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天然小分子诱生机体抗病毒细胞因子研究

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摘 要:天然小分子是中药、药用植物和天然药物的重要活性成分,是重要的药物资源研究方向和内容。大多数抗病毒药用植物,如夏枯草、黄芪和黄芩等,其活性成分均为天然小分子。抗病毒细胞因子为一类生物体中具有联系机体固有免疫和特异性免疫应答,捕杀或抑制体内病毒的小分子功能蛋白。近年来研究表明,植物中的多酚类、苷类以及寡糖等小分子化合物可调控机体内源抗病毒细胞因子的表达水平,继而作用于各类 DNA 或 RNA 病毒:一方面刺激机体产生抗病毒蛋白,直接捕杀病毒;另一方面联动机体固有免疫和获得性免疫应答,抑制病毒复制,抗病毒感染,清除被病毒感染的细胞。本文综述了近几十年药用植物天然小分子诱生机体细胞因子抗病毒的作用及机制研究,并由此提出这类活性天然小分子将可能成为新一类的抗病毒药物。

关键词:抗病毒中药;抗病毒细胞因子;天然小分子;作用机制

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Natural Micromolecule Inducing Antiviral Cytokines

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Abstract: Natural micromolecules are important active ingredients of traditional Chinese medicine, medicinal plants and natural medicines, which are also an important research field and content of studies on the resources of medicinal plant. For most antiviral plants, such as *Prunella vulgaris*, *Astragalus membranaceus* and *Scutellaria baicalensis*, the active ingredients are natural micromolecules. Antiviral cytokines are a diverse group of small functional proteins (or peptides) which can active innate and specific immunity response, inhibit or kill virus in the body. Recently research indicates that polyphenols, glycosides and oligosaccharide from plants is concerned with antiviral cytokine modulation, and then act on DNA or RNA viruses: On one side, inducing the production of antiviral protein direct act on the virus; On the other side, they regulate the immune system to inhibit viral replication, resistance to virus infection and clear the infected cells. This paper reviewed researches on the effects and mechanisms of natural micromolecule inducing antiviral cytokines in recent years, and proposed that the natural micromolecule could become one kind of potential new antiviral medicine.

Key words: antivial traditional Chinese medicine; antiviral cytokines; natural micromolecule; mechanisms

中医药具有五千多年的历史,国内外科学家对中药、天然药、民间药和民族药物进行了大量的研究,具有抗病毒药用植物约 100 余种[1],如金银花(*Lonicera japonica*)、黄芩(*Scutellaria baicalensis*)、黄芪(*Astragalus membranaceus*)、五味子(*Schisandra chinensis* (Turcz.))、夏枯草(*Prunella vulgaris*)、连翘(*Forsythia suspensa*)等(见表 1),据迄今为止的研究表明天然小分子(Natural micromolecule)为这些抗病毒药用植物活性的物质基础。

抗病毒细胞因子(Antiviral cytokines)曾在 Nasu K[2] 和 Fakruddin JM[3] 等人发表的学术论文中提及过,但未曾对其作出具体的定义。为系统地开展细胞因子抗病毒作用及其作用机制研究的研究,有必要对抗病毒细胞因子进行明确地定义:抗病毒细胞因子是由机体细胞分泌的,具有联动机体固有免疫和特异性免疫应答,进而抑制或捕杀体内病毒的小分子蛋白。抗病毒细胞因子可分两大类:一类是可直接作用体细胞产生抗病毒蛋白,即 1)干扰素(In-

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terferon)：IFN-α、IFN-β、IFN-γ 和 IFN-λ(IL-28、IL-29)[4-7]；2)肿瘤坏死因子(Tumor Necrosis Factor)[8]：TNF-α 和 TNF-β；干扰素和肿瘤坏死因子可直接激活细胞内 JAK(Janus activated kinase)-STAT(signal transducer and activator of transcription)信号通路[9-13]，随后引起下游信号级联反应，包括 MTOR 信号通路、PI3K 信号通路、MAPK 信号通路均被激活，最终启动细胞核中一些关键的蛋白基因进行转录，翻译出抗病毒蛋白进而对细菌、病毒以及癌细胞等产生防御作用[14](见图 1)。另一类是能激活巨噬细胞、自然杀伤细胞(NK 细胞)和毒性 T 淋巴细胞(CTL)等细胞，进而捕杀或吞噬体内病毒的细胞因子(见图 1)，即白介素(Interleukin)：IL-1β、IL-2、IL-6、IL-8、IL-12、IL-15、IL-17、IL-18、IL-21、IL-27 等[15-20]。

基于细胞因子对捕杀或抑制病毒方面的作用，本文综述了国内外迄今为止报道的可诱生抗病毒细胞因子的天然小分子(见图 2，图 3)，其中以多酚类、苷类居多，还有部分物质基础未明确的提取物，有待进一步研究。

1 多酚类化合物(Polyphenolic compounds)

