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甜叶菊化学成分及药理活性研究进展

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摘要:甜叶菊是一种具有广阔前景的菊科植物,主要化学成分包括黄酮类、二萜类、挥发油类等;甜叶菊提取物具有抗氧化、抑菌、抗病毒、抗肿瘤、调节免疫等药理活性。本文对甜叶菊化学成分及药理活性进行了综述,为其深度开发和高效综合利用提供参考。

关键词:甜叶菊;二萜;类黄酮;挥发油;药理活性

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Review on Chemical Compositions and Pharmacological Activities of *Stevia rebaudiana* (Bertoni) Hemsl.

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Abstract: *Stevia rebaudiana* (Bertoni) Hemsl was a valuable shrub of Asteraceae family, in order to clarify the comprehensive utilization values of *S. rebaudiana*, its chemical compositions and pharmacological activities were reviewed. The chemical compositions of *S. rebaudiana* include diterpenes, flavonoids, volatile oils, etc. *S. rebaudiana* extracts showed antioxidation, antibacterial, antiviral, antitumor, immune and other pharmacological activities. The study on chemical compositions and pharmacological activities can provide reference for the further development and utilization of *S. rebaudiana*.

Key words: *Stevia rebaudiana* (Bertoni) Hemsl.; diterpenes; flavonoids; volatile oils; pharmacological activity

甜叶菊(*Stevia rebaudiana* (Bertoni) Hemsl.)又名“甜菊”、“甜草”、“甜茶”等,属菊科(Compositae)斯台维亚属多年生草本植物,原产于南美洲巴拉圭和巴西交界的阿曼拜山脉,最初被当地人作为甜茶食用^[1,2]。我国于1976年从日本引进甜叶菊试种成功。现已成为世界上种植甜叶菊面积最多的国家,也是世界上甜叶菊糖苷最大的生产国和出口国^[3]。甜叶菊由于其二萜类成分“甜菊糖苷”被广为人知^[4],近年来,国内外学者陆续发现甜叶菊提取物具有抗氧化、抑菌、抗病毒、抗肿瘤、辅助治疗糖尿病、调节免疫等药理活性,同时,对甜叶菊中化合物的药理和毒理研究也在逐步深入。本文以国内外发表的文献为依据,针对甜叶菊化学成分和药理作用进行了较为全面的综述,以期为进一步开发和高效利用甜叶菊资源提供参考。

1 甜叶菊主要化学成分

甜叶菊叶片提取物中具有药理活性的化学成分

主要为二萜类及衍生物、黄酮类、酚类及衍生物、挥发油类等。

1.1 二萜类及衍生物

甜叶菊二萜类成分“甜菊糖苷”一直是研究的热点。继甜菊苷和甜菊双糖苷被分离后,1976年,Kohda等^[5]首先从甜叶菊叶片中分离得到Rebaudiosides A和Rebaudiosides B,随后,多种甜菊糖苷被分离和鉴定。近年来,随着科学技术的改善,研究者又分离得到多种新的二萜类物质,Chaturvedula^[11]基于核磁共振二维谱(2D NMR)和质谱(MS)技术从甜叶菊叶片提取物中分离得到三种新颖的二萜苷类化合物;Chaturvedula等^[12]从甜菊叶提取物中分离得到两种新的二萜类苷并确定其结构;Chaturvedula^[13]等从甜叶菊叶片提取物中分离得到4种新的二萜类苷并确定其结构。2016~2017年,研究者又于甜菊叶中分离出4种二萜类物质,鉴定后命名为甜菊糖苷 R、S、T、U^[14,15]。

