中药活性成分共晶研究进展

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摘要: 中药包含众多单体活性成分, 这些成分具有丰富的药理作用。然而, 大多数中药活性成分的理化性质较差, 难以应用于临床。共晶技术在改善中药难溶性有效成分的溶解性和生物利用度等方面具有巨大潜力。本文系统阐述了中药活性成分共晶的研究现状, 并简要介绍了不同类别活性成分的结构与共晶配体结构之间的联系, 旨在为中药活性成分共晶的研究与共晶在医药领域的进一步拓展提供参考。

关键词: 中药; 活性成分; 共晶; 黄酮类; 生物碱类; 酚类

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Research progress on the cocrystals of active ingredients of traditional Chinese medicine

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Abstract: Traditional Chinese medicine contains numerous monomeric active ingredients, which have rich pharmacological effects. However, many of these active ingredients have poor physicochemical properties, making them challenging to use in clinical settings. Cocrystal technology has demonstrated significant potential in enhancing the solubility and bioavailability of these poorly soluble active ingredients. This article provides a comprehensive overview of the current research on cocrystals of active ingredients in traditional Chinese medicine and briefly discusses the relationship between the structures of these active ingredients and the cocrystal formers. The aim is to provide reference for further research on cocrystals of active ingredients of traditional Chinese medicine and their broader applications in the pharmaceutical industry.

Key words: traditional Chinese medicines; active ingredient; cocrystal; flavonoid; alkaloid; phenol

中药活性成分是指中药中具有医疗效用或生理活性的单体化合物, 是药物开发利用的基础。从中药中提取和分离纯化的单体数目繁多, 主要分为黄酮类、生物碱类、酚类、萜类、苯丙素类、糖苷类, 具有抗病毒、抗氧化、抗菌、抗肿瘤、抗疟疾、免疫调节等药理活性, 在疾病的预防或治疗中发挥重要作用。然而, 许多活性成分存在水溶性低、稳定性差、吸湿性高等问题, 限制了其制剂与剂型的开发及临床应用。

共晶是指两种或两种以上不同组分按照一定的化学计量比通过非共价键 (氢键、π-π堆积和范德华力等分子间弱作用力) 相互作用形成的结晶物质[1], 共晶中一种活性组分为药物分子 (active pharmaceutical ingredient, API), 另一组分称为共晶配体 (cocrystal former,

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CCF)。药物共晶可在保证或提高中药活性成分的活性前提下, 改善其溶解度、溶出度、稳定性等理化性质, 进而增强药物的生物活性[2-4]。因此, 中药活性成分共晶的研究对其药物的研发生产及有效利用具有重大意义。本文对中药活性成分共晶的研究进行综述, 以期为中药活性成分共晶的开发研究提供参考。

1 中药活性成分共晶研究进展

1.1 黄酮类 黄酮类化合物以2-苯基色原酮为母核结构, 广泛分布于芸香科、菊科、玄参科、伞形科、苦苣苔科、豆科等被子植物中, 是一类具有抗氧化、抗肿瘤、抗炎等多种药理活性的化合物。然而, 大部分黄酮类化合物存在溶解度差, 口服生物利用度低的问题, 使其临床应用受到了很大的限制。因此, 研究人员通过共晶技术来改善黄酮类化合物的性质。如黄酮醇类化合物槲皮素, 可与多种配体如烟酰胺[2]、甜菜碱[3]、茶碱[3]、*L*-脯氨酸[3]、己酮可可碱[3]等形成共晶。Zhang等[4]研制了抗血栓药物阿哌沙班–槲皮素共晶, 共晶同时改善了这两种药物的溶解度和生物利用度。Veverka等[5]研究表明, 槲皮素与吡唑、咪唑烷酮和巴氯芬3种配体形成的共晶在2～20 ℃的各种相对湿度条件下稳定; 槲皮素与*N*-乙酰胞嘧啶、肉碱和曲酸形成共晶可增强对蛋白酶的抑制活性。同时, 槲皮素–曲酸对人宫颈癌细胞 (HeLa) 和人结肠癌细胞 (Caco-2) 的细胞毒性较槲皮素有所提高。此外, Liu等[6]研究表明, 槲皮素–异烟肼共晶也提高了槲皮素的溶解度和生物利用度, 并显著降低了异烟肼的肝毒性。上述研究数据表明, 槲皮素形成共晶后, 在一定程度上提高了槲皮素的稳定性、溶解度、药理活性及生物利用度。

