9,HSP90AA1,ATF4,PTK2,PRKAA1,PIK3CG,MTOR,FASLG,CHUK,PRKAA2,PTEN,TLR4,PIK3CD,BAD,SPP1,INS,BCL2,RELA,CDKN1A,IL6,CREB1,PRKCA,PIK3R1,AKT1,VEGFA,MYC	48	6.21E-35
Alzheimer disease	hsa05010	MAPK1,PIK3R2,NFKB1,EIF2S1,MAP2K2,MAPK3,IL1B,PIK3CA,CACNA1C,APP,CACNA1D,PIK3CB,MAP2K1,EIF2AK3,CASP3,CYC1,BACE1,BID,GSK3B,NOS2,CASP9,ATF4,CTNNB1,FAS,CASP8,MTOR,CACNA1S,BECN1,PTGS2,ATF6,CHUK,CACNA1F,PIK3CD,BAD,MAPK8,INS,RELA,IL6,MAPK9,TNF,PIK3R1,PSMD9,DDIT3,AKT1	44	2.54E-30
Human papillomavirus infection	hsa05165	MAPK1,PIK3R2,RPS6KB1,COL1A1,NFKB1,CCND1,CDKN1B,CDK4,CCND2,MAP2K2,MAPK3,PIK3CA,CDK2,RB1,TP53,EGFR,NOTCH1,PIK3CB,BAX,MAP2K1,CASP3,GSK3B,PTK2,CTNNB1,E2F1,FAS,CASP8,MTOR,PTGS2,FASLG,CHUK,PTEN,HDAC1,PIK3CD,BAD,SPP1,RELA,CDKN1A,CREB1,TNF,PIK3R1,AKT1,VEGFA	43	1.09E-30
Human immunodeficiency virus 1 infection	hsa05170	MAPK1,NFKBIA,PIK3R2,RPS6KB1,NFKB1,MAPK14,TLR2,MAP2K2,MAPK3,PIK3CA,PIK3CB,BAX,CRK,MAP2K1,PRKCB,FOS,CASP3,BID,CDC25C,CASP9,MAPK11,PTK2,FAS,CASP8,MTOR,FASLG,CHUK,JUN,TLR4,PIK3CD,BAD,MAPK8,BCL2,RELA,CXCR4,NFATC1,IRAK4,MAPK9,TNF,PRKCA,PIK3R1,AKT1	42	5.84E-37
Hepatitis C	hsa05160	MAPK1,NFKBIA,PIK3R2,NFKB1,CCND1,IFNG,EIF2S1,CDK4,MAP2K2,MAPK3,PIK3CA,STAT3,CDK2,RB1,TP53,EGFR,PIK3CB,BAX,MAP2K1,EIF2AK3,CASP3,BID,GSK3B,CASP9,CTNNB1,E2F1,FAS,CASP8,FASLG,CHUK,PIK3CD,BAD,RELA,CDKN1A,PPARA,TNF,PIK3R1,AKT1,LDLR,NR1H3,MYC	41	8.41E-40
MAPK signaling pathway	hsa04010	MAPK1,NFKB1,MAPK14,MAP2K2,MAPK3,IL1B,CACNA1C,TP53,EGFR,NTRK2,CACNA1D,CRK,MAP2K1,CD14,PRKCB,FOS,CASP3,CACNB2,MAPK11,ATF4,FAS,CACNA1A,CACNA1S,FASLG,CHUK,JUN,CACNA1B,CACNA1F,MAPK8,INS,RELA,NFATC1,IRAK4,MAPK9,TNF,PRKCA,CACNB4,DDIT3,AKT1,VEGFA,MYC	41	2.15E-30
Epstein-Barr virus infection	hsa05169	NFKBIA,PIK3R2,NFKB1,CCND1,CDKN1B,MAPK14,CDK4,TLR2,CCND2,PIK3CA,STAT3,ICAM1,CDK2,RB1,TP53,PIK3CB,BAX,CASP3,BID,CASP9,MAPK11,E2F1,FAS,CASP8,CHUK,JUN,HDAC1,PIK3CD,MAPK8,BCL2,RELA,CDKN1A,IL6,IRAK4,MAPK9,TNF,PIK3R1,VIM,AKT1,MYC	40	2.66E-35
Metabolic pathways	hsa01100	SIRT1,HMOX1,GSR,DAO,GCLC,CAT,CYP2C9,PIK3CA,CYP11A1,HMGCR,PIK3CB,CYP2A6,FASN,GAA,PLA2G1B,CYC1,NQO1,MDH2,NOS2,CYP3A4,MAOA,CYP1A2,	40	4.44E-07

