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MINI-REVIEW ARTICLE

Predictive Analysis of *Rosmarinus officinalis* L. Quality Marker (Q-Marker) Based on Chemical Composition, Activity and Network Pharmacology

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Abstract: *Rosmarinus officinalis* L. is a long-honored medicinal and edible aromatic plant extensively employed in the food, pharmaceutical, and spice industries. It is rich in various bioactive compounds, including flavonoids, terpenes, phenylpropanoic acids, quinones, and steroids, which exhibit a range of effects such as antimicrobial, anti-inflammatory, antioxidant, antitumor, hypoglycemic, hypolipidemic, hepatoprotective, and nephroprotective properties. To further explore the application potential of *Rosmarinus officinalis*, we predicted the quality marker (Q-Marker) based on the measurability of chemical constituents, traditional medicinal properties, and effectiveness. This approach was informed by research on the components, biological activities, and mechanisms of action, followed by network pharmacology analysis. Ultimately, 17 practical components were selected as potential biomarkers, including carnosic acid, carnosol, rosmanol, isorosmanol, epirosmanol, 7-methoxyrosmanol, 7-ethoxyrosmanol, rosmaridiphenol, rosmadial, rosmarinic acid, 1,8-cineole, rosmarinine, royleanone, horminone, homovanillic acid, ferruginol, and cryptotanshinone. Most of these compounds belong to the categories of terpenoids and organic acids. Through enrichment analysis, we identified the targets and pathways of these components in various diseases, such as microbial infection, cancer, apoptosis, oxidative stress, and abnormal glycolipid metabolism. This integrated approach that combines plant components, big data, and pharmacology for marker screening is more rational. The results provide a reference for the development, research, and quality evaluation of rosemary resources.

Keywords: *Rosmarinus officinalis* L., quality marker, quality control, flavonoids, terpenes, phenylpropanoic acids.

1. INTRODUCTION

Rosemary (*Rosmarinus officinalis* L.), also known as Dew of the Sea, is a perennial evergreen shrub belonging to the Lamiaceae family. It is native to the Mediterranean coast and grows widely in Europe and North Africa. Rosemary has long been a common spice in the traditional Mediterranean diet [1], and it also has a rich history as an herb used in European folk medicine to treat gastrointestinal, skin, and respiratory diseases [2, 3]. Recently, the European Medicines Agency (EMA) updated the herbal monograph on rosemary, systematically describing the indications, dosage, administration, and contraindications of rosemary leaves and essential oil [4]. According to the Compendium of Materia Medica, an ancient Chinese medicine text, rosemary was introduced to China from the Western regions during the reign of Emperor Wei Wen [5]. In another traditional Chinese medicine book, the Supplement to Materia Medica, rosemary was officially recorded for the first time as a medicinal material, characterized as "hot, warm, non-toxic," and noted for "treating Qi and blood imbalance." In China, rosemary is traditionally used by the Yi and Zhuang ethnic groups, who believe it is effective in treating abdominal pain, bloating, dizziness, headaches, obesity, and other ailments. Additionally, as a safe and effective natural antioxidant, preservative, and flavoring agent, rosemary is widely used in the modern food industry [6]. It has been approved by the European Union as an additive for various food categories [7]. However, the low

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bioavailability of certain components limits its therapeutic efficacy. To address this issue, an increasing number of studies are exploring new delivery systems. Novel green nanoparticles have effectively enhanced the bioavailability of components.

In recent years, with the development of natural medicine resources, research on rosemary and its diverse biological activities has gradually become a hot topic [8]. More bioactive ingredients are being discovered and utilized through extraction processes, and the identification of components is continuously evolving. Multi-component and multi-target characteristics define medicinal plants. Therefore, it is necessary to establish a more scientific quality evaluation system based on their pharmacological activities. Due to the complexity of plant extracts, standardizing their quality is challenging. However, the normative documents on the quality of rosemary issued by most countries are too brief, and there is insufficient research on quality evaluation. The theory of Quality Markers (Q-Markers) aligns well with the characteristics of herbal medicine. It provides an effective quality control system for medicinal materials. The purpose of the Q-Marker theory is to study quality evaluation and control methods, addressing the existing problems of herbal medicine products and further establishing quality control technology [9]. Exploring the quality markers of rosemary is significant for enhancing its safety and effectiveness in food, health care products, and medicinal materials. Consequently, the concept of Q-Markers is used to identify the critical components of rosemary, which can serve as a reference for the quality evaluation of multifunctional herbs.

Currently, the development of natural products is facing challenges. The discovery of new active components and mechanisms of action has revealed certain limitations. There is no information about these components in traditional quality assessment methods. This restricts our ability to conduct more in-depth research on their potential functions. In this study, we conducted high-throughput screening using network pharmacology to provide a new solution for the quality evaluation of natural products. By integrating the relationships between ingredients, targets, and pathways, we can comprehensively assess the quality of herbal products.

2. CHEMICAL COMPONENTS

The active components of rosemary are categorized into non-volatile and volatile substances, which include flavonoids, terpenes, volatile oils, and organic acids. Flavonoids such as quercetin, luteolin, galangin, diosmetin, chrysin, and 8-methoxy kaempferol represent an important class of compounds that exhibit significant antioxidant activity in rosemary [10]. Similar to other plants in the Lamiaceae family, many terpenoids, including monoterpenes, sesquiterpenes, diterpenes, and triterpenes, have been isolated from rosemary. Monoterpenes and sesquiterpenes primarily constitute the essential components of volatile oils, which include 1,8-cineole, camphor, pinene, borneol, verbenone, and caryophyllene, among others. Diterpenoids in rosemary are further divided into diterpenoid phenols and diterpenoid quinones. Most of these components share a similar parent nucleus, indicating that some may be classified as secondary metabolites. Diterpene phenols include carnosic acid, carnosol, and rosmanol, while the main diterpenoid quinones are cryptotanshinone, royleanone, and rosmanol quinone. The content of diterpenoids is relatively high, and they are considered to play significant roles in antioxidant and antitumor effects [11]. Triterpenoids include betulin, oleanolic acid, and ursolic acid. Volatile oils are the characteristic components of rosemary essential oil, with more than 90% comprising terpenes that exhibit potent antibacterial effects [12]. Representative substances include camphor, 1,8-cineole, pinene, and verbenone. Additionally, rosmarinic acid, caffeic acid, and ferulic acid are also widely studied components of rosemary. The classification information of specific chemical components is shown in Table **1**.

3. STUDIES ON BIOLOGICAL ACTIVITIES AND MECHANISMS OF ACTIONS

3.1. Antibacterial Action

Rosemary exhibits broad-spectrum antibacterial activity. It strongly inhibits *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* [29]. Some researchers used an ethanol extract of rosemary (200 mg/mL) to treat bacterial colonies associated with oral infections. The results showed that colony densities decreased, the bacteria were loosely connected, and biofilm formation ability was effectively inhibited, with Candida albicans being the most significantly affected [30]. One study combined a rosemary water extract with selenium nanoparticles through biosynthesis. This nanocarrier exhibits potent antibacterial activity against Gram-positive bacteria [31]. The volatile oil of rosemary also exhibits strong antibacterial activity. The main components of rosemary essential oil recognized by the European Pharmacopoeia are volatile oils, including 1,8-cineole, camphor, and α-pinene [32, 33]. The MIC of rosemary essential oil against *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae* ranges from 1 μg/mL to 300 μg/mL, with the strongest inhibitory effect observed against *Staphylococcus aureus* [34]. Researchers used ethyl acetate and n-hexane as extractants to isolate components with different polarities from the extracts, finding that n-hexane-soluble components, which are the main volatile compounds, were identified by GC-MS. These include camphor (19.6%), 1,8-cineole (11.7%), verbenone (11.5%), borneol (10.6%), α-pinene (5.8%), and linalool (5.7%), all of which exhibited the most potent antibacterial activity against *Staphylococcus aureus* (MIC = 78 μg/mL) [35].

Rosmarinic Acid (RA) destroyed cytoskeletal proteins of various bacteria and inhibited intracellular Na+/K+-ATPase activity, playing an antibacterial role against *Escherichia coli*, *Salmonella*, and others [36, 37]. RA, as a covalent modifier of Keap1 and a specific inducer of Nrf2, formed covalent bonds with cysteine 151 of Keap1 in the BTB domain, preventing proteasome-mediated degradation caused by Keap1 binding to Nrf2. This promoted the nuclear translocation of Nrf2 and induced the bactericidal activity of macrophages through the autophagy pathway [38]. RNAIII is an effector of the Agr Regulatory System in *Staphylococcus aureus*, and psmα is a virulence regulator of the bacterium. Carnosic Acid (CA) and Carnosol (CL) are specific inhibitors of these factors, reducing bacterial virulence in a concentration range of ≥ 5 μM [39].

Table 1. Classifications of the main chemical components in *R. officinalis* L.