白藜芦醇(1，Resveratrol，10 mol/L)能上调人外周血单核细胞 IL-1β、IL-6、TNF-α，调节免疫细胞功能[21]。从姜黄(*Curcuma longa*)根茎分离的天然多酚姜黄素(2，Curcumin)，通过激活人细胞内 MAPK 以及 MTOR 等信号通路，调节下游 STATs 蛋白磷酸化水平，控制 TNF-α、IL-1 和 IL-6 的表达分泌[22]，姜黄素还可以显著的调控 TRAIL(TNF 相关凋亡诱导配基)，有研究显示姜黄素(10 μmol/L 和 25 μmol/L)和 TRAIL(20 ng/mL)联合使用能够促进胞内半胱天冬酶的前体 Procaspase-3，8，9 的分裂，并使得线粒体释放细胞色素 C，导致细胞毒性的增强[23]。茶多酚复方制剂(50～150 mg/kg)可增强小鼠淋巴细胞增殖能力，提高血清溶菌酶活性，上调血清中 IFN-γ 分泌[24]。番茄(*Lycopersicum esculentum*)的多酚提取物能够调节牛中性粒细胞 TNF-α 基因的表达，加热处理的提取物可显著上调 IFN-γ 的分泌[25]，具有增强动物和人类固有免疫的潜在活性。由咖啡酸(3，Caffeic acid)、阿魏酸(4，Ferulic acid)和对香豆酸(5，*p*-Coumaric acid)酶促聚合的多酚(20～100 μg/mL)，通过和 T 细胞表面 $CD4^+$ 蛋白结合，激活下游信号通路后上调小鼠脾脏细胞中的 IFN-γ 和 GM-CSF(Granulocyte-macrophage Colony-stimulating Factor)分泌量[26]，增强机体固有免疫。

从 Cocoa 提取的黄酮类化合物，能够减少小鼠腹膜巨噬细胞活性氧和 NO 的生成，上调 IFN-γ 和 TNF-α 的作用[27]。中药黄芪(*Astragalus membranaceus*)和黄芩(*Scutellaria baicalensis*)是传统的抗病毒药材，主含槲皮素(6，Quercetin)、黄芩素(7，Baicalein)等天然小分子。Nair[28] 等人报道，槲皮素(5 μmol/L)可调节外周血单核细胞 IFN-γ 和 IL-4 的分泌，从而促使 Th0 细胞向 Th1 细胞分化；随后进行了攻毒试验，发现诱生的 IFN-γ 具有很强的抗 VSV(vesicular stomatitis virus)活性。Johari 等[29] 报道槲皮素和黄芩素抑制 JEV(Japanese Encephalitis Virus)的 IC_{50} 分别为 212.1、14.28 μg/mL，提示黄芩素比槲皮素具有更好的抗 JEV 作用。有研究表明，黄芩素可直接抑制病毒血凝素和神经氨酸酶[30]。

桂皮醛(13，Cinnamaldehyde，1 mg/kg)[31,32] 可上调小鼠血清中 IL-2、IL-10 的分泌量，其诱生机制可能与 Toll 样受体的激活有关。从百屈菜中提取得到血根碱(14，6-acetonyl-5，6-dihydrosanguinarine)[33]，体外实验证实其可诱导巨噬细胞和树突状细胞分泌 TFN-α、IL-6、IL-8 等抗病毒细胞因子，对其诱生机制的研究表明，血根碱可激活 MAPK 通路中 ERK，NF-kB 循环活化机制也参与其中，共同调控了下游抗病毒细胞因子的表达。朱晓新等人[34] 从紫茸贯众分离得到四种多酚化合物：4′-hydroxybenzalacetone (HBAc)，3′，4′-dihydroxybenzalacetone (DHBAc)、4-hydroxybenzaldehyde (HBAI)、3，4-dihydroxybenzaldehyde (DHBAI)，其中 HBAI(15，10-100 ug/mL)、DHBAI(16，10-100 ug/mL)可激活胞内 NF-kB 通路，可显著上调小鼠腹膜细胞分泌 TNF、IL-1β、IFN-γ 等，诱生机制可能和 iNOS(一氧化氮合成酶)的激活和 NO 的生成有关。

2 苷类化合物(Glycosides)

研究表明苷类化合物具有抗肿瘤抗病毒活性[35]；桔梗(*Platycodon grandiflorum*)中分离得到的单体桔梗苷 D(8，Platycodin D，0.0016～0.2 μg/mL)[36]，能够上调 IL-2、IFN-γ 的 mRNA 表达水平，调控 Th1/Th2 细胞的转录因子 T-bet 和 CATA-3 表达，同时，桔梗苷 D 可以提高 OVA 致敏小鼠抗体水平，具有免疫调节作用。王先远等[37] 研究苦瓜总皂

