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Aromatherapy and appetite suppression: molecular mechanism by system biology

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ABSTRACT

Obesity is a complex disease that results from chronic metabolic disorders and has become a significant global health concern. It is a medical issue and a significant risk factor for serious conditions such as insulin resistance, type 2 diabetes, cardiovascular disease, and certain types of cancer. Additionally, the psychological impact of obesity should not be overlooked, as it can lead to severe pathologies such as depression, phobias, generalized anxiety, and low self-esteem. While many conventional methods have been used to address this disorder, their severe side effects limit their efficacy and tolerability among the general population. In recent years, there has been a growing interest in aromatherapy as a safe method for preventing obesity. Essential oils (EOs) have demonstrated efficacy in promoting weight loss. EOs are mixtures of aromatic substances produced by various plants, especially those possessing medicinal and aromatic properties. In this study, we investigated the molecular mechanisms of bergamot, orange, lemon, peppermint, and ginger in the treatment of obesity using a systems biology approach.

1. 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 ≥ 25) and obese (BMI ≥ 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).

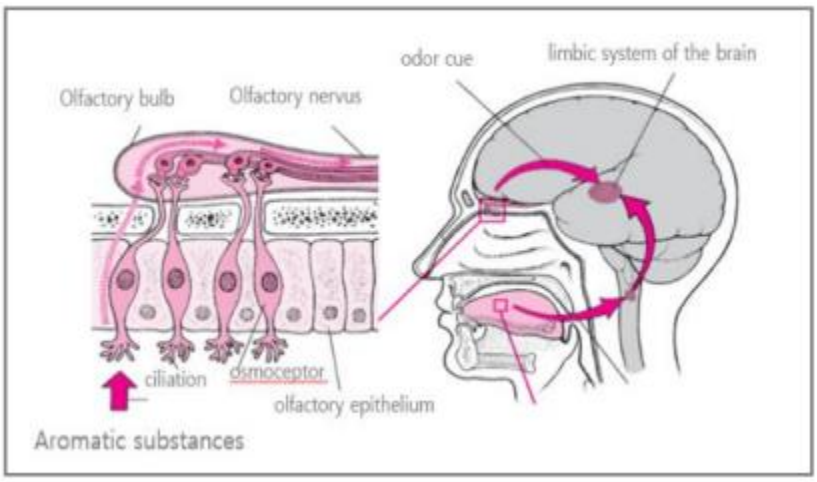

Figure 1. Olfactory sense (Song et al., 2024)

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 and method

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 and discussion

According to GeneCards, there are 11,177 genes involved in obesity. In order to assess the effectiveness of ginger, peppermint, orange, lemon, and bergamot in treating obesity, we collected all potential targets of these herbs that are triggered by bioactive compounds and compared them to obesity target genes. Our analysis revealed that there are 229 common targets between obesity and the herb's targets, providing evidence for the high efficacy of these herbs' bioactive compounds in treating obesity (Figure 2).

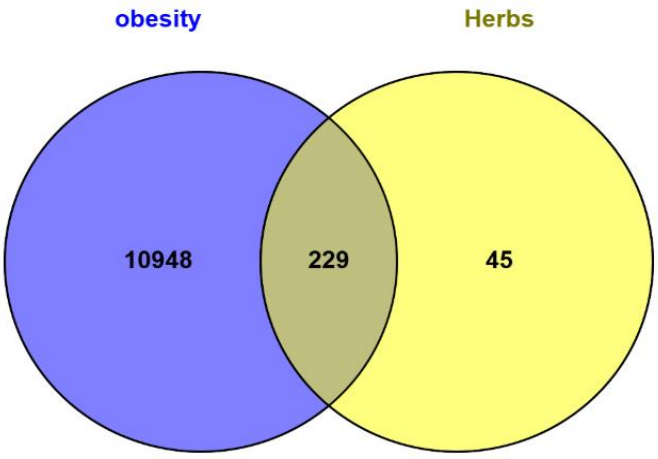

Figure 2. Venn diagram of the herb's compound targets and obesity constructed by linking the overlapped targets (between targets of selected herbs and obesity related targets)

According to the results, ginger has 36 known targets, of which 32 were found to target obesity-related proteins. The most active compounds in ginger are 10-gingerol, dibutyl phthalate, and galanthamine. The root and stem of *Zingiber officinale* have been widely used in traditional remedies. Studies have shown that ginger oil can improve blood circulation by increasing artery flow, which may contribute to its positive effects on fat burning (Kim et al., 2020).

Bergapten is the most active compound found in bergamot, and it has the ability to target five different obesity-related factors. Depression is a complex condition that is characterized by a combination of symptoms, including emotional distress (such as sadness and anhedonia), cognitive impairment, and physical symptoms (such as changes in appetite and sleep patterns). Bergamot oil has been shown to have a positive impact on blood pressure and heart rate, as well as promoting better sleep and reducing restlessness (Muz & Tasci, 2017).