Class	Number	Name	Molecular Formula	CAS NO	References
Flavonoids	1	Chrysin	$C_{15}H_{10}O_4$	480-40-0	[13]
	2	Apigenin	$C_{15}H_{10}O_5$	520-36-5	[13-17]
	3	Apigenin-7-*O*-glucoside	$C_{21}H_{20}O_{10}$	578-74-5	[16]
	4	Genkwanin	$C_{16}H_{12}O_5$	437-64-9	[15, 16, 18]
	5	Hispidulin	$C_{16}H_{12}O_6$	1447-88-7	[14, 15]
	6	Homopsyllidin	$C_{22}H_{22}O_{11}$	17680-84-1	[15, 16, 19]
	7	Cirsimaritin	$C_{17}H_{14}O_6$	6601-62-3	[16]
	8	Vicenin 2	$C_{27}H_{30}O_{15}$	23666-13-9	[20]
	9	Luteolin	$C_{15}H_{10}O_6$	491-70-3	[14, 16, 17]
	10	Cynaroside	$C_{21}H_{20}O_{11}$	5373-11-5	[20]
	11	Luteolin-7-*O*-glucuronide	$C_{21}H_{18}O_{12}$	29741-10-4	[16, 21]
	12	Nepetin	$C_{16}H_{12}O_7$	520-11-6	[14]
	13	Cirsiliol	$C_{17}H_{14}O_7$	34334-69-5	[15]
	14	Diosmetin	$C_{16}H_{12}O_6$	520-34-3	[14]
	15	Diosmin	$C_{28}H_{32}O_{15}$	520-27-4	[14]
	16	Galangin	$C_{15}H_{10}O_5$	548-83-4	[13]
	17	Kaempferol	$C_{15}H_{10}O_6$	520-18-3	[13]
	18	Quercetin	$C_{15}H_{10}O_7$	117-39-5	[13]
	19	Rutin	$C_{27}H_{30}O_{16}$	153-18-4	[13]
	20	Isorhamnetin	$C_{16}H_{12}O_7$	480-19-3	[13, 16]
	21	5-Hydroxy-4',7-dimethoxyflavone	$C_{17}H_{14}O_5$	5128-44-9	[16]
	22	Myricetin	$C_{15}H_{10}O_8$	529-44-2	[13]
	23	Eriodictyol	$C_{15}H_{12}O_6$	552-58-9	[16]
	24	Hesperetin	$C_{16}H_{14}O_6$	520-33-2	[16]
	25	Hesperidin	$C_{28}H_{34}O_{15}$	520-26-3	[13, 16, 21]
	26	Naringin	$C_{27}H_{32}O_{14}$	10236-47-2	[13]
	27	8-Methoxykaempferol	$C_{16}H_{12}O_7$	571-74-4	[22]
	28	6-Methoxyluteolin	$C_{16}H_{12}O_6$	520-11-6	[22-24]
Monoterpenes	29	Myrcene	$C_{10}H_{16}$	123-35-3	[17, 25, 26]
	30	Geraniol	$C_{10}H_{18}O$	106-24-1	[17]
	31	Nerol	$C_{10}H_{18}O$	106-25-2	[17]
	32	Linalool	$C_{10}H_{18}O$	78-70-6	[17, 23, 26]
	33	α-Phellandrene	$C_{10}H_{16}$	99-83-2	[23, 25, 26]
	34	α-Terpinene	$C_{10}H_{16}$	99-86-5	[23, 25, 26]
	35	γ-Terpinene	$C_{10}H_{16}$	99-85-4	[23, 26]
	36	Terpinolene	$C_{10}H_{16}$	586-62-9	[23, 26]

(Table 1) Contd….

Class	Number	Name	Molecular Formula	CAS NO	References
	37	Limonene	$C_{10}H_{16}$	138-86-3	[14, 17, 23]
	38	β-Phellandrene	$C_{10}H_{16}$	555-10-2	[23]
	39	Carvone	$C_{10}H_{14}O$	99-49-0	[23]
	40	*trans*-Carveol	$C_{10}H_{16}O$	1197-07-5	[17]
	41	*m*-Cymene	$C_{10}H_{14}$	535-77-3	[23]
	42	*p*-Cymene	$C_{10}H_{14}$	99-87-6	[17, 23, 26]
	43	Thymol	$C_{10}H_{14}O$	89-83-8	[17]
	44	Carvacrol	$C_{10}H_{14}O$	499-75-2	[17, 26]
	45	4-Terpineol	$C_{10}H_{18}O$	562-74-3	[17, 23, 26]
	46	α-Terpineol	$C_{10}H_{18}O$	98-55-5	[17, 23, 26]
	47	α-Campholenal	$C_{10}H_{16}O$	4501-58-0	[23]
	48	*p*-Cymen-8-ol	$C_{10}H_{14}O$	1197-01-9	[17]
	49	Isothujol	$C_{10}H_{14}O$	513-23-5	[23]
	50	α-Thujene	$C_{10}H_{16}$	2867-05-2	[23]
	51	Sabinene	$C_{10}H_{16}$	3387-41-5	[17, 25, 26]
	52	*cis*-Sabinol	$C_{10}H_{16}O$	3310-02-9	[23]
	53	α-Thujone	$C_{10}H_{16}O$	546-80-5	[17]
	54	β-Thujone	$C_{10}H_{16}O$	471-15-8	[17]
	55	Isopinocamphone	$C_{10}H_{16}O$	15358-88-0	[17]
-	56	*cis*-Verbenol	$C_{10}H_{16}O$	1845-30-3	[23]
	57	Verbenone	$C_{10}H_{14}O$	80-57-9	[23, 25, 26]
	58	Fenchone	$C_{10}H_{16}O$	1195-79-5	[23]
	59	Camphene	$C_{10}H_{16}$	79-92-5	[17, 23, 26]
	60	α-Fenchene	$C_{10}H_{16}$	471-84-1	[23]
	61	Camphor	$C_{10}H_{16}O$	76-22-2	[17, 25, 26]
	62	Borneol	$C_{10}H_{18}O$	507-70-0	[17, 25, 26]
	63	Isoborneol	$C_{10}H_{18}O$	124-76-5	[23]
	64	Bornyl acetate	$C_{12}H_{20}O_2$	76-49-3	[17, 23, 25]
	65	1, 8-cineole	$C_{10}H_{18}O$	470-82-6	[17, 23, 25]
	66	α-pinene	$C_{10}H_{16}$	80-56-8	[17, 23, 26]
	67	α-Pinene oxide	$C_{10}H_{16}O$	1686-14-2	[23]
	68	β-Pinene	$C_{10}H_{16}$	127-91-3	[17, 23, 25]
	69	Verbenene	$C_{10}H_{14}$	4080-46-0	[17]
	70	Myrtenol	$C_{10}H_{16}O$	515-00-4	[17, 23, 25]
	71	Myrtenal	$C_{10}H_{14}O$	564-94-3	[23]
	72	Homomyrtenol	$C_{11}H_{18}O$	128-50-7	[17]
	73	Chrysanthenone	$C_{10}H_{14}O$	473-06-3	[17]
	74	Pinocarvone	$C_{10}H_{14}O$	30460-92-5	[17, 23, 25]
Sesquiterpenes	75	α-Caryophyllene	$C_{15}H_{24}$	6753-98-6	[17, 25, 26]

(Table 1) Contd….

Class	Number	Name	Molecular Formula	CAS NO	References
-	76	β-Elemene	$C_{15}H_{24}$	515-13-9	[17]
	77	α-Elemene	$C_{15}H_{24}$	5951-67-7	[26]
	78	Abscisic acid	$C_{15}H_{20}O_4$	21293-29-8	[13]
	79	α-Amorphene	$C_{15}H_{24}$	20085-19-2	[17, 26]
	80	α-Muurolene	$C_{15}H_{24}$	10208-80-7	[17]
	81	t-Muurolol	$C_{15}H_{26}O$	19912-62-0	[17]
	82	γ-Cadinene	$C_{15}H_{24}$	39029-41-9	[17]
	83	δ-Cadinene	$C_{15}H_{24}$	483-76-1	[17, 26]
	84	α-Cadinol	$C_{15}H_{26}O$	481-34-5	[17]
	85	α-Calacorene	$C_{15}H_{20}$	21391-99-1	[17]
	86	α-Eudesmol	$C_{15}H_{26}O$	473-16-5	[26]
	87	γ-Eudesmol	$C_{15}H_{26}O$	1209-71-8	[26]
	88	β-Eudesmol	$C_{15}H_{26}O$	473-15-4	[17]
	89	β-Selinene	$C_{15}H_{24}$	17066-67-0	[17]
	90	α-Copaene	$C_{15}H_{24}$	3856-25-5	[17, 26]
	91	Manool	$C_{20}H_{34}O$	596-85-0	[17]
	92	α-Guaiene	$C_{15}H_{24}$	3691-12-1	[17]
	93	β-Caryophyllene	$C_{15}H_{24}$	87-44-5	[22]
	94	Caryophyllene oxide	$C_{15}H_{24}O$	1139-30-6	[17, 25, 26]
	95	*trans*-Caryophyllene	$C_{15}H_{24}$	87-44-5	[17, 25, 26]
	96	Spathulenol	$C_{15}H_{24}O$	6750-60-3	[17]
	97	Alloaromadendrene	$C_{15}H_{24}$	25246-27-9	[17]
	98	Viridiflorol	$C_{15}H_{26}O$	552-02-3	[17]
Diterpenoids	99	Rosmadial	$C_{20}H_{24}O_5$	85514-31-4	[14, 16, 19]
	100	Rosmaridiphenol	$C_{20}H_{28}O_3$	91729-95-2	[15, 16]
	101	Carnosic acid	$C_{20}H_{28}O_4$	3650-09-7	[14, 16, 20]
	102	Methyl carnosate	$C_{21}H_{30}O_4$	82684-06-8	[15]
	103	Ferruginol	$C_{20}H_{30}O$	514-62-5	[22]
	104	Isorosmanol	$C_{20}H_{26}O_5$	93780-80-4	[27]
	105	20-Deoxocarnosol	$C_{20}H_{28}O_3$	94529-97-2	[27]
	106	12-*O*-Methylcarnosic acid	$C_{21}H_{30}O_4$	62201-71-2	[16]
	107	Royleanonic acid	$C_{20}H_{26}O_5$	350590-46-4	[27]
	108	Carnosol	$C_{20}H_{26}O_4$	5957-80-2	[14, 16, 21]
	109	Pisiferal	$C_{20}H_{28}O_2$	24035-37-8	[28]
	110	7-Methoxy-epirosmanol	$C_{21}H_{28}O_5$	24703-38-6	[28]
	111	7-*O*-Isopropyl-epirosmanol	$C_{23}H_{32}O_5$	-	[28]
	112	7-*O*-Isopropyl rosmaquinone	$C_{23}H_{30}O_5$	-	[28]

(Table 1) Contd….