表 1 抗病毒药用植物

Table 1 Antivial Medical Plants

序号 No	药用植物 Medicial plant	基源种 Species	部位 Parts	天然小分子 natural micromolecule	分布 Distribution
1	人参叶	*Panax ginseng* C. A. Mey.	叶 Leaves	人参皂苷(ginsenoside) Rb_1、Rb_2、Rc、Re、Rf、Rg_1、Rg_3、Rg_4、Rh_1、Rh_2、Rh_3、F1、F2、F3、F4、La、20-(R)-人参皂苷[20-(R)-ginsenoside]Tg2、Rh_2、20-(S)人参皂苷 Rh_2[20-(S)-ginenoside-Rh_2]等[50]	吉林、辽宁、黑龙江
2	大叶桉叶	*Eucalyptus robusta* Smith.	叶 Leaves	大叶桉酚(robustaol)等[51]	华南、西南等地
3	大青叶	*Isatis indigotica* Fort.	叶 Leaves	靛蓝(indigotin),菘蓝苷(isatin)B,靛玉红(indirubin)等[52]	河北、江苏、安徽
4	大蒜	*Allium sativum* L.(Garlic)	茎 Stem	大蒜辣素(18, Allitridin)[40]*	西亚和中亚山东江苏新疆等地
5	大蓟	*Cirsium japonicum* Fisch. ex DC.	地上部分 Aerial parts	全草含生物碱,挥发油,根含乙酸蒲公英甾醇(taraxasteryl acetate),豆甾醇(stigmasterol),α-香树脂醇(α-amyrin),β-香树脂醇(β-amyrin),β-谷甾醇(β-sitosterol)等[53]	各地均有分布
6	山白菊	*Aster ageratoides* Turcz.	全株 Whole herbs	-	东北、华北、华东、中南、西南及西藏等地
7	天花粉	*Trichosanthes kirilowii* Maxim *T. rosthornii* Herms	根 Root	葫芦素(cucurbitacin)等[54]	河南、广西、山东、江苏、贵州、安徽等地
8	五叶藤	*Ipomoea cairica*(L.) Sweet	根 Root	牛蒡苷元(arctigenin)等[55]	华南
9	五味子	*Schisandra chinensis*(Turcz.) *S. sphenanthera* Rehd. et Wils.	果实 Fruits	五味子素(Schisandrin)等[56]	东北、华北
10	太子参	*Pseudostellaria heterophylla*(Miq.)Pax	根 Root	皂苷(Saponins),sapogenins 等[46][57]	华东、华中、华北、东北和西北等地
11	毛蕊花	*Verbascum thapsus* L.	全株 Whole herbs	叶含鱼藤酮(rotenone)和香豆素(coumarin)等[58]	新疆、江苏、浙江、四川、云南、西藏
12	升麻	*Cimicifuga heracleifolia* Komar. *C. dahurica*(Turcz.) Maxim. *C. foetida* L. 第 5 章	根茎 Root and Stem	阿魏酸(4, ferulic acid)[59]*,异阿魏酸(isoferulic acid),咖啡酸(3, Caffeic acid)*等[60]	黑龙江、四川、内蒙古
13	乌毛蕨贯众	*Blechnum orientale* L.	根茎 Root and Stem	根茎含绿原酸(chlorogenic acid),类脂(lipids),甾醇类(sterol)等[61]	西南及浙江、江西、福建、台湾、湖南、广东、海南、广西等地
14	乌蔹莓	*Cayratia japonic*(Thunb.) Gagnep. 第 6 章	全株 Whole herbs	芹菜素(apigenin),木犀草素(luteolin)等[62]	山东、江苏、浙江、江西、湖南、福建、广东
15	甘草	Glycyrrhiza uralensis Fisch. G. inflata Batal. G. glabra L.	根茎 Root and Stem	山柰酚-3-*O*-β-D-葡萄糖苷(astragalin, Ⅴ),槲皮素-3-*O*-芸香糖苷(rutin, Ⅵ),槲皮素-3-*O*-β-D-葡萄糖苷(quercetin-3,3′-dimethylether)等[63]	内蒙古、宁夏、新疆、甘肃
16	石韦	*Pyrrosia lingua*(Thunb.) Farw. *P. sheareri*(Bwk.) Ching *P. petiolosa*(Christ) Ching 第 7 章	叶 Leaves	槲皮素(6, quercetin)*,香草酸(vanillic acid),原儿茶酸(protocatechuic acid),延胡索酸(fumaric acid),咖啡酸(3, caffeic acid)*等[64]	长江以南各地均有分布
17	石蒜	*Lycoris radiata*(L′Herit.) Herb.	茎 Stem	雪花胺(galanthamine),石蒜碱(lycorine)等[65]	华东、中南及西南
18	平地木	*Ardisia japonica*(Thunb.) Bl.	全株 Whole herbs	三萜皂苷(triterpenoid saponin)等[66]	陕西及长江流域以南各地均有分布(海南未发现)