		CS,PIK3CG,PTGS1,FH,PTGS2,CYP17A1,CYP2C19,PTEN,GLO1,ALOX5,NEU1,PIK3CD,APRT,CYP1A1,ITPA,CYP19A1,GSTP1,ENO2		
Measles	hsa05162	NFKBIA,PIK3R2,NFKB1,IL2,CCND1,CDKN1B,EIF2S1,CDK4,TLR2,CCND2,IL1B,PIK3CA,STAT3,CDK2,TP53,PIK3CB,BAX,FOS,EIF2AK3,CASP3,BID,GSK3B,CASP9,FAS,CASP8,FASLG,CHUK,JUN,TLR4,PIK3CD,BAD,MAPK8,BCL2,RELA,IL6,IRAK4,MAPK9,PIK3R1,AKT1	39	6.63E-39
Prostate cancer	hsa05215	MAPK1,NFKBIA,PIK3R2,NFKB1,CCND1,CDKN1B,MAP2K2,MAPK3,PIK3CA,CDK2,RB1,TP53,EGFR,PIK3CB,MMP3,MAP2K1,GSK3B,CASP9,HSP90AA1,ATF4,CTNNB1,E2F1,ZEB1,MTOR,CHUK,PTEN,MMP9,AR,PIK3CD,BAD,INS,BCL2,GSTP1,RELA,CDKN1A,CREB1,PIK3R1,AKT1	38	1.57E-42
MicroRNAs in cancer	hsa05206	SIRT1,MAPK1,HMOX1,PIK3R2,NFKB1,CCND1,CDKN1B,CCND2,MAP2K2,MAPK3,PIK3CA,STAT3,TP53,EGFR,NOTCH1,PIK3CB,CRK,MAP2K1,PRKCB,CASP3,CDC25C,E2F1,ZEB1,MTOR,PTGS2,PTEN,MMP9,HDAC1,PIK3CD,BCL2,ABCC1,CDKN1A,PRKCA,PIK3R1,VIM,ABCB1,VEGFA,MYC	38	1.79E-35
Human T-cell leukemia virus 1 infection	hsa05166	MAPK1,NFKBIA,PIK3R2,NFKB1,IL2,CCND1,CDK4,MMP7,CCND2,MAP2K2,MAPK3,PIK3CA,ICAM1,CDK2,RB1,TP53,PIK3CB,BAX,MAP2K1,FOS,SMAD3,ATF4,E2F1,CHUK,JUN,PTEN,PIK3CD,MAPK8,RELA,CDKN1A,IL6,CREB1,NFATC1,MAPK9,TNF,PIK3R1,AKT1,MYC	38	1.52E-31
Endocrine resistance	hsa01522	MAPK1,MMP2,PIK3R2,RPS6KB1,CCND1,CDKN1B,MAPK14,CDK4,MAP2K2,MAPK3,PIK3CA,RB1,TP53,EGFR,NOTCH1,PIK3CB,BAX,MAP2K1,FOS,MAPK11,PTK2,ESR2,E2F1,CYP2D6,MTOR,JUN,MMP9,SRC,PIK3CD,BAD,MAPK8,BCL2,CDKN1A,MAPK9,ESR1,PIK3R1,AKT1	37	3.33E-41
Proteoglycans in cancer	hsa05205	MAPK1,MMP2,PIK3R2,RPS6KB1,COL1A1,CCND1,MAPK14,TLR2,MAP2K2,MAPK3,PIK3CA,STAT3,TP53,EGFR,PIK3CB,MAP2K1,PRKCB,CASP3,MAPK11,PTK2,CTNNB1,FAS,MTOR,FASLG,MMP9,SRC,TLR4,PIK3CD,CDKN1A,TNF,ESR1,PRKCA,PIK3R1,HIF1A,AKT1,VEGFA,MYC	37	2.23E-31
AGE-RAGE signaling pathway in diabetic complications	hsa04933	MAPK1,MMP2,PIK3R2,COL1A1,NFKB1,CCND1,CDKN1B,MAPK14,CDK4,MAPK3,IL1B,PIK3CA,STAT3,ICAM1,PIK3CB,BAX,VCAM1,PRKCB,CXCL8,CASP3,SMAD3,MAPK11,JUN,PIK3CD,PRKCD,MAPK8,BCL2,RELA,IL6,NFATC1,MAPK9,TNF,PRKCA,PIK3R1,AKT1,VEGFA	36	2.38E-39
Fluid shear stress and atherosclerosis	hsa05418	KEAP1,HMOX1,MMP2,PIK3R2,NFKB1,IFNG,MAPK14,IL1B,PIK3CA,ICAM1,TP53,PIK3CB,VCAM1,FOS,NQO1,MAPK11,HSP90AA1,PTK2,CTNNB1,PRKAA1,CHUK,JUN,PRKAA2,MMP9,SRC,PIK3CD,MAPK8,NFE2L2,BCL2,GSTP1,RELA,MAPK9,TNF,PIK3R1,AKT1,VEGFA	36	1.16E-35