目前, 黄酮类药物共晶的研究取得了较大进展。如表1[2-49]中统计了16种黄酮类活性成分共晶的研究概况, 在这些共晶中配体多为含氮的环状化合物, 如异烟肼、烟酰胺、哌嗪、4,4′-联吡啶及生物碱类活性成分咖啡因和茶碱等。共晶形成的相互作用力主要包括氢键、范德华力、卤素键、π-π堆积。这些共晶配体主要通过氢键和π-π堆积等相互作用力与黄酮类活性成分形成共晶。例如, 白杨素分别与4,4′-联吡啶和1,4-双 (吡啶-4-基甲氧基) 苯通过氢键和π-π堆积相互作用力形成共晶。两种共晶结构中白杨素的-OH通过氢键与两种配体的吡啶环N相连, 形成链状结构。在磷酸盐缓冲液 (pH 7.4) 中, 两种共晶的溶解度及溶解速度均较白杨素显著提高, 且细胞毒性研究表明, 其具有良好的生物学适应性[16]。

药物形成共晶后, 其空间结构发生了改变, 进而改变其理化性质及生物利用度。表1中共晶性质研究数据表明, 黄酮类活性成分形成共晶后, 改善了原料药的生物利用度或药理活性, 除染料木黄酮–脯氨酸共晶外, 其余共晶均提高了原料药的稳定性和溶解度。综上, 几乎所有的黄酮类活性成分共晶均表现出良好的溶解度及口服生物利用度。但部分文献只对共晶的制备表征及晶体空间结构等进行研究, 尚未对其理化性质及生物利用度进行考察, 且药效学及药代学研究只是停留在大鼠等动物身上, 未进行人体临床试验。共晶技术在改善黄酮类化合物的理化性质及生物利用度方面具有重要潜力。 然而, 目前针对黄酮类活性成分共晶的研究仍处于初步阶段, 其形成机制、结构特征及性能调控尚需进一步深入探索。

1.2 生物碱类 生物碱是一类含氮碱性有机化合物, 广泛存在于罂粟科、豆科植物、毛茛科等双子叶植物中。生物碱类活性成分具有抗肿瘤、抗病毒、镇痛、抗菌、抗糖尿病和杀虫等广泛的药理活性。大多数生物碱具有复杂的环状结构, 含有碱性氮原子、芳香环、杂环结构和含氮基团等。目前, 生物碱类活性成分的共晶研究主要以小檗碱、茶碱、咖啡因居多, 川穹嗪、延胡索乙素、四氢小檗碱等共晶的数量相对较少。

表2[13,14,20,25,26,28,36,37,42,50-70]统计了10种生物碱类活性成分的研究概况。生物碱类活性成分多数含有N杂环, 其中的N原子可以参与氢键的生成。因此, 生物碱类活性成分多被用作共晶配体与黄酮类活性成分形成共晶, 以改善药物的溶解度和生物利用度。如Li等[42]报道了染料木黄酮–川芎嗪共晶晶格中染料木黄酮的两个羟基分别与两分子川芎嗪中吡嗪环上N原子以O-H···N氢键相互作用形成一维链。在大鼠口服给药后, 染料木素–川芎嗪共晶的C_{max}及生物利用度分别是纯染料木黄酮的5.49和1.84倍。同时, 该共晶还改善了川芎嗪的易升华的缺点。此外, 盐酸小檗碱常用作配体与天然药物杨梅素[25]、二氢杨梅素[25]、白杨素[14]、大黄素[53]等形成共晶, 以改善天然药物的溶解度和生物利用度。