19	白毛夏枯草	*Ajuga decumbens* Thunb.	全株 Whole herbs	黄酮提取物(flavone)等[67]	各地均有分布
20	白芍	*Paeonia lactiflora* Pall.	根 Root	芍药苷(paeoniflorin)等[68]	安徽、东北三省、河北等地
21	白屈菜	*Chelidonium majus* L.	全株 Whole herbs	血根碱(14, sanguinarine)*等[33]	东北、内蒙古、河北、河南、山东、山西、江苏、江西、浙江等地
22	白扁豆	*Dolichos lablab* L.	种子 Seeds	Dolichin 等[69]	辽宁、河北、山西、陕西、山东、江苏、安徽、浙江、江西、福建、台湾、河南、湖北、湖南、广东、海南、广西、四川、贵州、云南等地。
23	玄参	*Scrophularia ningpoensis* Hemsl.	根 Root	哈帕苷(harpahide),玄参苷(harpagoside)等[70]	安徽、江苏、浙江、福建、江西、湖南、湖北、贵州、陕西等地
24	丝瓜	*Luffa acutangula* (L.) Roxb.	果实 Fruits	三萜皂苷(triterpene saponins),丝瓜苷(acutoside)等[71]	东亚地区
25	丝瓜藤	*Luffa cylindrica* (L.) Roem. *L. acutangula* (L.)	茎 Stem	三萜皂苷(triterpene saponins),丝瓜苷(acutoside)等[71]	各地均有分布
26	扛板归	*Polygonum Porfoliatum* L.	全株 Whole herbs	槲皮素(6, quercetin)*,儿茶素(Catechin)等[72]	各地均有分布
27	地骨皮	第 8 章 *Lycium chinense* Mill.	根皮 Root barks	β-谷甾醇(beta-sitosterol),盐酸甜菜碱(betaine hydrochloride),东莨菪素(scopoletin)等[73]	大部分地区有分布
28	西洋参	*Panax quinque folium* L.	根 Root	人参皂苷(ginsenosides) Rb1、Rb2、Rd、Re、Rf、Rg1、Rg2、Rg3、Rh1、R0 和 RA0,胡萝卜苷(daucosterin)等[74]	原产北美洲的加拿大南部和美国北部,福建、云南等高海拔山区的引种成功
29	百花射干	*Irisdic hotoma* Pall.	全株 Whole herbs	–	东北、华北、陕西、宁夏、甘肃、青海、山东、安徽、江苏、江西、河南等地
30	百部	*Stemona sessilifolia* (Miq.) Franch. et bar. *S. japonica* (Bl.) Miq. *S. tuberosa* Lour.	根 Root	百部碱(stemonine),原百部碱(protostemonine)等[75]	山东、安徽、江苏、浙江、福建、江西、湖南、湖北、四川、陕西等地
31	红芪	*Hedysarum polybotrys* Hand. -Mazz.	根 Root	香草酸(vanillic acid)等[76]	甘肃
32	红药子	Polygonum cillinerve (Nakai) Ohwrz	根 Root	大黄素(emodin),大黄素甲醚(physcion)等[77]	东北、西北和湖北、湖南、四川、贵州等地
33	苍耳子	*Xanthium sibirlcum* Patrin. ex wider. *X. mongdic*km Kitag	根 Root	胡萝卜素(daucosterol)等[78]	各地均有分布
34	苏铁蕨	*Brainea insignis* (Hook.) J. Smith	地上部分 Aerial parts	Brainicin 等[79]	福建、台湾、广东、广西、贵州、云南等地
35	连翘	*Forsythia suspensa* (Thunb.) Vahl.	果实 Fruits	连翘苷(phillyrin),芸香苷(rutin)等[80]	辽宁、河北、河南、山东、江苏、湖北、江西、云南、山西、陕西、甘肃等地
36	牡丹皮	*Paeonia suffruticosa* Andr.	根皮 Root barks	芍药苷(paeonifolrin)等[81]	河北、河南、山东、四川、陕西、甘肃等地
37	辛夷(望春花、玉兰或武当玉兰)	*Magnolia biondii* Pamp. *M. denudata* Desr. *M. sprengeri* Pamp.	花 Flowers	木脂素(lignans)等[82]	山东、四川、江西、湖北、云南、陕西南部、河南
38	灵香草	*Lysimachia foenum-graecum* Hance	地上部分 Aerial parts	黄酮类(flavonoids)提取物等[83]	湖南西南部、广东北部、广西、四川、贵州、云南东南部