Class	Number	Name	Molecular Formula	CAS NO	References
-	113	7β-Ethoxy rosmaqunione	$C_{22}H_{28}O_5$	-	[27]
	114	Rosmaquinone B	$C_{21}H_{26}O_5$	864962-10-7	[28]
	115	7-Acetoxy atuntzensin A	$C_{22}H_{26}O_7$	-	[27]
	116	Galdosol	$C_{20}H_{24}O_5$	52591-18-1	[28]
	117	Rosmanol	$C_{20}H_{26}O_5$	80225-53-2	[14, 16, 19]
	118	7-Methoxyrosmanol	$C_{21}H_{28}O_5$	113085-62-4	[28]
	119	7-Ethoxyrosmanol	$C_{22}H_{30}O_5$	111200-01-2	[22]
	120	Epirosmanol	$C_{20}H_{26}O_5$	93380-12-2	[15, 16, 19]
	121	Rosmanol quinone	$C_{20}H_{24}O_5$	121927-71-7	[18]
	122	Royleanone	$C_{20}H_{28}O_3$	6812-87-9	[22]
Triterpenoids	123	Betulin	$C_{30}H_{50}O_2$	473-98-3	[18]
	124	Betulinic acid	$C_{30}H_{48}O_3$	472-15-1	[16, 18, 27]
	125	Oleanolic acid	$C_{30}H_{48}O_3$	508-02-1	[14]
	126	Ursolic acid	$C_{30}H_{48}O_3$	77-52-1	[14]
Coumarins	127	Ellagic acid	$C_{14}H_6O_8$	476-66-4	[13]
Lignans	128	Medioresinol	$C_{21}H_{24}O_7$	40957-99-1	[16]
Phenylpropanoic acids	129	Cinnamic acid	$C_9H_8O_2$	621-82-9	[13]
	130	*p*-Coumaric acid	$C_9H_8O_3$	7400-08-0	[13, 16, 17]
	131	Caffeic acid	$C_9H_8O_4$	331-39-5	[13, 16, 17]
	132	Ferulic acid	$C_{10}H_{10}O_4$	1135-24-6	[17]
	133	Chlorogenic Acid	$C_{16}H_{18}O_9$	327-97-9	[13, 14, 17]
	134	Neochlorogenic acid	$C_{16}H_{18}O_9$	906-33-2	[14]
	135	Rosmarinic acid	$C_{18}H_{16}O_8$	20283-92-5	[16, 17, 20]
	136	Salvianolic acid A	$C_{26}H_{22}O_{10}$	96574-01-5	[20, 21]
	137	Salvianolic acid L	$C_{36}H_{30}O_{16}$	389065-74-1	[21]
	138	Eugenol	$C_{10}H_{12}O_2$	97-53-0	[17]
	139	Methyleugenol	$C_{11}H_{14}O_2$	93-15-2	[17]
	140	Elemicin	$C_{12}H_{16}O_3$	487-11-6	[17]
Quinones	141	Taxadione	$C_{20}H_{26}O_3$	19026-31-4	[22]
	142	Horminone	$C_{20}H_{28}O_4$	21887-01-4	[22]
	143	Cryptotanshinone	$C_{19}H_{20}O_3$	35825-57-1	[22]
Steroids	144	Taraxasterol	$C_{30}H_{50}O$	1059-14-9	[22]
	145	Cholesterol	$C_{27}H_{46}O$	57-88-5	[22]
	146	Campesterol	$C_{28}H_{48}O$	474-62-4	[22]
	147	Sitosterol	$C_{29}H_{50}O$	83-46-5	[22]

(Table 1) Contd….

Class	Number	Name	Molecular Formula	CAS NO	References
Others	148	4-Hydroxybenzoic acid	$C_7H_6O_3$	99-96-7	[13, 16]
	149	Protocatechuic acid	$C_7H_6O_4$	99-50-3	[13]
	150	Vanillic acid	$C_8H_8O_4$	121-34-6	[13]
	151	Homovanillic acid	$C_9H_{10}O_4$	306-08-1	[22]
	152	Gallic acid	$C_7H_6O_5$	149-91-7	[13, 17]
	153	Syringic acid	$C_9H_{10}O_5$	530-57-4	[13, 17]
	154	Quinic acid	$C_7H_{12}O_6$	77-95-2	[21]
	155	Citric acid	$C_6H_8O_7$	77-92-9	[21]
	156	7, 24-Tirucalladien-3β, 27-diol	$C_{30}H_{50}O_2$	6138-94-9	[18]
	157	Tirucalla-7, 24-dien-3β, 21, 23-triol	$C_{30}H_{50}O_3$	135383-76-5	[18]
	158	3-Octanol	$C_8H_{18}O$	589-98-0	[23]
	159	2-Methyl-3-octanone	$C_9H_{18}O$	923-28-4	[23]
	160	1-Octen-3-ol	$C_8H_{16}O$	3391-86-4	[17, 23]
	161	Filifolone	$C_{10}H_{14}O$	4613-37-0	[17]
	162	Rosmarinine	$C_{18}H_{27}NO_6$	520-65-0	[22]

3.2. Anti-inflammatory and Antioxidant Effects

Rosemary contains a variety of terpenoids, phenylpropanoic acids, and flavonoids, and it acts on multiple targets to exert anti-inflammatory and antioxidant activities. The methanol extract of rosemary has been found to have a therapeutic effect on ulcerative colitis in rats. By measuring the levels of antioxidant indices and inflammatory factors *in vivo* and *in vitro* and observing histopathological changes, it was demonstrated that the methanol extract of rosemary exerted a significant therapeutic effect on ulcerative colitis in rats within a safe dose range, even outperforming SASP, a positive control drug [40]. One study evaluated the therapeutic effect of inhaling atomized rosemary aqueous extracts on ovalbumin-induced asthma in rats, showing a significant reduction in immunoglobulin E and inflammatory cytokine levels, along with a decrease in the number of inflammatory and goblet cells. Concurrently, antioxidant enzyme levels increased, suggesting that aqueous extracts may alleviate allergic asthma symptoms through antioxidant and anti-inflammatory mechanisms [41].

Studies have shown that CA and CL clear intracellular ROS, upregulate antioxidant defense, and regulate various inflammatory signaling pathways, such as NF-κB, MAPK, Nrf2, and the NLRP3 inflammasome. Additionally, the expressions of pro-inflammatory cytokines, adhesion molecules, chemokines, and prostaglandins were decreased [42]. Kim *et al*. found that CA alleviated renal tubule damage after LPS injection in mice by downregulating Scr and BUN levels, inhibiting NF-κB-mediated inflammation and Caspase-3-dependent apoptosis, and regulating oxidative stress through antioxidant enzymes [43]. MPTP (10 μmol/L) induced morphological atrophy of dopamine neurons, decreased cell viability, and increased abnormal expression of caspase-3, which were reversed by CA treatment. Furthermore, MDA concentration decreased, and SOD activity increased, further confirming the antioxidant capability of CA [44]. CL was bound to heat shock protein 90 to block the activation of the NLRP3 inflammasome, which holds positive significance for treating endotoxemia [45]. In neuroinflammatory conditions, RA regulated the expressions of hypoxia-inducing factors by controlling the PDPK1/Akt/mTOR pathway. As a result, M1-type polarization of microglia was inhibited, leading instead to the transformation of cells into the M2 phenotype with anti-inflammatory effects [46]. 1,8-cineole reduced inflammation in mice with colitis by inhibiting the NF-κB signaling pathway, preventing the nuclear translocation of NF-κB, and enhancing PPARγ expression. Additionally, it played an antioxidant role by promoting Nrf2 nuclear translocation, activating the Nrf2/Keap1 system, and enhancing the expressions of HO-1 and NQO1 to improve the activities of SOD and CAT [47, 48]. Furthermore, 1,8-cineole also influenced the arachidonic acid pathway involving 5-LOX and COXs by blocking the production of LTB4 and PGE2, both of which are pro-inflammatory mediators activated by serum amyloid A [49]. α-Pinene inhibited the NF-κB signaling pathway and the expression of iNOS in human chondrocytes stimulated by IL-1β [50]. Similar results indicated that α-pinene blocked the activation of MAPK and NF-κB pathways in LPS-induced peritoneal macrophages of mice, leading to decreases in the expression of iNOS, the activity of COX-2, and the secretions of IL-6, TNF-α, and NO [51].

3.3. Antitumor Effect

It is a hot research topic to search for compounds with antitumor potential from extracts of natural plant sources. Recent studies have found that components of rosemary exhibit significant antitumor activity. Among prostate cancer cells, PC-3 cells are androgen-insensitive, while 22RV1 cells are androgen-sensitive. Treatment with rosemary extracts

significantly inhibited the proliferation of these cancer cells while inducing apoptosis and reducing migration. In contrast, the extract did not affect PNT1A, a normal prostate epithelial cell. The overactivation of the PI3K/Akt/mTOR pathway in prostate cancer cells is associated with cell proliferation, increased viability, drug tolerance, and overall poor prognosis. Some results indicated that rosemary extracts also reduced the phosphorylation levels of Akt and mTOR, effectively inhibiting the activation of this pathway [52]. Silver nanoparticles are effective nano-drugs for inhibiting cancer cell proliferation, and plant extracts serve as excellent reducing agents for synthesizing nanoparticles [53]. The silver nanoparticles synthesized from the aqueous extract of rosemary exhibit significant cytotoxicity toward human breast cancer cell lines and may have synergistic effects [54]. Bouzas *et al*. prepared a Supercritical Extract (SFRE) of rosemary, with CA and CL content of 12%-16%, which inhibited the proliferation of non-small cell lung cancer cell lines H1299 and H1975 in a dose-dependent manner. SFRE reduced ATP levels in tumor cells and activated apoptosis by decreasing glycolysis and mitochondrial oxidative phosphorylation. Currently, lipid metabolism genes are being used as prognostic indicators and therapeutic targets for tumors. Fortunately, SFRE regulated a range of lipid metabolic targets, including SREBF1, FASN, and SCD1 involved in lipogenesis; HMGCR for cholesterol production; ACSL for fatty acid activation; ABCA1 and ApoA1 for cholesterol homeostasis; and CHKA and AGPAT for membrane phospholipid biosynthesis and remodeling. In addition, SFRE inhibited carcinogenic pathways mediated by EGFR and JAK1, which were involved in cell proliferation and inflammation, respectively. Surprisingly, SFRE synergized with clinical therapeutic agents such as cisplatin, pemetrexed, and pembrolizumab [55]. In patients with advanced cancer, the incidence of cachexia ranges from 50% to 80%. This condition is characterized by a wasting syndrome involving systemic metabolic disorders, progressive loss of muscle and fat, weight reduction, and progressive failure of systemic organs.