The known targets of peppermint were 38, of which 34 were common targets with obesity and mostly targeted by L-menthol, eucalyptol, and beta-bourbonene. Menthol is highly valued for its cooling properties, which have served medicinally to alleviate conditions like fatigue, hysterical fits, and nervous disorders. Since one of the crucial factors leading to excessive eating is anxiety and stress, applying peppermint with known antistress effects seems effective.

Lemon has 76 known targets, with 56 of them also being common targets for obesity. Among these, fisetin, naringin, ferulic acid, caffeic acid, butein, diosmin, esculetin, and hesperidin have shown the most involvement in targeting obesity-related proteins. In a study on mice with drug-induced

obesity over a 45-day experimental period, treatment with lime essential oil resulted in weight loss from 33 g to 23 g and suppressed weight gain (Asnaashari et al., 2010).

According to the results, among 229 common targets of herbs and obesity, the most common targets belong to orange. This herb is estimated to trigger 156 targets of obesity, mostly through the compounds naringenin, citric acid, limonene, chlorogenic acid, and alpha-terpineol. Research has been conducted on Moro oranges, which contain anthocyanins, and vitamins C and E, and hesperidin, which is also found in oranges and lemons, has shown potential in early studies to promote the production of brown fat, which helps prevent abdominal obesity (Lee, 2000). Additionally, these compounds have been found to have anti-stress effects. According to Matsumoro (2014), inhaling *Citrus junos* after olfactory stimulation substantially reduced total mood disturbance and the four subscores of emotional symptoms (tension-anxiety, depression-dejection, anger-hostility, confusion) for up to 30 minutes. The fragrant effects of yuzu likely mitigate negative emotional stress by reducing activity in the sympathetic nervous system. Another crucial compound found in citrus is limonene, which has been reported to have a positive effect on hyperglycemic mice with high-fat diet-induced obesity (HFD). Limonene was also found to be beneficial in reducing both white and brown adipocytes, as well as blood sugar levels (Rashed et al., 2016). Song et al. (2024) provided evidence to support the immediate and remarkable impact of orange and peppermint aromatherapy on appetite suppression in individuals with severe obesity.

Figure 3 represent the Compound-target network, as shown naringenin, caffeic acid, naringin, hesperidin, ferulic acid, menthol, and fisting triggered more targets than other compounds thus they can be considered as the most active compounds in obesity treatment.

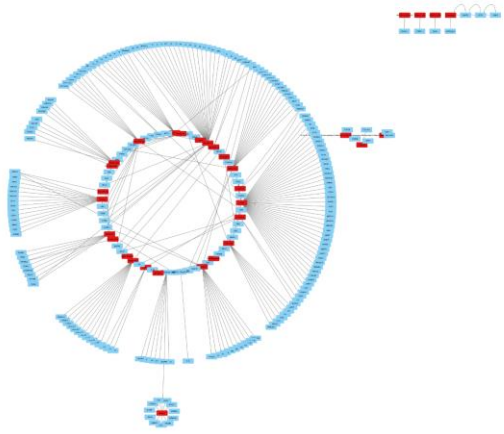

Figure 3. Compound-target network of bergamot, peppermint, orange, lemon, and ginger. Blue rectangles represent the targets, and red rectangles represent the herb's bioactive compounds

To identify the most active genes in obesity, PPI network was constructed showing the most important proteins in this disease based on their interactions (Figure 4).