Table 3. GO Enrichment analysis

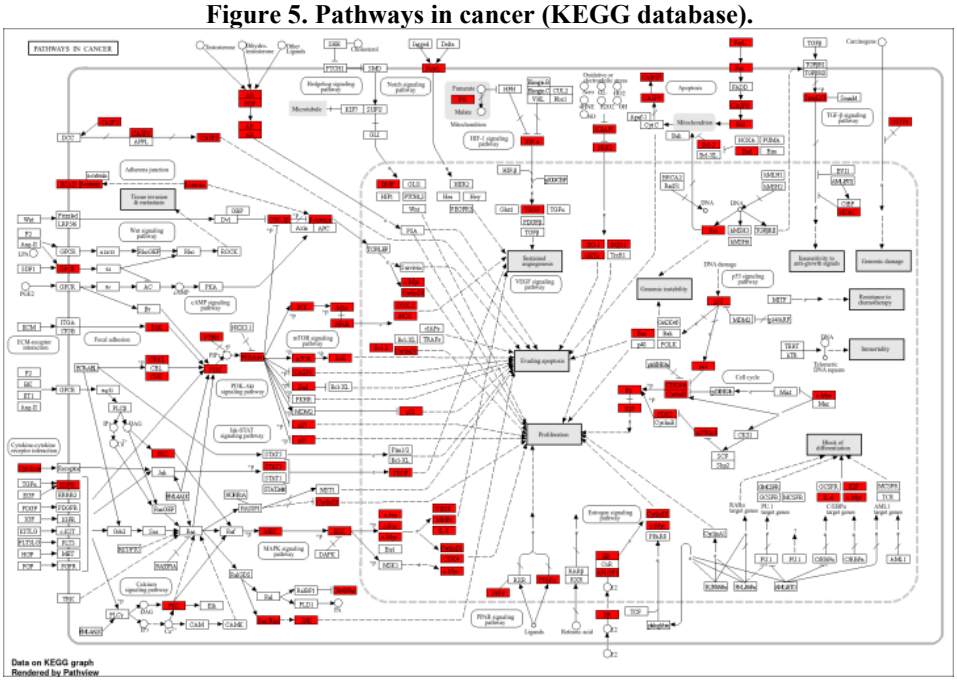
GO Category	Pathway	Pathways genes counts	P value	Enrichment FDR
Biological process (BP)	Cellular process	228	5.56E-25	4.23E-23
	Biological regulation	217	1.00E-30	1.19E-28

	Regulation of biological process	210	6.09E-29	6.07E-27
	Response to stimulus	205	1.83E-52	1.38E-49
	Regulation of cellular process	202	4.49E-26	3.65E-24
	Cellular response to stimulus	191	1.11E-54	1.19E-51
	Metabolic process	187	8.68E-34	1.45E-31
	Positive regulation of biological process	183	2.74E-51	1.86E-48
	Response to chemical	180	2.31E-72	7.42E-69
	Organic substance metabolic process	180	6.40E-33	9.45E-31
Cellular component (CC)	Cellular anatomical entity	229	3.83E-10	2.50E-08
	Organelle	206	6.09E-14	1.72E-11
	Intracellular	203	6.34E-09	2.69E-07
	Membrane-bounded organelle	201	1.68E-16	7.14E-14
	Cytoplasm	195	2.78E-18	2.36E-15
	Intracellular organelle	193	1.10E-11	1.56E-09
	Intracellular membrane-bounded organelle	183	3.46E-15	1.18E-12
	Membrane	150	5.23E-09	2.28E-07
	Nucleus	128	2.47E-08	9.78E-07
	Cellular anatomical entity	229	3.83E-10	2.50E-08
Molecular function (MF)	Binding	215	1.88E-26	2.03E-23
	Protein binding	174	1.21E-34	3.93E-31
	Ion binding	128	4.47E-14	8.04E-12
	Organic cyclic compound binding	125	2.51E-14	4.77E-12
	Heterocyclic compound binding	120	1.13E-12	1.40E-10
	Catalytic activity	115	1.62E-12	1.80E-10
	Enzyme binding	100	3.79E-34	6.13E-31

	Molecular function regulator	87	2.46E-13	3.79E-11
	Cation binding	79	6.57E-06	0.00019
	Small molecule binding	77	8.78E-16	2.84E-13

According to the KEGG enrichment results, the Pathways in cancer (hsa05200) pathway showed the highest enrichment score among all identified pathways (Figure 5). Moreover, several core genes, including MAPK8 and CASP3, were involved in multiple signaling pathways associated with obesity.