RA inhibited the nuclear translocation of Gli1 and promoted its degradation through the proteasome pathway, reducing the malignant degree of PDAC [56]. CL and its analogs inhibited the NF-κB pathway and activated the AKT pathway to alleviate muscle atrophy in mouse tumor-associated cachexia models. Another experiment found that CL improved the disorder of fat degradation in 3T3-L1 cells and inhibited the breakdown of triglycerides and the release of free glycerol by regulating the AMPK pathway [57]. Hasei *et al*. found that stimulation of HepG2 cells with CA (10 μM) upregulated the tumor suppressor p53, which is inhibited by the rapamycin complex 1 (mTORC1), and increased Caspase-3 activation through AMPK-related targets. These factors led to the inhibition of proliferation and induction of apoptosis in hepatoma cells [58]. CA also increased the levels of proteins such as Sestrin2 and MRP2 associated with the Nrf2/ARE pathway in HepG2 cells, which protected cells from oxidative stress and carcinogens, thereby inhibiting cancer progression [59].

3.4. Hypoglycemic and Lipid-lowering Effects

Abnormal metabolism of sugars and lipids is becoming a global health problem. Dietary therapy based on plant products and their extracts as dietary supplements has significant benefits in improving diabetes, hyperlipidemia, and other related diseases. Multiple studies have shown that the various components of rosemary have notable hypoglycemic and lipid-lowering effects. Impaired insulin function in its effector cells leads to elevated blood sugar levels, while compensatory increases in insulin further exacerbate insulin resistance and contribute to the progression of type 2 diabetes. Extracts of rosemary have been shown to alleviate insulin resistance in muscle cells induced by high glucose and high insulin, improving glucose uptake in L6 myotube cells by reducing the phosphorylation of IRS-1, mTOR, and p70S6K. Ultimately, the biological effects of insulin were restored. Additionally, increased intracellular phosphorylation of AMPK stimulated downstream ACC proteins and GLUT4 on the plasma membrane [60].

This indicates that rosemary regulates glucose transport and metabolism in multiple ways. Compared with irbesartan, an adjuvant drug used in treating diabetes, CA demonstrated a better hypoglycemic effect by preventing islet damage and alleviating insulin resistance [61]. Yamamotoya *et al*. proved that CA and CL inhibited the expression of G6PC, PCK1, and other gluconeogenesis-related genes induced by cAMP in insulin resistance [58]. Islet function gradually recovers due to the reduced supply of lipolysis and gluconeogenic substrates. By regulating reverse cholesterol transport, RA reduced body weight, blood sugar, total cholesterol, and triglycerides in hyperlipidemic mice. Further studies found that RA increased the expression of cholesterol-uptake transporters such as SR-B1, LDL-R, ABCG5, and ABCG8 in liver tissue. In addition, the activity of CYP7A1 was enhanced, promoting the excretion of cholesterol. Notably, fatty acid oxidation was also stimulated through AMPK-mediated expression of CPT1A [62]. These findings suggest that RA plays multiple regulatory roles in lipid metabolism.

3.5. Anti-nerve Damage Effect

Rosemary is often used in traditional medicine to refresh the mind and improve sleep, reflecting its unique role in neuroregulation. Alrashdi *et al*. observed the behavioral and neurobiological effects of rosemary extract in an epileptic rat model induced by PTZ. They conducted Morris water maze experiments with rats in different treatment groups and found that the spatial learning and memory abilities of the rats treated with the extract were improved. The evaluation results revealed a decrease in the epilepsy score, along with a reduction in spasticity and a delay in the onset of the first myoclonus. Biochemical indicators showed increased levels of oxidative stress markers in the epileptic rat model. In contrast, the extract elevated antioxidant markers and maintained the typical morphology of rat brain tissue [63].

Yi-Bin *et al*. developed a nanocarrier to deliver CA to the brain, inhibiting the transcriptional activity of CEBP-β by reducing the interaction between CEBP-β and NF-κB in the brains of APP/PS1 transgenic mice [64]. It was demonstrated that CA regulated the CEBP β-NF κB-cytokine network associated with AD, playing a neuroprotective role. RA and ursolic acid inhibited neurotoxicity induced by Aβ1-42 and reduced the accumulation of amyloid plaques in the hippocampus of AD mice by directly binding to Ki-67 and dicorti-

cotin, which improved impaired social memory and hippocampal neurogenic disorders in these mice [65]. A comprehensive study demonstrated that the protective effect of CL on the nervous system involves multiple targets. CL activated gene expression related to mitochondrial dynamics and improved the structural homeostasis of mitochondrial membrane proteins. It restored ND protein homeostasis by inhibiting the IIS pathway, regulating the MAPK pathway, and activating chaperones. CL also prevented neuronal damage by inhibiting the deposition of Aβ, poly-Q, and α-SYN. It is generally believed that Aβ mediates cholinergic nervous system diseases, while poly-Q and α-SYN induce ASH and damage to dopaminergic neurons. CL reduced neuronal lesions associated with these toxic proteins by activating the Notch and Wnt pathways [66].

3.6. Hepatoprotective and Nephroprotective Effects

The active ingredients in rosemary play significant roles in protecting the liver and kidneys. Rosemary tincture has been shown to exhibit hepatoprotective activity in rats with liver injury. The tincture contains a considerable amount of polyphenols and terpenes, including phenolic diterpenes (CA, CL, rosmanol, rosmadial) and RA. These compounds exert hepatoprotective effects through antioxidant mechanisms [67]. Formulating rosemary essential oil into a nanoemulsion reduces its hydrophobicity. Researchers evaluated the effect of this nanoemulsion on liver injury induced by thioacetamide in Wistar rats. Oral administration of the nanoemulsion significantly improved transaminase levels and pathological changes in the liver [68]. CTX induces cellular oxidative stress and liver toxicity. Rosemary exhibits strong antioxidant activity and is a potential therapeutic agent against liver toxicity. After 16 days of treatment with rosemary extract, liver toxicity induced by CTX in mice improved, significantly reducing levels of AST and lipids while mitigating histological damage [69]. RA reduced ALT and AST levels in the serum of mice with liver injury induced by APAP and alleviated histological lesions in the liver. It upregulated the expressions of Nrf2 and downstream HO-1, which are suppressed during liver injury. The increase in these proteins inhibited ROS activity and the NEK7-NLRP3 pathway, leading to decreased secretions of IL-1β and IL-18 in liver tissue [70]. Moreover, it was reported that RA reversed the increase of Bax and the decrease of Bcl-2 induced by APAP, which are markers of apoptosis. Additionally, RA increased the levels of SOD, GSH, and GSH-PX by activating the Nrf2/HO-1 signaling pathway and inhibited lipid peroxidation, which benefited the alleviation of acute liver injury induced by lipopolysaccharide/D-galactosamine in mice [71].

Rosemary has potential protective effects against renal toxicity caused by heavy metal pollutants. For example, potassium dichromate and nickel chloride induce oxidative stress in the kidneys. The accumulation of ROS leads to renal dysfunction and structural changes in kidney tissue. Rosemary extract possesses significant antioxidant and metal-chelating capabilities. After treatment with the extract, renal tissue damage in rats was significantly ameliorated, and biochemical indicators were restored [72, 73]. CA had a therapeutic effect on renal toxicity caused by cadmium chloride (CdCl2) and other factors. A low dose of CL (5 μM) effectively inhibited the apoptosis of normal renal epithelial (NKE) cells induced by CdCl2 (40 μM). Experiments conducted both *in vitro* and *in vivo* found that CA removed free radicals and inhibited cell fibrosis. It also inhibited the TGF-β1/Smad/Collagen IV pathway by activating Nrf2/HO-1, which reduced the renal toxicity of cadmium [74]. Diabetic Nephropathy (DN) is one of the most severe complications of diabetes. Urinary creatinine and protein levels in Db/db mice were reduced after 14 weeks of CA treatment, indicating that glomerular necrosis and mesangial dilation were alleviated. Similarly, kidney damage was significantly improved in streptozotocin-induced diabetic rat models after 20 weeks of CA treatment. In a high-glucose microenvironment, CA activated Nrf2 in murine Glomerular Mesangial Cells (mGMCs) and downregulated the expression of genes related to the NF-κB signaling pathway. This was beneficial for inhibiting several fibrotic factors, such as renal transforming growth factor-β1, fibronectin, and E-cadherin [61]. One study designed nanoparticles for delivering RA, which can accumulate in the kidneys over an extended period in cases of acute kidney injury induced by ischemia-reperfusion, significantly improving renal function. This delivery system reduces oxidative stress, the inflammatory response, and the apoptosis of renal tubular cells, providing a new strategy for treating acute kidney injury [75].