生物碱类活性成分除作为共晶配体外, 还可与磺酸类和带羧基的化学药物形成共晶。如卢琪[50]制备的盐酸小檗碱–柠檬酸共晶、盐酸小檗碱–乳酸共晶, 以及相关文献报道的盐酸小檗碱–*L*(+)-乳酸–水合物共晶[51]和盐酸小檗碱–富马酸共晶[52]。这些共晶的稳定性和溶解度与盐酸小檗碱相比有显著的提高。He等[54]制备了小檗碱–罗格列酮共晶, 改善了糖尿病KKAy小鼠的糖脂代谢和胰岛素抵抗。吕扬等[55]采用加液球磨法制备了小檗碱–布洛芬共晶。该共晶改善了原料药在水和盐酸混合体系中的释放情况, 提高了溶解速率和药物在大鼠体内的吸收速度与血药浓度, 并延长了作用时间。表2中生物碱类活性成分共晶性

Table 1　Research overview on the cocrystals of flavonoids. API: Active pharmaceutical ingredient; CCF: Cocrystal former; ▲: Improved stability; ●: Improved solubility or dissolution rate; ■: Improved activity or bioavailability; ▼: Reduce stability; ◆: Reduced solubility or dissolution rate

API	CCF	Acting force	Property	Ref.
Quercetin	Nicotinamide		●■	[2]
	Betaine		●■	[3]
	Theophylline		●■	[3]
	L-Proline		●■	[3]
	Pentoxifylline		●■	[3]
	Apixaban	O-H···O, O-H···N	●■	[4]
	Pyrazol			[5]
	Imidazolidinone			[5]
	Baclofen			[5]
	N-Acetylcytosine		■	[5]
	Carnitine		■	[5]
	Kojic acid		■	[5]
	Isoniazid		●■	[6]
Luteolin	*L*-Proline	*π*-*π*, O-H···O, N-H···O	■	[7]
	Piperazine		▲	[8]
	Isoniazid	C-H···N, N-H···N	▲●	[9]
	Caffeine		▲●■	[9]
	Lysine		▲●	[10]
	Arginine		▲●	[10]
	Isonicotinamide			[11]
	4,4′-Bipyridine		■	[12]
Chrysin	Piperazine		●	[13]
	Ethionamide	O-H···N, O-H···O, C-H···O N-H···O, N-H···S		[13]
	Berberine hydrochloride		■	[14]
	Cytosine	*π*-*π*, C-H···O, N-H···O, O-H···N	●■	[15]
	Thiamine hydrochloride	*π*-*π*, O-H···O, N-H···O, N-H···Cl	●	[15]
	4,4′-Bipyridine	*π*-*π*, O-H···O, O-H···N	●■	[16]
	1,4-Bis(pyridin-4-ylmethoxy) benzene	*π*-*π*, O-H···O, O-H···N	●■	[16]
Kaempferol	4,4′-Bipyridine	*π*-*π*, O-H···O, O-H···N	■	[17]
	Piperazine	*π*-*π*, O-H···O, C-H···O N-H···O, N-H···N	▲●	[13]
	Tetramethylprazine	C-H···O, O-H···O, O-H···N	▲●	[13]
	Pyrazinamide	*π*-*π*, C-H···N, C-H···O N-H···O, O-H···O	▲●	[13]
	Palbociclib	O-H···N, N-H···N, O-H···O	▲●■	[18]
	5-Fluorouracil		●■	[19]
Myricetin	4,4′-Bipyridine	*π*-*π*, O-H···O, C-H···O, O-H···N	■	[20]
	Nicotinamide		●	[21]
	Isonicotinamide		●	[21]
	4-Cyanopyridine		●	[21]
	Caffeine	O-H···O, O-H···N	●	[22]
	Proline	O-H···O, C-O···N	●■	[23]
	Tetramethylprazine	*π*-*π*, O-H···O, C-H···O, O-H···N	●	[13]
	Tegafur		▲●	[24]
	Berberine hydrochloride	O-H···O, C-H···O, O-H···Cl	▲●■	[25]
Dihydromyricetin	Theophylline	O-H···O, C-H···O, C-H···N O-H···N, O-H···O=C	▲●	[26]
	Benzamide	N-H···O, C-H···O, O-H···O		[26]
	Caffeine	O-H···O, C-H···O, C-H···N O-H···N, O-H···O=C	●	[26]
	Berberine hydrochloride	O-H···O, C-H···O, O-H···Cl	▲●■	[25]
	Pentoxifylline		●■	[27]
Apigenin	Theophylline	O-H···N	●■	[28]
	Nicotinamide		●	[29]
	Piperazine		●■	[30]
	4,4′-Bipyridine	*π*-*π*, C-H···*π*, O-H···O, O-H···N	●■	[31]
Daidzeine	Piracetam		●	[32]