39	忍冬藤	*Lonicera japonica* Thunb.	茎 Stem	木犀草素(luteolin),槲皮素(6 quercetin)*等[84]	浙江、四川、江苏、河南、陕西、山东、广西、湖南等地
40	鸡挂骨草	*Pogostemon glaber* Benth.	全株 Whole herbs	–	云南北、南部及东南部
41	青木香	*Aristolochia debilis* Sieb. Et Zucc.	果实 Root	马兜铃酸(aristolochic acid)等[85]	各地均有分布
42	青蒿	*Artemisia annua* L.	地上部分 Aerial parts	青蒿素(19, Artemisinin)*等[41]	中国、东南亚
43	金盏菊花	*Calendula Officinalis* L.	花 Flowers	绿原酸(chlorogenic acid)等[86]	各地均有分布
44	苦丁茶	*Ilex cornuta* Lindl. Ex Paxt. *I. kudincha* C. J. Tseng*I. Latifolia* Thunb. *Ligustrum purpurascens* Y. C. Yang*L. Robustum* (*Roxb.*) Bl.	叶 Leaves	Ligupurpuroside A、B,2-(3,4-dihydroxy-phenyl) ethyl (3-*O*-α-*L*-rhamno pyranosyl)(4-O-coumaroyl)-*O*-β-*D*-glucopyranoside, osmanthuside B,阿克苷(12, acteoside)*等[49]	广西、广东、海南、云南及贵州等地
45	苦木	*Picrasma quassioides* (D. Don) Benn.	枝干 Branches	苦木素(quassin)等[87]	产于黄河流域以南各地均有分布
46	苦瓜	*Momordica charantia* L.	果实 Fruits	苦瓜苷(Charantin)等[88]	各地均有分布均有栽培
47	苦参	*Sophora flavescens* Ait.	根 Root	苦参碱(matrine)等[89]	俄罗斯、日本、印度、朝鲜、中国大陆等地
48	板蓝根	*Isatis indigotica* Fort.	根 Root	靛玉红(indirubin)等[90]	内蒙古、陕西、甘肃、河北、山东、江苏、浙江、安徽、贵州等地
49	欧绵马	*Dryopteris filix-mas* (L.) Schott	根茎 Root and Stem	–	新疆北部地区
50	软蒺藜	*Atriplex sibirica* L. *A. centralasiatica* Iljin	果实 Fruits	–	西伯利亚、中亚
51	虎杖	*Polygonum cuspidatum* Sieb. Et Zucc.	根茎 Root and Stem	虎杖苷(Polydatin)等[91]	中部及南部
52	败酱	*Patrinia villosa* (Thunb.) Juss. *P. scabwsaefdia* Fisch.	全株 Whole herbs	β-谷甾醇(β-sitosterol),白花败酱醇(villosol),槲皮素(6, quercetin)*,阿魏酸(4, ferulic acid)*等[92]	四川、江西、福建等地
53	知母	*Ane - marrhena asphodeloides* Bunge.	根茎 Root and Stem	知母皂苷(timosaponin)等[93]	东北、华北、宁夏、甘肃、山东、江苏等地
54	佩兰	*Eupatorium fortunei* Turcz.	地上部分 Aerial parts	香豆酮(benzofuranol)等[94]	广东、贵州、湖北、浙江、广西、陕西
55	金沸草	*Inula britanica* L. *I. linariifolia* Turcz; *I. japonica* Thunb.	地上部分 Aerial parts	槲皮素(6, quercetin)*等[95]	江苏、四川等地
56	金银花	*Lonicera japonica* Thunb. *L. confuse* (sweet) DC. *L. hypoglauca* Miq. *L. fulvotomentosa* Hsu et S. C. Cheng	花 Flowers	绿原酸(chlorogenic acid)等[96]	各地均有分布,除西藏外
57	肿节风	*Sarcandra glabra* (Thunb.) Nakai	全株 Whole herbs	落新妇苷(astilbin)、异秦皮素(isofraxidin)等[97]	华东、中南、西南
58	鱼腥草	*Houttuynia cordata* Thunb.	全株 Whole herbs	芸香苷(rutin),绿原酸(chlorogenic acid),叶含槲皮素(6, quercitrin)*等[98]	长江流域以南各省
59	单花芥	*Pegaephyton scapiflorum* (Hook. f. et Thoms.) Marq. et Shaw	全株 Whole herbs	–	青海、四川西南部、云南西北部及西藏
60	荆芥	*Nepeta cataria* Linn Sp.	地上部分 Aerial parts	挥发油(Volatile Oil,4a-α, 7-α, 7a-β-nepetalactone, 4a-α, 7-β, 7a-α-nepetalactone)等[99]	安徽、江苏、浙江、江西、湖北、河北等地

61	茶叶	*Camellia sinensis* (L.) O. Kuntze[*Theasinensis*L.]	叶 Leaves	咖啡因(caffeine),槲皮素(6, quercetin)*等[100]	长江流域及其以南各地均有分布
62	荔枝草	*Sylvia plebeia* R. Br.	地上部分 Aerial parts	槲皮素(6, quercetin)*, 木犀草苷(cynaroside),异泽兰黄素(eupatilin)等[101]	江苏、浙江、安徽
63	南板蓝叶	*Baphicacanthus cusia* (Nees) Bremek.	叶 Leaves	靛玉红(indirubin),靛蓝(indigo)等[102]	江苏、浙江、福建、湖北、广东、广西、四川、贵州、云南
64	柠檬	*Citrus limon* (L.) Burm. F	果实 Fruits	黄酮提取物(flavonoid)等[103]	长江以南各省(自治区)
65	刺五加	*Acanthopanax senticosus* (Rupr. et Maxim.) Harms	茎皮 Stem barks	–	东北及河北、山西等地
66	鸦胆子	*Brucea javanica* (L.) Merr.	果实 Fruits	苦木素(Quassinoid)等[104]	福建、台湾、广东、海南、广西、贵州、云南等地
67	香排草	*Lysimachia capillipes* Hemsl.	全株 Whole herbs	槲皮素(6, quercitin)*等[105]	浙江、江西、福建、台湾、河南、湖北、湖南、广东
68	穿山龙	*Discorea nipponica* Makino.	根茎 Root and Stem	皂苷类提取物(saponins)等[106]	东北、华北、山东、河南、安徽、浙江北部、江西(庐山)、陕西(秦岭以北)、甘肃、宁夏、青海南部、四川西北部。也产于日本本州以北及朝鲜和俄罗斯远东地区
69	孩儿茶	*Acacia catechu* (L. f.) Willd.	枝干 Branches	槲皮素(6, quercetin)*等[107]	云南南部地区,海南岛有栽培
70	莱菔	*Raphanus sativus* L.	种子 Seeds	阿魏酸(4, Ferulic acid)*等[108]	各地均有分布
72	夏枯草	*Prunella vulgaris* Linn.	果实 Fruits	芸香苷(rutin),金丝桃苷(hyperoside),咖啡酸(3, caffeic acid)*,槲皮素(quercitin)*等[110]	安徽、江苏、湖南
73	柴胡	*Radix Bupleuri*	根 Root	柴胡皂苷(Saikosaponin)等[111]	湖北、四川等地;朝鲜、日本、俄罗斯也有分布
74	铁色箭	*Lycoris anrea* (L′Herit.) Herb.	茎皮 Stem barks	生物碱(alkaloids)等[112]	西南及江苏、安徽、浙江、江西、福建、台湾、湖北、湖南、广东、广西等地
75	射干	*Belamcanda chinensis* (L.)DC.	根茎 Root and Stem	鸢尾甲黄素(Iristectorigenin)等[113]	各地均有分布
76	海南粗榧	*Cephalotaxus hainanensis* Li.	茎皮 Stem barks	三尖杉酰胺(cephalotaxinamide),去甲基桥氧三尖杉新碱(demethylneodrupacine),脱氧三尖杉酯碱酸(deoxyharringtonic acid)和异三尖杉酯碱酸(isoharringtonic acid)等[114]	广东、海南、广西、云南、西藏等地
77	浮萍	*Spirodela polyrrhiza* (L.)Schleid.	全株 Whole herbs	硝基酚(Nitrophenol)等[115]	南北均有分布
78	桑叶	*Morus alba* L.	叶 Leaves	芸香苷(rutin),槲皮素(6, quercetin)*等[116]	江苏、浙江
79	黄皮叶	*Clausena lansium* (Lour.) Skeels	全株 Whole herbs	Lansiumamide B 等[117]	西南及福建、台湾、广东、海南、广西等地
80	稀花黄堇	*Corydalis dubia*	全株 Whole herbs	比枯枯灵碱(bicuculline),碎叶紫堇碱(cheilanthifoline)等[118]	西藏
81	黄芩	*Scutellaria baicalensis* Georgi.	根 Root	黄芩素(7, Baicalein)*等[119]	河北、山西北部、内蒙中东部和东北三省大部