1.2 黄酮、酚类及衍生物

黄酮类化合物广泛分布于各种植物体中,如果蔬、药草、可可、大豆和茶叶等^[16]。甜叶菊黄酮类成分主要为芦丁、黄酮醇及衍生物、山柰酚及衍生物、

槲皮素及衍生物、芹菜素及衍生物, 酚类成分包括咖啡酸及衍生物、奎宁酸及衍生物等。甜叶菊黄酮类成分因具有抗氧化、抑菌、抗癌、治疗抑郁等多种药理活性越来越受到人们关注。Molinacalle 等^[17] 使用液相色谱—质谱分析(LC-MS)和四极杆—飞行时间质谱分析对甜菊叶片提取物中的主要化合物进行了鉴定, 共发现 19 种酚类物质; Se 等^[18] 通过 LC-MS 测定用 HCl/MeOH 水解后的甜叶菊总多酚成分, 检测到 11 种黄酮类化合物; Ghanta^[19] 等在甜叶菊叶片乙酸乙酯提取物中分离得到 6 种黄酮类化合物。

1.3 挥发油类

Markovic 等^[20] 利用气相色谱-质谱分析(GC-MS)检测甜叶菊叶片精油的化学组成, 通过对水蒸馏法获得的甜菊叶精油提取物定性分析确定了 88

种化合物。Siddique 等^[21] 通过两种不同的提取方法(水蒸馏和水蒸汽蒸馏法)获得甜叶菊叶片精油, 采用 GC-MS 测定了精油的化学组成, 结果发现水蒸馏的精油共检测出 132 个峰, 确定了其中 62 种主要的化合物, 水蒸汽蒸馏的精油中共检测出 50 种化合物。甜叶菊叶片中挥发油类物质大部分是单倍萜和倍半萜, 主要物质有: *a*-cadinol、caryophyllene oxide、(-)-spathulenol、*b*-guaiene 等。

1.4 其他成分

甜叶菊中的其他成分主要包括: 生物碱、甾醇、多糖、脂肪酸、氨基酸、嘌呤等。值得一提的是, 甜叶菊叶片脂肪酸中棕榈酸含量很高, 占总脂肪酸的 80% 以上。

表 1 甜叶菊主要二萜类成分
Table 1 Main diterpenes in *S. rebaudiana*

编号 No.	化合物 Chemical components	参考文献 Ref.
1	rebaudiosides A	5
2	rebaudiosides B	5
3	steviol	6
4	rebaudioside C	7
5	rebaudioside D	8
6	rebaudioside E	8
7	rebaudiosides F	9
8	dulcosides A	10
9	dulcosides B	10
10	13-[(2-O- β -D-glucopyranosyl-3-O- β -D-glucopyranosyl- β -D-glucopyranosyl) oxy] <i>ent</i> -kaur-15-en-19-oic acid	11
11	13-[(2-O- β -D-glucopyranosyl-3-O- β -D-glucopyranosyl- β -D-glucopyranosyl) oxy]-16- β -hydroxy- <i>ent</i> -kauran-19-oic acid	11
12	13-methyl-16-oxo-17-nor- <i>ent</i> -kauran-19-oic acid- β -D-glucopyranosyl ester	11
13	13-[(2-O-6-deoxy- β -D-glucopyranosyl- β -D-glucopyranosyl) oxy] <i>ent</i> -kaur-16-en-19-oic acid β -D-glucopyranosyl ester	12
14	13-[(2-O-6-deoxy- β -D-glucopyranosyl-3-O- β -D-glucopyranosyl- β -D-glucopyranosyl) oxy] <i>ent</i> -kaur-16-en-19-oic acid β -D-glucopyranosyl ester	12
15	13-[(2-O- β -D-glucopyranosyl- β -D-glucopyranosyl) oxy]-kaur-15-en-18-oic acid β -D-glucopyranosyl ester	13
16	13-[(2-O- β -D-glucopyranosyl- β -D-glucopyranosyl) oxy]-kaur-16-en-18-oic acid-(6-O- β -D-xylopyranosyl- β -D-glucopyranosyl) ester	13
17	13-[(2-O- β -D-glucopyranosyl- β -D-glucopyranosyl) oxy]-17-hydroxy-kaur-15-en-18-oic acid β -D-glucopyranosyl ester	13
18	13-[(2-O- β -D-glucopyranosyl- β -D-glucopyranosyl) oxy]-17-oxo-kaur-15-en-18-oic acid β -D-glucopyranosyl ester	13
19	rebaudioside R	14
20	rebaudioside S	14
21	rebaudioside T	15
22	rebaudioside U	15