3.7. Other Effects

Rosemary ingredients are effective in relieving various skin symptoms. RA increased the expression of NHE1 in the stratum corneum, a crucial factor in activating ceramide synthetase, which helped reduce skin water loss, increase hydration, and improve skin barrier function [76]. Imiquimod, an inducer of psoriasis in laboratory animals, caused neutrophil infiltration and increased levels of IL-23 and IL-17A, resulting in redness, swelling, and scaling in the skin tissues of mice [77]. The pathological condition of the mice improved after RA gavage. CL reduced the abnormal expressions of immunoglobulin E and IL-1β in the serum of mice induced by UV-B. Similarly, markers associated with skin inflammation in the backs of mice, such as iNOS, COX-2, and STAT3, were significantly inhibited [78]. Many toxic components, including dioxins, environmental pollutants, and Malassezia metabolites, are associated with AhR, which can easily lead to skin diseases. Studies have found that CA, CL, 7-Methoxy-epirosmanol, 5-Hydroxy-4', 7-dimethoxyflavone, and betulinic acid exhibit strong antagonistic effects against these components, suggesting that rosemary extract may prevent or treat skin diseases caused by AhR [79]. Dry Eye Disease (DED) often causes sustained oxidative stress and inflammation in the eyes. Researchers combined RA with gelatin nanogels for DED treatment. This formulation inhibits the production of inflammatory factors and ROS while promoting mucin secretion. This strategy provides a novel reference for ocular drug delivery [80].

4. PREDICTION ANALYSIS OF Q-MARKER OF ROSEMARY

4.1. Q-marker Prediction of Rosemary Based on the Measurability of Chemical Constituents

Stability and testability are essential conditions for screening Q-markers. Terpenes and phenylpropanoic acids are the primary contributors to the antioxidant activity of

rosemary. Rapid and efficient quantitative determination of their contents is crucial for evaluating the quality of rosemary. Li and Liao used HPLC to establish fingerprints with typical peaks identified in different parts of the plant, such as stems and leaves. The results showed that the types of components were nearly the same, primarily phenylpropanoic acids and diterpenoids [81]. They identified the characteristic peaks of ferulic acid, RA, and CA. Li *et al*. employed HPLC-ELSD to determine the contents of RA, CL, CA, oleanolic acid, and ursolic acid in rosemary, demonstrating that the method was sensitive and reproducible [82]. Sharma *et al*. used UHPLC-ESI-QTOF-MS to analyze the components in rosemary extracts obtained through nine different extraction methods. The results indicated that the contents of RA, luteolin-7-O-glucuronide, CA, CL, and ursolic acid in the extracts were stable [83].

Due to substantial differences in the chemical composition of rosemary essential oils from various regions, distinct chemical types have been formed. For instance, gas chromatography-mass spectrometry analysis of three rosemary essential oils from Algeria revealed two distinct chemical types dominated by α-pinene or camphor [84]. Similar results were found in the chemical analysis of Egyptian rosemary volatile oil samples [85]. In contrast, rosemary volatile oil from the United Arab Emirates is characterized by high levels of monoterpenes, classifying it as the 1,8-cineole chemical type [86]. Wu *et al*. determined the chemical compositions and contents of rosemary from multiple producing areas using GC-MS and UPLC-Q-TOF-MS, ultimately identifying 47 main components. The characteristic compounds included volatile components such as 1,8-cineole, verbenone, terpinene, camphor, and borneol, as well as non-volatile components like RA and CA. While the types of ingredients were consistent across different producing areas, their contents varied. It is worth noting that the levels of verbenone differ significantly, which may serve as a new marker to distinguish rosemary from various regions [87].

There are many terpenoids in rosemary extract, most of which are secondary metabolites. Diterpenoids exhibit high thermal stability and can be easily extracted, separated, and detected. The contents of CL (4.21%), CA (0.39%), and rosmanol (0.12%) are relatively high [88]. Cao *et al*. simulated the degradation of these diterpenoids in the human body by preparing artificial body fluids. They found that CA was oxidized to CL and rosmanol in the artificial intestinal fluid, which was further converted to 7-methoxyrosmanol, 7-ethoxyrosmanol, or CA. This suggests that the oxidation of CA may produce a variety of diterpenoids in rosemary [89]. Therefore, we should control quality by comparing the relative contents of these compounds.

In addition, CA and CL are the primary lipophilic components in rosemary extract, while RA is the most significant hydrophilic component. Adjusting the solvent composition is essential for improving extraction efficiency. Mo *et al*. utilized CCE to simultaneously extract CA and RA, collecting the supernatant and precipitate as water-soluble and fat-soluble extracts, respectively. This approach represents an efficient extraction strategy [90]. It is also important to consider how different solvents affect the content of quality markers. At present, there is little research on establishing quality standards for rosemary. The methods for the extraction, separation, and determination of the components mentioned above serve as references for the quality control of rosemary.

4.2. Q-marker Prediction of Rosemary Based on the Traditional Medicinal Properties

In traditional Chinese medicine, herbs are distinguished by their "Flavors" and "Natures." The medicinal properties of rosemary, as recorded in the Supplement to Materia Medica, are classified as "hot" and "warm." Modern pharmacology has demonstrated that the medicinal properties of herbs are closely related to their active ingredients. Some studies have found that "hot" and "warm" herbs often contain high levels of volatile oils and possess a strong aroma [91]. One of the uses of rosemary is the extraction and processing of essential oil, which serves as a raw material in cosmetics, medicine, food, and other fields. One study categorized the types and contents of various essential oils into 1,8-cineole, verbenone, camphor, and α-pinene based on different markers [92]. El Mrabet *et al*. employed FT-MIR to detect the content of 1,8-cineole and quantify the levels of adulterants in rosemary essential oil, demonstrating high effectiveness in evaluating essential oil quality [93]. Wei *et al*. analyzed the volatile components of small-leaf and large-leaf rosemary using GC-MS. The results showed significant differences in the relative contents of 1,8-cineole and geraniol between the two types of rosemary, which could serve as potential markers for their differentiation [94].

Due to differences in harvesting times and drying methods, the composition of various components in rosemary may differ significantly. The chemical compositions of volatile oils before and after drying were analyzed using GC-MS, revealing that the contents of α-pinene, 1,8-cineole, verbenone, and borneol changed to varying degrees [95]. To maximize oil yield in the preparation of rosemary essential oil products, it is recommended to shorten the drying time [96]. Additionally, when harvesting and drying rosemary, increased temperatures may lead to the degradation of volatile components. Therefore, it is advisable to avoid harvesting at noon and to use low-temperature or shade-drying methods [97]. In conclusion, components in rosemary essential oil, such as α-pinene, 1,8-cineole, verbenone, borneol, and geraniol, can serve as candidate markers that are useful for screening essential oil products.

4.3. Q-marker Prediction of Rosemary Based on the Effectiveness of Chemical Constituents

From the perspective of traditional efficacy and modern pharmacology, rosemary is recognized for its powerful antioxidant effects. The European Union has also approved rosemary extract as a safe and effective natural antioxidant [98]. A report on rosemary identifies the components most relevant to its biological activity as CA, CL, RA, and ursolic acid, in that order [99]. Fernandez-Ochoa *et al*. utilized HPLC-ESI-QTOF-MS to analyze plasma samples from mice taken at different time points to study the absorption and metabolism of phenolic compounds in rosemary leaf extract. Although the absorption rate of flavonoids was the highest, the antioxidant capacity of these compounds in the plasma

samples was not enhanced. It was speculated that the binding of flavonoids to plasma proteins might impair their biological activity. The active components are more likely to be diterpenes, triterpenes, and their metabolites [100].

Excessive free radicals are the primary factors leading to the disruption of the antioxidant balance in the body and triggering oxidative stress. Rosemary extract is rich in polyphenols, which possess strong free radical scavenging abilities. Most of these mechanisms are associated with oxidative stress pathways [101]. Generally, antioxidants can neutralize free radicals by providing hydrogen atoms through a hydrogen atom transfer mechanism. Additionally, free radicals can be eliminated by donating electrons directly *via* the single electron transfer mechanism.

In molecular orbital theory, the energy difference between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) is referred to as the energy gap, which significantly impacts molecular activity. A lower LUMO energy level makes it easier for a molecule to gain electrons, while a higher HOMO energy level increases the likelihood of the molecule losing electrons. Based on the energy gap, we can predict the antioxidant capacity of various compounds: a smaller energy gap indicates that electrons can be more readily excited and transitioned, which corresponds to higher radical scavenging activity of the molecule [102].

To begin our study, we searched the PubChem database to obtain the molecular structures of representative polyphenols in rosemary. The frontier orbital energy of each component was then analyzed at the B3LYP-D3(BJ)/6-311G** level using density functional theory (DFT), with calculations completed using the ORCA 6.0.1 program. Comparisons revealed that the reactivities of rosmarinic acid and several major diterpenoid phenolic compounds were higher than those of ursolic acid. The detailed DFT analysis model is shown in Fig. (**1**), demonstrating that these ingredients are effective at clearing free radicals in the body. Their strong antioxidant effects make them suitable as potential quality markers for rosemary.

5. FURTHER PREDICTIVE ANALYSIS OF Q-MARKERS FOR ROSEMARY BASED ON NETWORK PHARMACOLOGY

5.1. Prediction of Q-markers in Rosemary and Screening of Core Targets

We searched the HERB and BATMAN-TCM databases [103, 104] and combined them with information on components collected from Table **1** to screen for biological activities. Oral Bioavailability (OB) represents the percentage of an orally administered drug that reaches systemic circulation. High oral bioavailability is a crucial indicator for determining whether a bioactive molecule can be utilized as a therapeutic agent. Drug-Likeness (DL) is a qualitative concept used in drug design to evaluate the similarity between prospective compounds and marketed drugs, helping to predict whether a compound is druggable. For compounds included in the TCMSP database [105], a preliminary screening was conducted based on the criteria of OB ≥ 30% and DL ≥ 0.18, as recommended by the database. Chemical components not found in the TCMSP database were also temporarily included in the collection. All candidate compounds were imported into the Swiss ADME database [106], and core components were further identified based on high gastrointestinal absorption and scores for Lipinski's rule of five. This classic method evaluates the drug activity of compounds based on empirical rules, specifying five criteria for molecular weight: lipophilicity, the number of rotatable bonds, and the number of hydrogen bond donors and acceptors. In this study, we selected compounds that met three or more of these criteria.