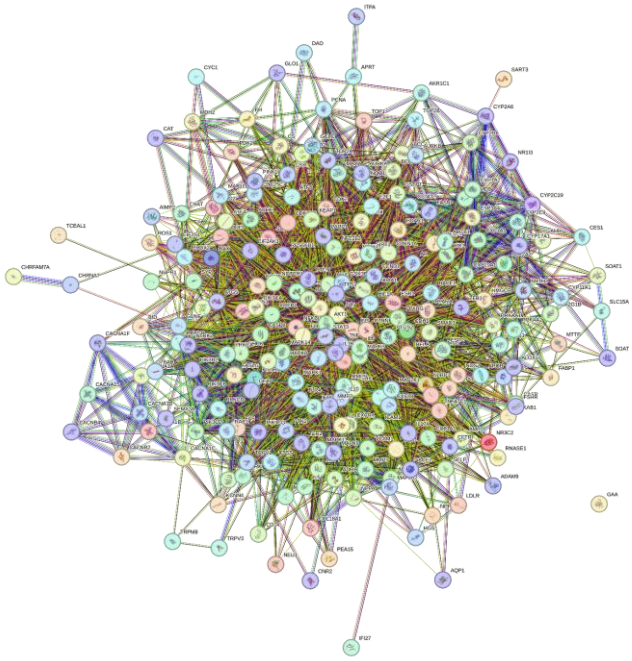

Figure 4. Common target protein interaction network of 229 target genes of herbs

Afterwards, we used Cytoscape to identify the hub genes. A total of 140 genes were recognized as hub genes based on their central closeness and betweenness. The top ten genes with the most interactions are listed in Table 1. One of the most crucial genes in obesity is serine/threonine kinase1 (AKT1), which belongs to the serine-threonine protein kinase family. Also known as protein kinase B (PKB), AKT1 is comprised of three isoforms: Akt1/PKB, Akt2/PKB, and Akt3/PKB, each encoded by a distinct gene (Whiteman et al., 2002). Akt1 is expressed ubiquitously, and its knockout results in smaller body size and growth retardation with normal glucose homeostasis, without compensatory elevation of Akt2 expression. To illustrate the role of AKT1 in metabolic control, Wan et al. (2011) placed Akt1 mice on a high-fat diet (HFD). They reported that mice with deletion of Akt1 were protected from diet-induced obesity and its associated insulin resistance.

Two other major genes associated with obesity are IL6 and TNF, both of which are inflammatory mediators. In the past decade, numerous studies have demonstrated elevated levels of IL-6 in obese patients (Royblat et al., 2000). Obesity triggers the activation of adipose tissue macrophages. Traditionally, adipose tissue was thought to simply store triacylglycerols and release free fatty acids. However, it is now recognized as an active endocrine organ, producing a variety of cytokines and bioactive mediators collectively known as adipokines. These adipokines play a role in various systemic reactions,

including hemostasis, lipid metabolism, blood pressure regulation, insulin sensitivity, and angiogenesis. There is mounting evidence that obesity is a chronic inflammatory condition, as evidenced by the increased expression, production, and release of several inflammation-related adipokines, such as TNF-a, IL-6, PAI-1, haptoglobin, and leptin, in obese individuals (Eder et al., 2009).

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 better understand the role of hub genes in obesity, the top 20 pathways were selected based on the number of involved genes and P value using KEGG (Table 2). The results showed that the most significant pathways were pathways in cancer (GO: hsa05200), Hepatitis B (GO: hsa05161), and Human cytomegalovirus infection (GO: hsa05163). Additionally, GO enrichment analysis was conducted to identify the biological functions of the hub genes in obesity. The results were categorized into three groups: biological process (BP), cellular components (CC), and molecular function (MF). The most significant enrichments were found in cellular process, cellular anatomical entity, and binding, respectively. Table 3 presents the top 10 BPs, top 10 CCs, and top 10 MFs based on the number of occurrences.

Table 2. KEGG pathway enrichment

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,CS,PIK3CG,PTGS1,FH,PTGS2,CYP17A1,CYP2C19,PTEN,GLO1,ALOX5,NEU1,PIK3CD,APRT,CYP1A1,ITPA,CYP19A1,GSTP1,ENO2	40	4.44E-07
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 results, the most significant pathway in obesity is the pathway in cancer (has 05200) (Figure 5). As shown in Figure 4, parts of the core targets, such as MAPK8 and CASP3, are involved in multiple signaling pathways in the treatment of obesity. The expression of MAPK8 and CASP3 was investigated in the peritesticular adipose tissue of obese rats at both the gene and protein levels (Zhang et al., 2023).

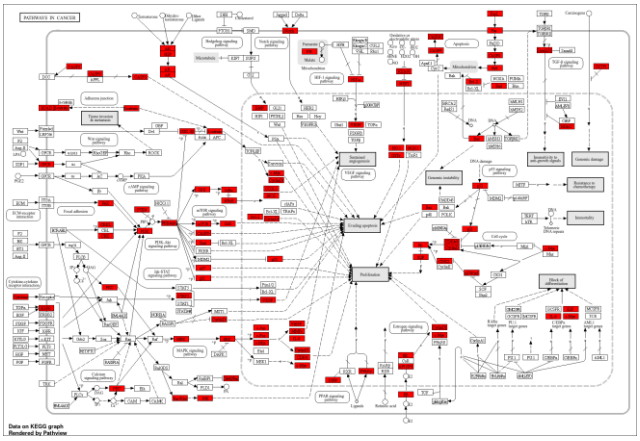

Figure 5. Pathway in cancer (keg database)

Conclusion

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.

Declaration Statements

The present research did not receive any financial support.

The authors declare that there is not any conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/ or falsification, double publication and/or submission, and redundancy has been completely observed by the authors.

No life science threat was practiced in this research.

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