82	黄芪	*Astragalus membranaceus* (Fisch.) *A. membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao	根 Root	槲皮素(6, Quercetin)*等[120]	内蒙古、甘肃、宁夏、山西、河北、陕西
83	黄连	*Coptis chinensis* Franch. *C. deltoidea* C. Y. Cheng et Hsiao. *C. teeta* Wall.	根茎 Root and Stem	鼠李黄素(rhamnetin),汉黄芩素(wogonin)(12),香草酸(vanillic acid),阿魏酸(4, ferulic acid)*等[121]	四川、贵州、湖北、陕西等地
84	黄断肠草	*Corydalis davidii* Franch.	根茎 Root and Stem	–	四川南部、贵州西北部、云南东北部
85	黄精	*Polygonatum kingianum* Coll. et Hemsl *P. sibiricum* Red. *P. cyrtonema* Hua.	根茎 Root and Stem	甾体皂苷(steroid saponins)等[122]	河北、内蒙古、陕西省等省区
86	野甘草	*Scoparia dulcis* L. 第9章	全株 Whole herbs	多酚类提取物(polyphenol)等[123]	福建、广东、广西、云南等地
87	野竹兰	*Epipactis yunnanensis* Schlecht	根 Root	–	云南
88	猕猴桃根	*Fructus Actinidiae* Chinensis.	根皮 Root barks	–	华东、中南、西南及陕西、甘肃
89	麻黄(草麻黄、中麻黄或木贼麻黄)	*Ephedra sinica* Stapf*E. intermedia* Schrenk et C. A. Mey. *E. equisetina* Bge.	茎 Stem	麻黄根素(ephedrannin),儿茶素(catechin)等[124]	山西、河北、甘肃、辽宁、内蒙古、新疆、陕西、青海、吉林等地
90	商陆	*Phytolacca ainosa* Roxb.	根 Root	商陆种苷(esculentoside)O、E等[47]	河南,湖北,安徽等地
91	淫羊藿	*Epimedium brevicornum* Maxim. *E. sagittatum* Maxim. *E. pubescens* Maxim. *E. koreanum* Nakai.	叶 Leaves	淫羊藿苷(icariin),金丝桃苷(hyperosde)等[125]	黑龙江、吉林、辽宁、山东、江苏、江西、湖南、广西、四川、贵州、陕西、甘肃
92	葛根	*Pueraria lobata* (Willd.) Ohwi*P. thomsonii* Benth.	根 Root	葛根素(Puerarin)等[126]	广东、广西、四川、云南等地
93	紫苏叶	*Perilla frutescens*	叶 Leaves	紫苏醛(Perillaldehyde)、紫苏醇(perillyl alcohol)等[127]	亚洲东部和东南部
94	紫其贯众	*Osmunda japonica* Thunb.	根茎 Root and Stem	葡萄糖基紫萁内酯(osmundalin)等[128]	安徽、浙江、江西、福建、河南、湖北、湖南、广东、广西、四川、贵州、云南等地
95	黑面叶	*Breynia fruticosa* (L.) Hook. f.	叶 Leaves	木栓醇(friedelan-3β-ol),无羁萜(friedelin)等[129]	浙江、福建、广东、广西、贵州、云南等地
96	温大青	*Goldfussia pentstemonoides* (Wall.) Nees	叶 Leaves	–	浙江;湖北;广西;四川;贵州;云南等地
97	蓝实	*Polygonum tinctorium* Ait.	果实 Fruits	山奈酚(Kaempferol)等[130]	辽宁、河北、陕西、山东等地
98	蓟罂粟	*Argemone mexicana* L.	全株 Whole herbs	小檗碱(berberine),血根碱(14, sanguinarine)*等[131]	福建、台湾、广东、海南、云南等地有庭园栽培,或逸为野生;北京、河南等地偶见栽培
99	蓼大青叶	*Polygonum tinctorium* Ait.	叶 Leaves	靛玉红(indirubin),靛蓝(indigo, indigotin)色氨酮(tryptanthrin)等[48]	辽宁、河北、陕西、山东等地
100	酸浆	*Physalis alkekengi*	全株 Whole herbs	–	东北地区