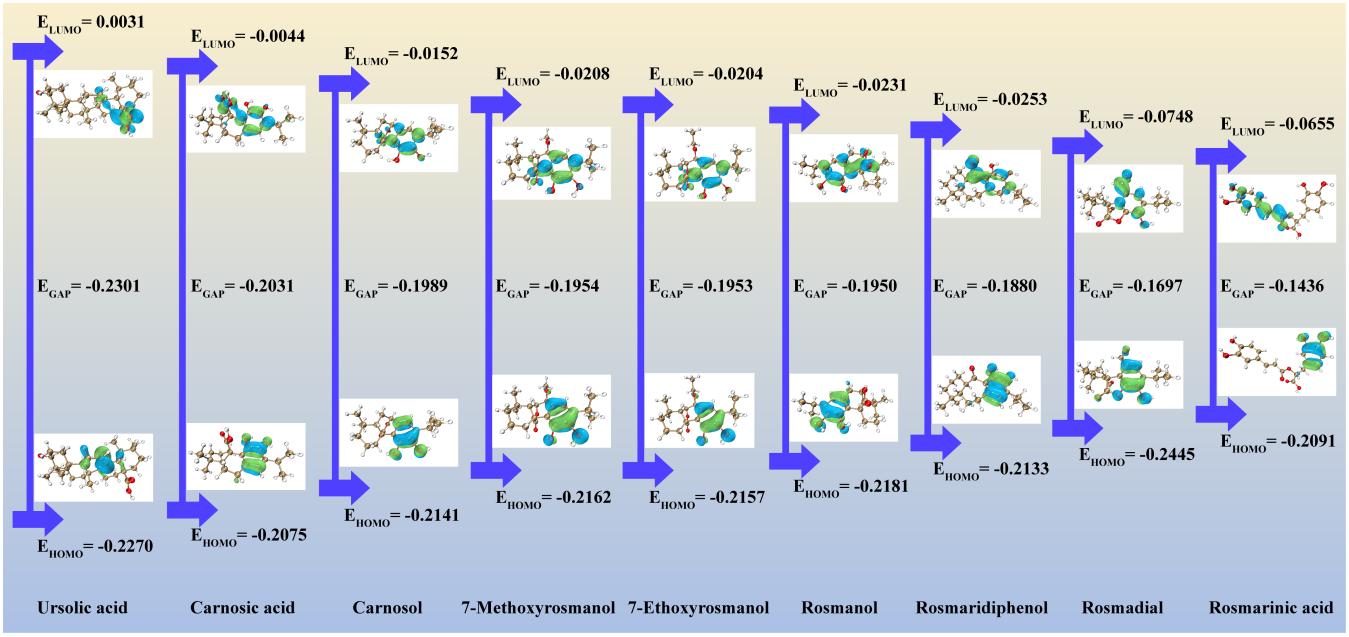
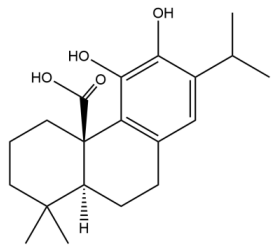
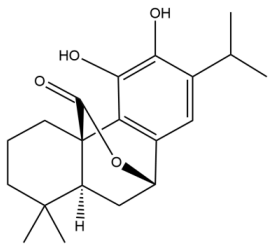


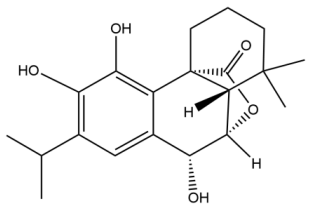
Fig. (1). Energy gap diagram of the main active ingredients in *R. officinalis* L. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



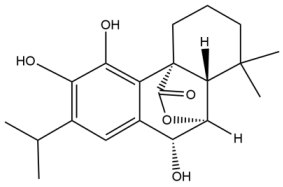
Carnosic acid



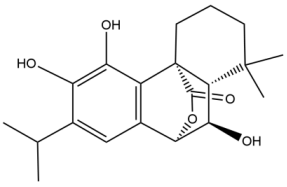
Carnosol



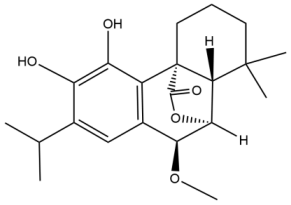
Rosmanol



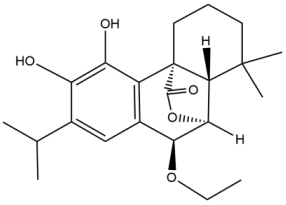
Epirosmanol



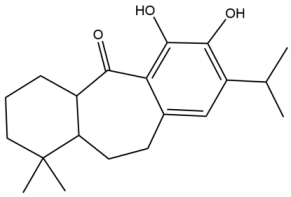
Isorosmanol



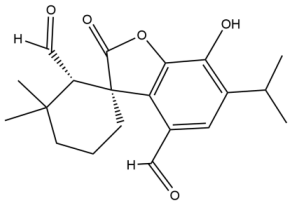
7-Methoxyrosmanol



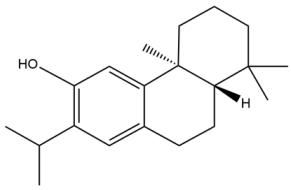
7-Ethoxyrosmanol



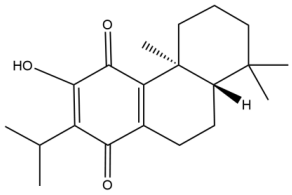
Rosmaridiphenol



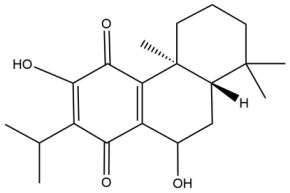
Rosmadial



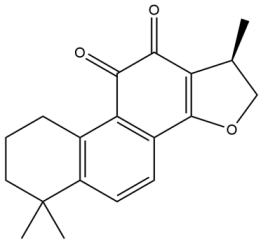
Ferruginol



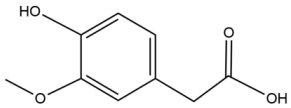
Royleanone



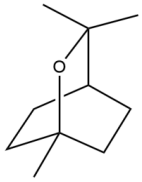
Horminone



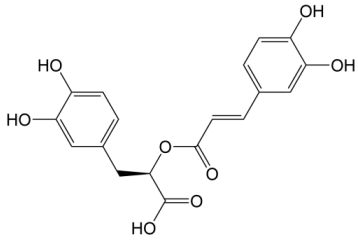
Cryptotanshinone



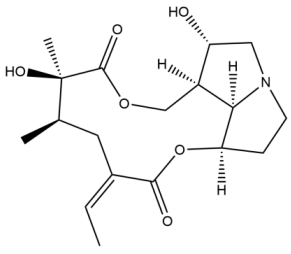
Homovanillic acid



1,8-Cineole



Rosmarinic acid



Rosmarinine

Fig. (2). Potential Q-markers of *R. officinalis* L.

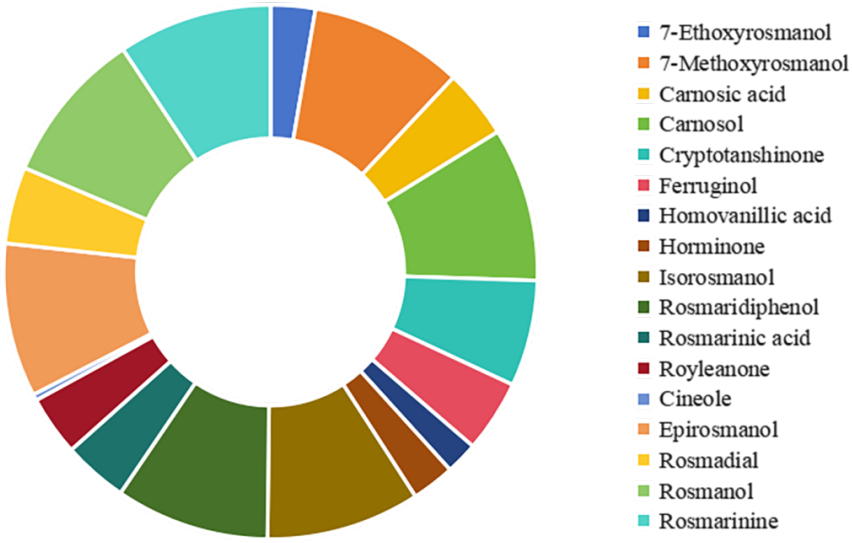


Fig. (3). Active components and targets distribution of *R. officinalis* L. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