表 2 甜叶菊主要黄酮和酚类成分

Table 2 Main flavonoids and phenols in *S. rebaudiana*

编号 No.	化合物 Chemical components	参考文献 Ref.	编号 No.	化合物 Chemical components	参考文献 Ref.
23	Kaempferol monoglycoside	17,18	38	Kaempferol-xylosyl-glucoside	18
24	Kaempferol rhamnoside	17	39	Quercetin-dirhamnoside	18
25	Flavonoid monoglycoside	17	40	Quercetin-3-O-arabinoside	19
26	Quercetin-3-O-arabinoside	17	41	Apigenin	19
27	Quercitrin	17-19	42	Apigenin-4-O-glucoside	19
28	Flavonoid diglycoside	17	43	Kuteolin	19
29	Rutin	17,18	44	Kaempferol-3-O-rhamnoside	19
30	Flavonoid coumaroyl glucosideglucoside	17	45	Quinate phosphate	17
31	Quercetin-3-O-(coumaroylglucoside)-7-O-glucoside	17	46	4-Caffeoylquinic acid	17
32	Quercetin galactoside	18	47	5-Caffeoylquinic acid	17
33	Quercetin-rhamnoside	18	48	3-Caffeoylquinic acid	17
34	Quercetin pentoside	18	49	1,5-Dicaffeoylquinic acid	17
35	Apigenin-galactoside	18	50	4,5-Dicaffeoylquinic acid	17
36	Quercetin-diglucoiside-rhamnoside	18	51	3,4-Dicaffeoylquinic acid	17
37	Kaempferol-glucosyl-rhamnosyl-glucoside	18	52	Quinic acid	17

表 3 甜叶菊中挥发油类成分

Table 3 The chemical components in volatile oils of *S. rebaudiana*

编号 No.	化合物 Chemical components	参考文献 Ref.	编号 No.	化合物 Chemical components	参考文献 Ref.
53	α -Pinene	22	87	2-Pentadecanone,6,10,14-trimethyl-	20
54	Carvacrol	22	88	Phallic acid, cyclohexyl isohexyl ester	20
55	Spathulenol	22	89	Pentadecacanoic,14-methyl-,methyl-	20
56	Limonene	22	90	1,2-Benzenedicarboxylic acid, butyl 2-ethyl	20
57	Epoxy- α -terpenyl acetate	20	91	3-Methyl-2-pent-2-enyl-cyclopent-2-enon	20
58	1-(2,6,6-Trimethyl-1,3-cyclo)-2-buten-1-one	20	92	1h-Naphtho [2,1-b] pyran,3-ethenydodecane	20
59	Cyclohexane,1-ethyl-1-methyl-2,4-bis-	20	93	9h-Naphtho [2,1-b] pyran-9-one,3-ethenyl	20
60	Caryophyllene	20	94	Pregnanetriol	20
61	Tricyclo [3.3.0.0(2,8) octan-3-one,4-methyl	20	95	Triteratracane	20
62	1,6,10-Dodecatriene,7,11-dimethyl-3-methyl	20	96	1,2-Benzenedicarboxylic acid, diisoctyl	20
63	3-Buten-2-one,4-(2,6,6-trimethyl-1-cyclo)-	20	97	Benzaldehyde	20
64	3-Buten-2-one,4-(2,6,6-trimethyl-7-oxab)-	20	98	5,4-Benzylxy-2-fluoro-5-hydroxy benzaldehyde	20
65	Naphthalene,1,2,3,5,6,7,8,8a-octahydro-	20	99	3-Bromobutyric acid	20
66	Heptasiloxane, hexadecamethyl-	20	100	Undecanol-5	20
67	Berjomotol,z- α -trans-	20	101	1-Hepten-3-ol	20
68	Lanceol,cis-	20	102	Cyclohexene,4-bromo-	20
69	2(4h)-Benzofuraone,5,6,7,7a-tetrahydro	20	103	Benzyl-diseryl phosphate	20
70	1,6,10-Dodecatrien-3-ol,3,7,11-trimethyl	20	104	1,3,5-Cycloheptatriene	20