101	蜜桶花	*Brandisia hancei* Hook. F.	花 Flowers	阿克苷(12, acteoside)*，金石蚕苷(poliumoside)，来江藤苷(brandioside)等[132]	中南及西南
102	薄荷	*Mentha haplocalyx* Briq.	地上部分 Aerial parts	黄酮提取物(flavonoid)等[133]	华北、华东、华南、华中及西南各地均有分布
103	广藿香	*Pogostemon cablin*	地上部分 Aerial parts	藿香苷(agastachoside)，金合欢素(acacetin)等[134]	东北、华东、西南及河北、陕西、河南、湖北、湖南、广东等地

注：* 已报道的可诱生抗病毒细胞因子的天然小分子

Note: * These natural micromolecules have been reported to induce antiviral cytokines.

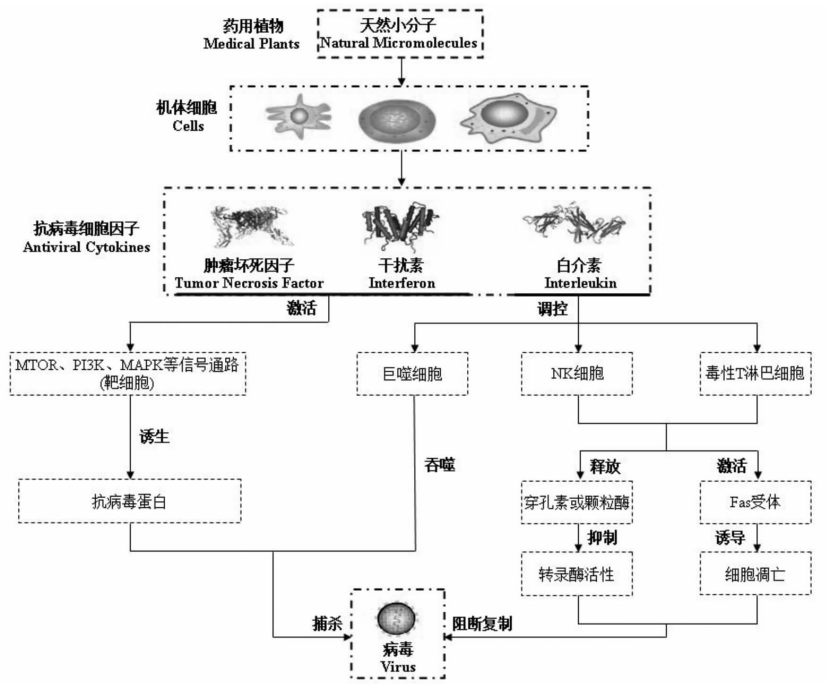

图 1 天然小分子诱生细胞因子抗病毒作用机制

Fig. 1 The mechanisms of antiviral activity of antiviral cytokines induced by natrual micromolecule

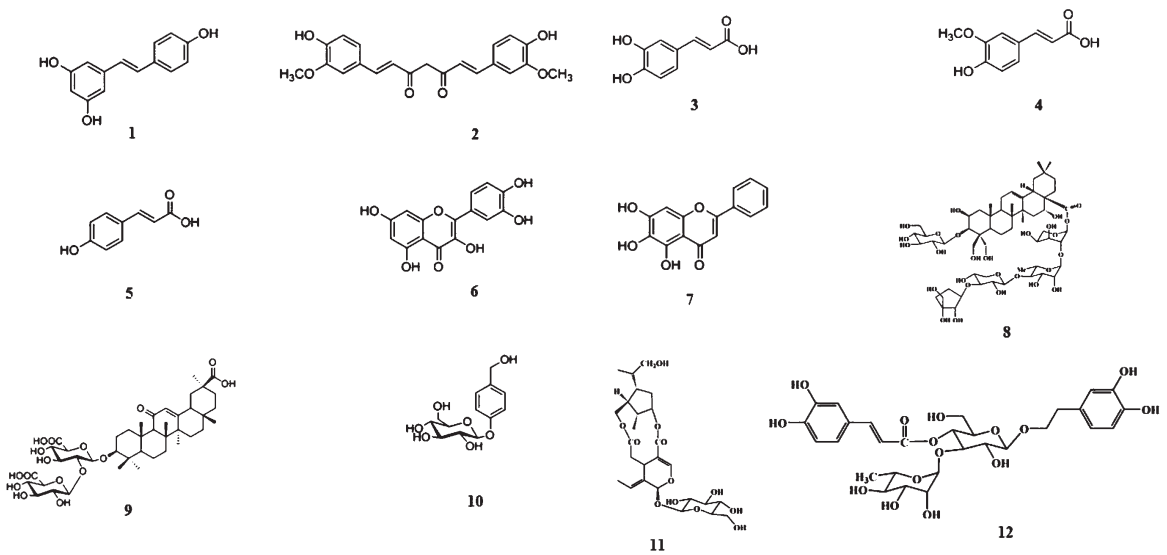

图 2 诱生抗病毒细胞因子的天然小分子 **1** ~ **12** 的化学结构式

Fig. **2** The chemical structure of natural micromolecule **1-12** with the function of inducing antiviral cytokines