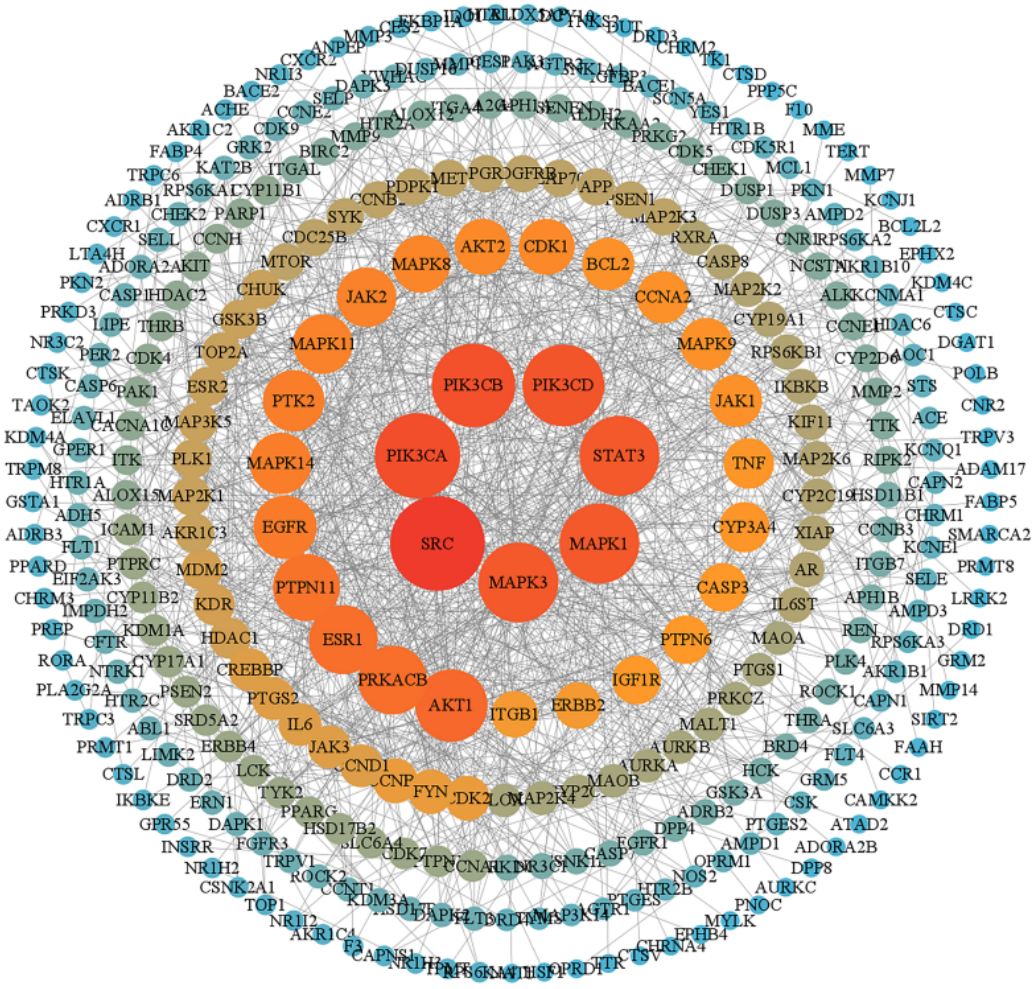


Fig. (4). The protein-protein interactions network of potential targets of Q-Markers of *R. officinalis* L. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

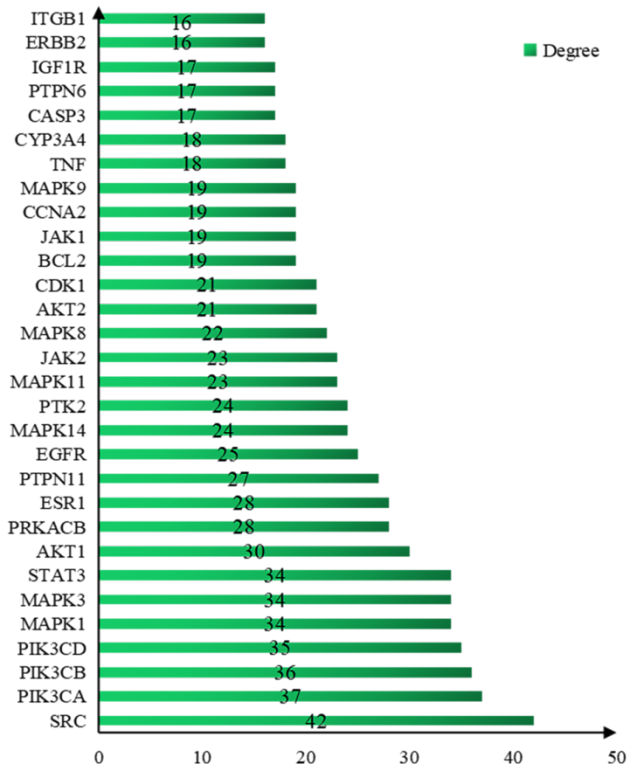


Fig. (5). The core target genes of Q-Markers in *R. officinalis* L. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

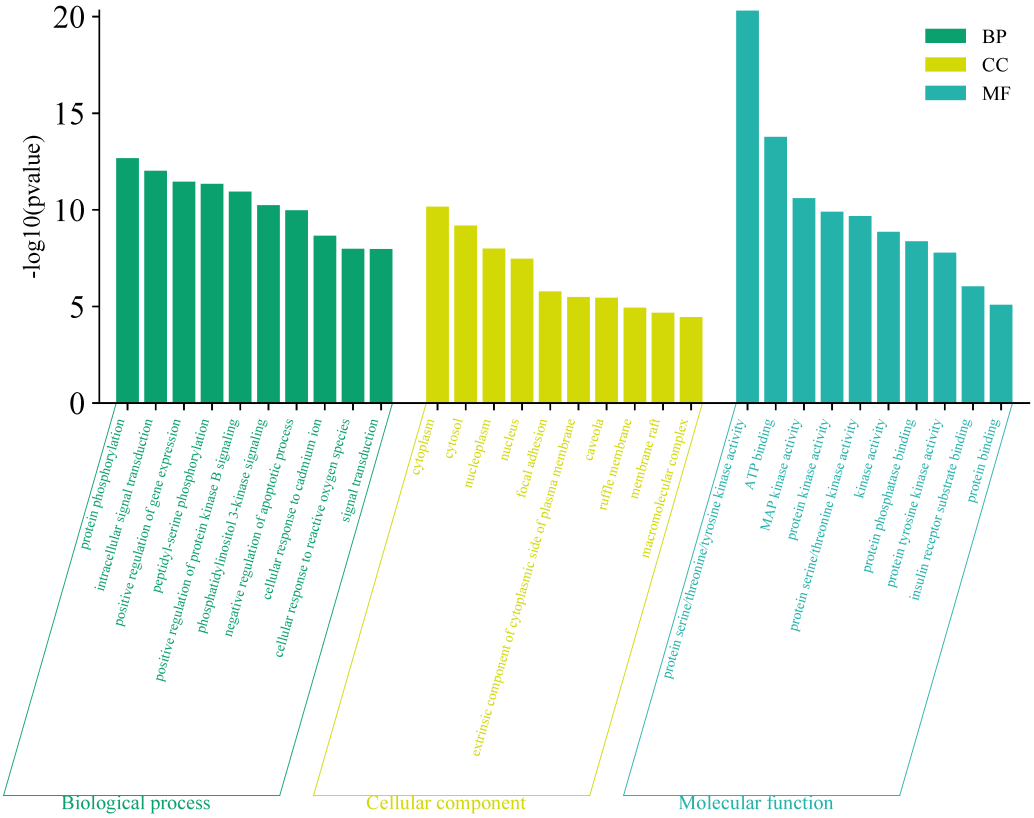


Fig. (6). GO function analysis of target genes of Q-Markers of *R. officinalis* L. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

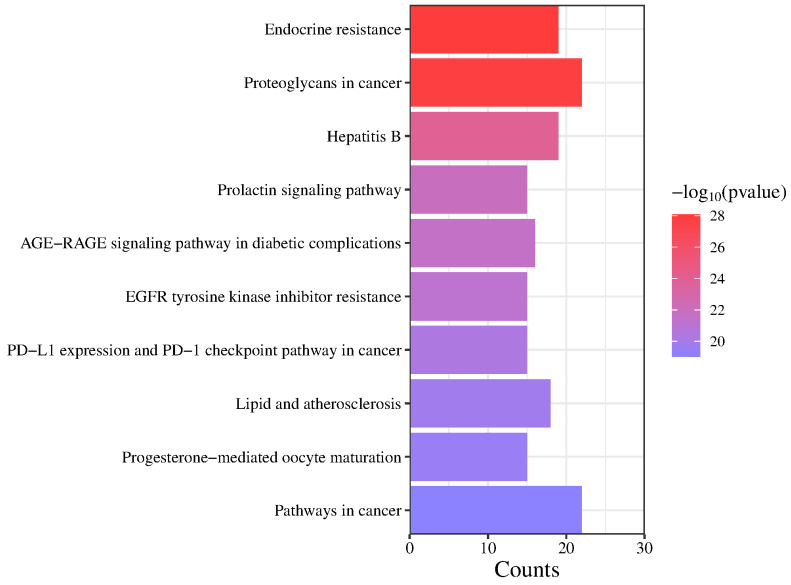


Fig. (7). Enrichment analysis of KEGG in Q-markers of *R. officinalis* L. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