Figure 5. Pathways in cancer (KEGG database).



Discussion

The present network pharmacology analysis demonstrated that 229 common targets were shared between obesity-related genes and the bioactive compounds of ginger, bergamot, peppermint, lemon, and orange, suggesting that these medicinal plants may regulate obesity through multiple molecular targets rather than a single signaling pathway. Such multi-target characteristics are consistent with the pharmacological properties of herbal medicines, in which numerous phytochemicals act synergistically to influence complex metabolic disorders.

Among the investigated herbs, orange exhibited the highest number of obesity-related targets (156), followed by lemon, peppermint, and ginger. The dominant compounds identified in citrus species, particularly naringenin, hesperidin, limonene, and chlorogenic acid, interacted with a large number of obesity-associated proteins, indicating their potential contribution to the anti-obesity activity of these herbs. Previous studies have reported that hesperidin promotes brown adipose

tissue activity, thereby reducing abdominal fat accumulation (Lee, 2000). Likewise, limonene has been shown to improve hyperglycaemia and reduce adipocyte accumulation in experimental models of diet-induced obesity (Rashed et al., 2016). Furthermore, Song et al. (2024) demonstrated that aromatherapy using orange and peppermint essential oils could suppress appetite in individuals with severe obesity, supporting the potential therapeutic role of citrus-derived compounds.

Although ginger exhibited fewer common targets than orange, most of its predicted targets were obesity-related. Ginger contains several biologically active compounds, including 10-gingerol, which has previously been associated with improved blood circulation and enhanced fat metabolism (Kim et al., 2020). These findings support the potential contribution of ginger-derived phytochemicals to obesity management.

Peppermint also demonstrated considerable overlap with obesity-associated targets. Menthol, the principal active compound, has long been recognized for its calming and anti-stress properties. Since psychological stress and anxiety are important contributors to excessive food intake, the observed molecular interactions may partially explain the beneficial effects of peppermint in obesity management.

Lemon showed a substantial number of common targets, mainly through flavonoids such as hesperidin, naringin, fisetin, and ferulic acid. Experimental evidence has demonstrated that citrus essential oils can suppress body weight gain and promote weight reduction in obese animal models (Asnaashari et al., 2010), supporting the relevance of the present findings.

The PPI analysis identified AKT1 as the highest-ranked hub gene. AKT1 plays a central role in insulin signalling, glucose metabolism, cell survival, and lipid metabolism. Previous experimental studies demonstrated that deletion of AKT1 protects mice against high-fat diet-induced obesity and insulin resistance (Wan et al., 2011), indicating that modulation of this pathway may contribute to the anti-obesity mechanisms predicted in the present study.

Other highly connected hub genes included IL6 and TNF, both of which are key inflammatory mediators. Chronic obesity is now recognized as a state of low-grade systemic inflammation characterized by increased secretion of adipokines and inflammatory cytokines from adipose tissue. Elevated circulating levels of IL-6 and TNF have consistently been reported in obese individuals (Royblat et al., 2000; Eder et al., 2009). Therefore, targeting these inflammatory regulators may represent one of the principal mechanisms through which the investigated herbal compounds exert their therapeutic effects.

KEGG enrichment analysis further demonstrated that obesity-associated genes were significantly enriched in pathways related to cancer, PI3K-Akt signalling, MAPK signalling, and inflammatory diseases. These findings highlight the close relationship between obesity, chronic inflammation, metabolic dysregulation, and multiple disease pathways. In particular, MAPK8 and CASP3 participated in numerous enriched pathways, suggesting that these proteins may serve as important molecular mediators linking obesity to inflammation and apoptosis. Consistent with

these findings, Zhang et al. (2023) reported altered expression of MAPK8 and CASP3 in adipose tissue from obese rats.

Overall, the present findings indicate that the anti-obesity potential of ginger, bergamot, peppermint, lemon, and orange is mediated through a complex network of bioactive compounds acting on multiple genes and signalling pathways. The integration of compound-target analysis, PPI network analysis, hub gene identification, and pathway enrichment provides mechanistic evidence supporting the potential application of these medicinal plants in obesity management.

Conclusions

Obesity is a complex disorder that has been treated with various methods, some of which have resulted in severe side effects for patients. While aromatherapy has been shown to be a safe treatment, the molecular mechanism of herbs in treating obesity remains unclear. In this study, we aim to clarify how peppermint, bergamot, orange, lemon, and ginger may affect the genes involved in obesity.

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Conflict of interest

The authors declare no conflict of interest.

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