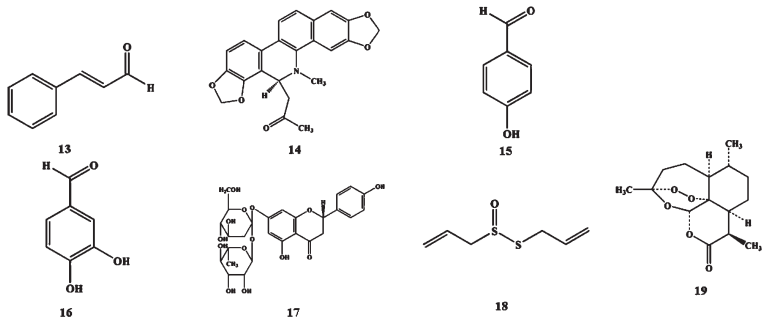

图 3 诱生抗病毒细胞因子的天然小分子 13 ~ 19 的化学结构式

Fig. **3** The chemical structure of natural micromolecule **13-19** with the function of inducing antiviral cytokines

苷对衰老小鼠免疫功能的影响,发现苦瓜总皂苷不仅可上调血清中 IL-2 水平,而且促进脾脏分泌 IL-2 及腹腔巨噬细胞分泌 TNF-α,其机制可能与 DNA 多聚酶 II 活性增强有关;苦瓜总皂苷促进 IL-2 分泌,改变 T 细胞亚群的组成,使机体免疫状态趋向年轻化。徐先祥等[38]人报道甘草皂苷(9,0.5 mg/mL)可抑制 98% 以上的 HIV 增殖,0.125 mg/mL 时,可抑制 98% 以上的 HIV 的增殖,并可抑制 50% 斑块的形成,其作用机制是诱生干扰素和增强 NK 细胞的活性抵抗 HIV。柚皮苷(17,naringin,20,40 and 80 mg/kg)[39]可上调 Th2 型细胞分泌 IL-4、IL-6、IL-10 等。

另外,本课题组开展天然小分子诱生机体抗病毒细胞因子的研究中,发现天麻素(10,Gastrodin,0 ~ 1000 μmol/L)、迎春花素(11,Jasminin,1-100 μmol/L)能够显著上调 RAW246.7 细胞分泌 TNF-α;从苦丁茶紫茎女贞(*Ligustrum purpurascens*)叶提取得到苯丙素总苷(crude phenylethanoid glycosides),属多酚类化合物,活性测试表明,苯丙素总苷(0.22 ~1.32 g/kg)具有免疫增强作用[49];进一步研究还发现,从苯丙素总苷分离得到的单体阿克苷(12,acteoside,0.8 ~200 μg/mL),能够显著上调 Balb/c 小鼠体内 IFN-γ 的表达水平,动物攻毒实验证实可显著抑制小鼠体内病毒载量。

3 其他

大蒜辣素(18,Allitridin,25 mg/kg/day)[40]可调节 CMV 感染小鼠体内 Foxp3 蛋白表达,上调机体 IFN-γ 和 IL-4 分泌,恢复 CMV 攻击造成的免疫系统紊乱。青蒿素(19,Artemisinin)[41]可显著刺激巨噬细胞分泌 IL-12,其诱生机制和 JNK 磷酸化的抑制有关。

滑菇(*Pholiota nameko*)提取物(20 ~ 60 mg/kg)[42]能够上调白介素、肿瘤坏死因子、干扰素等多种抗病毒细胞因子的分泌。

此外,许多中药提取物具有免疫增强作用[43],如黄芪提取物(100 ~200 μg/mL)、板蓝根提取物(100 ~ 200 μg/mL)能够刺激鸡外周血淋巴细胞 IFN-γ 的 mRNA 的表达量,并对 NDV(Newcastle disease virus)感染有抑制作用。人参叶提取物[44]可显著上调感染 H5N1 小鼠和雪貂肺部 IFN-γ 分泌,与空白对照组相比,动物的存活率可提高至 40% ~ 45%。五味子[45]和太子参[46]提取物,均可显著诱导正常细胞生成 TNF-α。商路提取物(50 mg/kg)[47]处理小鼠,每周喂食一次,可显著刺激小鼠淋巴细胞增殖,产生 IL-2,如果改变喂食频率,一周三次,IL-2 的分泌量则开始下降;此外,当剂量调整为 10 mg/kg,每周三次喂食,则可以刺激巨噬细胞分泌 IL-1,TNF,推测商路提取物可增强小鼠中巨噬细胞的活性,杀伤病变细胞。蓼大青叶提取物(1 ~ 100 mg/kg)[48]可显著增加小鼠脾脏 IFN-γ 的分泌。

4 结语

目前,用于临床的抗病毒药物主要有化学药物和疫苗两类,而通过诱生抗病毒细胞因子途径的药物有望成为第三类新型抗病毒药物。药用植物中的天然小分子结构复杂,资源丰富,成药性强,然而目前有关天然小分子诱生抗病毒细胞因子的研究缺乏系统性,尚待进行深入研究。对抗病毒药用植物进行提取分离及纯化,进行体外细胞模型筛选,并开展动物免疫学和动物病毒学研究,进而发现活性天然小分子,通过系统的基础研究,有望研发出诱生机体抗病毒细胞因子的抗感染性疾病的临床药物,我们预计此类相关的研究将成为抗病毒药物研发的新途

径。

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(上接第 1410 页)

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