续表3(Continued Tab. 3)

编号 No.	化合物 Chemical components	参考文献 Ref.	编号 No.	化合物 Chemical components	参考文献 Ref.
71	Epoxy- α -terpenyl acetate	20	105	α -Methyl- α -[4-methyl]-3-pentene	20
72	Benzene,1,1'-(1,1,2,2-tetramethyl-1,2-ethanediyl) bis-	20	106	1,6-Octadien-3-ol,3,7-dimethyl-	20
73	(-) -Spathulenol	20	107	Cis-3-hexenyl-iso-butylate	20
74	Caryophyllene oxide	20	108	Cyclopentasiloxane, decamethyl-	20
75	Cyclooctasiloxane, hexadecamethyl-	20	109	Phenylethyl alcohol	20
76	Santalol, cis- α -	20	110	2,6,6-Trimethyl-2-cyclohexene-1,4-dione	20
77	5 α -Hydroxy-4 α -8,10,11-tetra-	20	111	3-Cyclohexene-1-methanol	20
78	Isoaromadendrene epoxide	20	112	2-Isopropenyl-5-methylhex-4-enal	20
79	β -Guaiene	20	113	Bicyclo [2.2.1] hept-2-ene,1,7,7-trimethyl-	20
80	Ledene oxide-(ω)	20	114	5-Amino-2-methoxyphenol	20
81	Naphthalene,1,2,3,4,4a,5,6,8a-octa-hydro-	20	115	Geranyl vinyl ether	20
82	α -Cadinol	20	116	Cyclohexasiloxane, dodecamethyl-	20
83	Tricyclo [5.2.2.0(1,6)] undecan-3-ol,2-methyl	20	117	Indole	20
84	6-Isopropenyl-4,8a-dimethyl-1,2,3,5,6,7-hexahydroxyl	20	118	2-Methoxy-4-vinylphenol	20
85	Aristolene epoxide	20	119	Phenol,2-methoxy-3-(2-propenyl)	20
86	z,z,z-4,6,9-Nodadecatriene	20			

表4 甜叶菊中其他化学成分
Table 4 The other chemical components in *S. rebaudiana*

编号 No.	化合物 Chemical components	参考文献 Ref.	编号 No.	化合物 Chemical components	参考文献 Ref.
120	Caryophyllene	22	132	Palmitic acid	17
121	Caryophyllene oxide	22	133	Stearic acid	17
122	Cardinol	22	134	Oleic acid	17
123	Isopinocarveol	22	135	Oleic acid derivative	17
124	Ibuprofen	22	136	Oleic acid derivative	17
125	Steviamine	23	137	Gondoic acid derivative	17
126	Palmitamide	17	138	Gamma-cyclodextrin	21
127	Oleamide	17	139	Disaccharide	21
128	Estearamide	17	140	Trehalose	21
129	13-Docosenamide	17	141	Maltose phosphate	21
130	n-Stearoyl valine	17	142	Purine	21
131	Myristic acid	17	143	Retinol derivative	21

2 药理作用

2.1 抗氧化作用

多位研究者对甜叶菊抗氧化活性进行了测定,发现甜叶菊根和叶具有较强的抗氧化活性^[24],用不同溶剂提取甜叶菊叶片,发现水提和醇提物具有较强的抗氧化活性,同时发现抗氧化能力强的提取物中含有较多的黄酮类化合物。

Yildiz-Ozturk 等^[25]使用微波提取和超声辅助提取甜叶菊,测定了其活性成分,发现微波和超声提取

的总多酚含量分别为 80.13 mg/g 和 86.47 mg/g,总黄酮含量分别为 111.16 mg/g 和 126.70 mg/g,对 DPPH· 的清除率最高可达 91.39% 和 92.40%, IC₅₀ 值分别为 68 μ g/mL 和 >100 μ g/mL,并且未发现提取物有细胞毒性。Shukla 等^[26]发现甜叶菊水提物对 DPPH· 自由基的清除能力呈显著剂量效应,其清除 DPPH· 的 IC₅₀ 值分别为 83.45 μ g/mL 和 26.75 μ g/mL,总多酚的含量为 56.73 mg/g,对 ·OH、NO 和 O₂· 清除的 IC₅₀ 值分别为 100.86 μ g/mL、98.73 μ g/mL 和 100.86 μ g/mL。Shukla 等^[27]发现甜叶菊乙