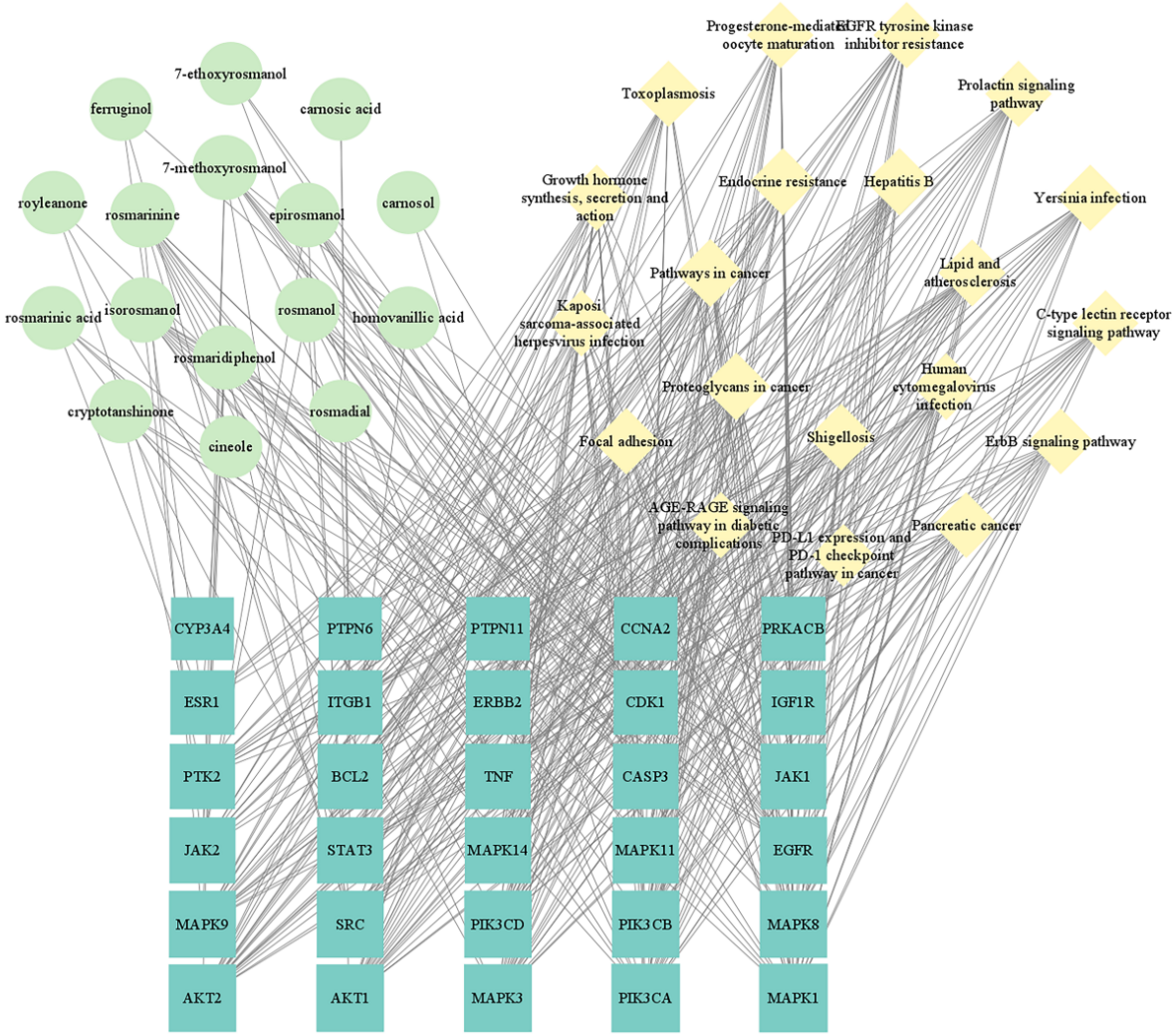


Fig. (8). "Component-target-pathway" network of Q-Markers of *R. officinalis* L. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Numerous studies on the active components of rosemary primarily focus on terpenoids and organic acids. The content of these components is high and relatively stable, making them suitable sources for the Q-Marker of rosemary. By referencing network pharmacological screening conditions, various principles of Q-Marker, and published literature, 17 components were ultimately selected as potential quality markers for rosemary. These components include cineole, carnosic acid, carnosol, rosmanol, isorosmanol, epirosmanol, rosmarinine, rosmaridiphenol, rosmadial, royleanone, horminone, homovanillic acid, ferruginol, cryptotanshinone, rosmarinic acid, 7-methoxyrosmanol, and 7-ethoxyrosmanol. Their structures are shown in Fig. (**2**). The majority of these compounds are diterpenoids, which possess excellent pharmacological properties. Carnosic Acid (CA) is a representative component; however, it decomposes under the influence of external factors, transforming into compounds such as CL, RA, and other similar derivatives. Monitoring the ratio of CA to CL is more rational than tracking a single component [107]. Another experiment analyzed the correlation between this ratio and the antioxidant activity of rosemary extract, revealing that CL enhances antioxidant activity. Consequently, they determined the optimal ratio of CA to CL. Therefore, we hypothesize that evaluating the ratio between CA and CL or its derivatives could serve as a new method of evaluation [108].

We obtained the gene targets related to the core components using SwissTargetPrediction [109], as shown in Fig. (**3**). After removing duplicates, we identified 526 targets, which were then imported into the STRING 12.0 online tool (https://string-db.org/) to create the protein interaction network. Single nodes without interactions in the network were removed. The results were subsequently imported into Cytoscape 3.9.1, where the "Analyze Network" function was used to calculate and sort the degree values of the network nodes (Fig. **4**). Finally, the top 30 nodes with the highest degree values were selected as the core target genes (Fig. **5**).

5.2. GO Analysis and KEGG Pathway Analysis

To further predict the potential targets and mechanisms of action, we imported 30 core target genes into the DAVID database for GO and KEGG network pharmacological analysis. The top 10 GO items and KEGG pathways were selected based on the *p*-value to create histograms (Figs. **6** and **7**). Additionally, the top 20 KEGG signaling pathways and 17 active components from rosemary, along with the 30 core target genes, were comprehensively analyzed to construct the "component-target-pathway" network (Fig. **8**). The results indicated that the biological processes related to the core targets of rosemary included protein phosphorylation, peptidyl-serine phosphorylation, positive regulation of protein kinase B signaling, phosphatidylinositol 3-kinase signaling, negative regulation of apoptosis, and the cellular response to reactive oxygen species, among others. In the KEGG enrichment analysis, the major pathways identified were endocrine resistance, proteoglycans in cancer, hepatitis B, lipid metabolism and atherosclerosis, EGFR tyrosine kinase inhibitor resistance, and the AGE-RAGE signaling pathway in diabetic complications, among others. It can be speculated that these core targets of rosemary interfere with the occurrence and development of diseases through the aforementioned processes and pathways.

CONCLUSION

Network Pharmacology is a methodology based on big data analysis. This approach not only provides significant support for modern drug research but also offers novel ideas for the quality control of traditional herbal medicines. Traditional quality control of herbal medicines primarily relies on chemical analysis methods, such as HPLC and GC-MS, to detect the content of individual components, often neglecting the diversity of active components in natural products. Network Pharmacology integrates efficacy data from various herbal medicines with molecular target information to construct interaction networks. By analyzing these interactions, the core components that influence the efficacy of the herbs can be identified. This method provides a more comprehensive way to evaluate the overall quality of various herbal medicines and offers a feasible solution for standardized quality control in other herbal products.

The diverse active ingredients in rosemary play a role in the occurrence and development of oxidation, inflammation, infections, tumors, and various organ lesions. Current research indicates that rosemary clears reactive oxygen species through classical antioxidant pathways, thereby enhancing the body's ability to resist oxidative stress damage. It inhibits inflammation *via* pathways such as NF-κB, MAPK, and Nrf2, effectively delaying disease progression. Network pharmacological predictions of the primary active component targets suggest that they ameliorate conditions such as inflammation, tumors, and abnormalities in glucose and lipid metabolism through related targets like PI3K, Akt, MAPK, and STAT3.

This study lists the chemical compositions and biological activities of rosemary and predicts 17 compoundsincluding CA, RA, rosmanol, CL, epirosmanol, rosmaridiphenol, rosmadial, and 1,8-cineole, as potential quality markers based on their chemical composition, measurability, effectiveness, and traditional medicinal properties. These substances represent the characteristic components found in rosemary leaves and essential oil products, providing a basis for establishing a quality evaluation system for rosemary. Currently, most countries lack detailed application specifications for rosemary, making the identification of quality markers significant for formulating future medicinal standards. Furthermore, existing research on the active ingredients and pharmacological mechanisms of rosemary remains insufficient, with most findings derived from animal experiments. Additionally, the bioavailability of some components is low, greatly limiting their applications. Therefore, further exploration of the formulation optimization and structural transformation of components is warranted.

Edible and medicinal herbs are generally safe and effective, positively contributing to human health. Rosemary, a traditional herb with a long history and high economic value, contains numerous compounds that exhibit antioxidant, anti-inflammatory, antibacterial, antitumor, and various other beneficial effects. Due to its considerable edible and medicinal value, the cultivation of rosemary has expanded in recent

years, presenting a wide range of utilization prospects. However, the relative lack of research on quality control has led to resource waste and environmental pressures. By continuously exploring the potential mechanisms of rosemary, we can establish a sustainable resource industry chain, allowing it to play a more significant role in food, healthcare, and medicine.

AUTHORS' CONTRIBUTIONS

Authors confirm their contribution to the paper as follows: Study conception and design: YH, Y.Z, TL. Data collection: ZT, JZ, CY, HX. Analysis and interpretation of results: TL, JZ, CY, WG, XJ. Draft manuscript: ZT, JZ, PL. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's Disease
AhR	=	Aryl Hydrocarbon Receptor Agonists
APAP	=	Acetaminophen
CCE	=	Column Chromatography Extraction
CTX	=	Cyclophosphamide
DFT	=	Density Functional Theory
DN	=	Diabetic Nephropathy
FT-MIR	=	Fourier Transform Mid-Infrared
GC-MS	=	Gas Chromatography-Mass Spectrometry
HPLC-ELSD	=	High-Performance Liquid Chromatography-Evaporative Light Scattering Detector
MIC	=	Minimal Inhibitory Concentration
MPTP	=	1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine
NHE1	=	Sodium Hydrogen Exchanger 1
PDAC	=	Pancreatic Ductal Adenocarcinoma
PTZ	=	Pentetrazol
SASP	=	Salazosulapyridine
UHPLC-ESI-QTOF-MS	=	Ultra-High-Performance Liquid Chromatography Electrospray Ionization Quadrupole Time-of-Flight Mass Spectrometry
UPLC-Q-TOF-MS	=	Ultra-Performance Liquid Chromatography/Quadrupole-Time-of-Flight Mass Spectrometry

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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