醇提取物对 DPPH[·]的清除能力也成显著的剂量效应,还对·OH、NO 和 O₂[·]都具有一定的清除作用。Tadhani 等^[28]使用甲醇和水分别提取叶片中的总黄酮和总多酚,并采用 FRAP 法和 DPPH[·]法评价了其抗氧化活性,发现叶片和愈伤组织中总酚类化合物含量分别为 25.18 mg/g 和 35.86 mg/g,类黄酮含量分别为 21.73 mg/g 和 31.99 mg/g;水提和醇提叶片总抗氧化活性变化为 9.66~38.24 mg 和 11.03~36.40 mg,愈伤组织为 9.44~37.36 mg 和 10.14~34.37 mg,对 DPPH[·]的清除能力变化为 33.17%~56.82%,醇提的愈伤组织对 DPPH[·]的清除能力最大。Muanda 等^[22]采用油提、水提和醇提甜叶菊叶片,发现甜叶菊的水提物和醇提取具有很高的抗氧化能力,且醇提取物的 DPPH[·]半清除率为 2.9 μg/mL,水提物的半清除率为 5.0 μg/mL;之后测定了其化学成分,发现水提和醇提取的主要化合分为槲皮素二水合物、原儿茶酸、槲皮素。

2.2 抑菌作用

研究者采取不同溶剂提取甜菊叶,对多种常见的食物致腐真菌、致病性细菌进行抑制活性研究。发现不同溶剂的提取物能分别对抗不同的真/细菌,其中水提、醇提和石油醚提取物具有广谱的抑菌活性。

Ghosh 等^[29]用甜叶菊叶片的 6 种溶剂(水、乙醇、石油醚、环己烷、丙酮和氯仿)提取物对抗 4 种食物致腐真菌(茄链菌、茄病长蠕孢菌、黑曲霉和产黄青霉菌)和 6 种致病性细菌(大肠杆菌、枯草芽孢杆菌、粪肠球菌、奇异变形杆菌、假单胞菌铜绿假单胞菌和金黄色葡萄球菌),发现石油醚提取物有良好的抗菌作用,250 μg/mL 石油醚提取物(最低抑菌浓度)足以抑制试验微生物大肠杆菌的生长,并且对金黄色葡萄球菌、粪肠球菌、产黄青霉菌和黑曲霉都有良好的抑制作用。Singh 等^[24]研究发现甜叶菊叶片甲醇提取物浓度为 500 mg/mL 时对枯草芽孢杆菌 NCIM 2708 和大肠杆菌 DM 4100 有较好的抗菌活性。Tadhani 等^[30]用水、甲醇、乙酸乙酯和己烷提取甜叶菊叶片,并对枯草芽孢杆菌、金黄色葡萄球菌、藤黄微球菌、铜绿假单胞菌、枯草芽孢杆菌、巨大芽孢杆菌、大肠杆菌、普通变形糖菌、酵母菌和黑曲霉菌进行抗菌活性检测,结果表明甜菊叶水提液对枯草芽孢杆菌和金黄色葡萄球菌均有活性。甲醇提取物对铜绿假单胞菌产生最高的抑制区域,巨大芽孢杆菌和酵母对乙酸乙酯和己烷提取物高度敏感。

Muanda 等^[22]采用油提(EO)、水提(WE)和醇

提(MWE)甜叶菊叶片,对金黄色葡萄球菌、枯草芽孢杆菌、大肠杆菌、铜绿假单胞菌、黑曲霉菌和白色念珠菌的抗菌活性进行研究,结果表明 EO 提取物的活性最低,WE 和 MWE 提取物活性高,之后测定了其化学成分,发现油提取物的主要成分为香芹酚、石竹烯、石竹烯氧化物、斯巴醇、心压畅啶、α-蒎烯、柠檬烯、异松香芹醇、布洛芬等,水提和醇提物的主要化合分为槲皮素二水合物、原儿茶酸、槲皮素。

2.3 抗病毒作用

Takahashi 等^[31]检测甜叶菊的热水提取物(SE)的抗人轮状病毒(HRV)活性,结果表明 SE 在体外抑制四种血清型 HRV 的复制,其抑制机制是阻断病毒结合。对抑制活性最强的甜叶菊成分进行纯化分析,发现该成分由分子量为 9800 的阴离子多糖组成。

Ceole 等^[32]研究甜叶菊叶片提取物多糖级分(分别为 SFW 和 SSFK-10RM)的抗 HSV-1 作用,发现 50 μg/mL 的 SSFK-10RM 和 SFW 分别能抑制感染的侧向扩散 40% 和 70%,100 μg/mL 的浓度下测试,两种级分都能 100% 抑制感染的横向传播。在吸附阶段和病毒穿透细胞后处理细胞,发现病毒糖蛋白 gB、gC 和 gD 表达部分减少;在感染的所有阶段处理细胞,病毒糖蛋白被完全抑制。

2.4 抗肿瘤作用

Jayaraman 等^[33]研究了甜叶菊叶片提取物的抗肿瘤活性。使用 MTT 法测定提取物对 Vero 和 HEp2 的细胞毒性作用。结果表明,甜叶菊叶片丙酮提取物的 1:8 稀释液对正常细胞(Vero)无毒,对癌细胞(HEp2)具有抗增殖活性。

2.5 治疗糖尿病作用

糖尿病是慢性肾功能衰竭的主要原因,Ozbayer 等^[34]测定 N-硝基-1-精氨酸(l-NNA)和甜菊叶提取物(SrB)对链脲佐菌素-烟酰胺(STZ-NA)诱导的糖尿病大鼠肾功能的影响,发现在 SrB 处理的糖尿病大鼠中 NOS 活力更高。与其他糖尿病组相比,SrB 治疗的糖尿病大鼠在较薄的肾切片中线粒体肿胀和空泡化较少,说明与 l-NNA 相比,SrB 对治疗糖尿病更加有益。Kujur 等^[35]用甜叶菊水、乙醚和甲醇提取物对大鼠进行抗糖尿病研究,发现在第 28 天,三种提取物处理的大鼠中血糖水平均有降低。Díaz 等^[36]研究表明纳米结构的 SrB(TiO₂-SrB)对于糖尿病和高血脂症具有较强的活性。

2.6 调节免疫作用

Shukla 等^[37]探索甜叶菊叶片水和乙醇提取物的免疫调节活性,结果发现口服甜叶菊叶乙醇和水

提物的大鼠嗜中性粒细胞粘附和滴度延迟型超敏反应(DTH)显著增加,表明甜叶菊叶具有调节免疫作用,对免疫紊乱具有治疗潜力。

此外,其他研究表明,甜叶菊提取物还具有抗肥胖作用^[38]、抗炎作用^[39]、预防龋齿^[40]、抗结核活性^[41]等。

3 结语

甜叶菊中二萜类成分“甜菊糖苷”甜度高、热量低,是一种天然非营养甜味剂,现对甜叶菊的研究及应用已经不止于甜味剂方面。近年来国内外的研究表明甜叶菊含有黄酮、多酚、挥发油、生物碱、甾醇等多种化学成分,在抗氧化活性、抑菌、抗病毒、抗糖尿病、抗肿瘤、调节免疫等方面发挥着重要的作用,这对甜叶菊的开发利用具有指导意义。但想要实现甜叶菊的综合应用,还需对甜叶菊的成分分析及其活性进行进一步研究,明确甜叶菊的功能特性成分,或对其加工工艺进行研究,明确各步骤可以获得的物质及其功效。同时,可以利用现代生物技术,阐明甜叶菊活性成分生物合成途径,真正做到可控地调节活性成分的生物合成,甚至在体外实现特征成分的表达。综上,通过对甜叶菊的活性成分、加工方法及合成途径等方面进一步探索,将更好地实现甜叶菊在食品、药品等领域的应用价值。

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