Continued

API	CCF	Acting force	Property	Ref.
	L-Proline		●	[33]
	Lornoxicam		▲●	[34]
	L-Pyroglutamic acid		●	[35]
Baicalein	Theophylline	O-H···O, N-H···O, O-H···N, N-H···N	●■	[36]
	Caffeine	*π*-*π*, O-H···O, O-H···N		[37]
	Nicotinamide	O-H···O, O-H···N, O-H···C=O N-H···C=O	●■	[38]
Fisetin	Isonicotinamide	C-H···O, N-H···O	●	[39]
	Nicotinamide/ hemiethanolate (1∶2)	N-H···O, O-H···O, O-C···N	●	[39]
	Nicotinamide		●	[39]
	Caffeine		●	[39]
Genistein	Proline		▼◆	[7]
	Nicotinamide			[11]
	Caffeine	*π*-*π*, C-H···O, O-H···N, O-H···O	▲●	[40]
	Isonicotinamide	*π*-*π*, C-H···*π*, O-H···O, O-H···N		[41]
	Tetramethylpyrazine	*π*-*π*, C-H···*π*, C-H···O, O-H···N	▲●■	[42]
Naringenin	Isonicotinamide	*π*-*π*, O-H···N, O-H···O, N-H···O=C	●■	[43]
	Picolinic acid		●	[43]
	Betaine	*π*-*π*, O-H···O, O-H···O=C	●	[43]
	Flavone	*π*-*π*, O-H···O, C-H···O, C-H···O=C	●	[44]
	4-Hydroxypyridine	O-H···O, N-H···O	●	[44]
	Anthranilamide	O-H··N, O-H···O, N-H··O	●	[44]
	4,4′-Bipyridine	O-H··N, C-H···O		[44]
Hesperetin	Picolinic acid		●■	[45]
	Nicotinamide	N-H···N, O-H···N O-H···O=C, O-H···N	●■	[45]
	Caffeine	O-H···N, O-H···O=C	●	[45]
	Temozolomide	O-H···O, N-H··O	●■	[46]
Daidzein	Theophylline		▲●■	[28]
	4,4′-Bipyridine	O-H···N, C-H···O	●	[47]
Isoliquiritigenin	Nicotinamide	*π*-*π*, N-H···O, O-H···O C-H···O, O-H···N	●■	[48]
	Isonicotinamide	*π*-*π*, N-H···O, O-H···N, C-H···O	●■	[48]
Phloretin	Nicotinamide	*π*-*π*, N-H···O, O-H···O, C-H···O	●	[49]
	Isonicotinamide	*π*-*π*, O-H···O, N-H···O, O-H···N	●	[49]

质的研究结果表明, 只有茶碱–阿魏酸共晶、可可碱-1-羟基-2-萘甲酸共晶的溶解度较原料药低, 其余共晶均提高了生物碱类原料药的溶解度。因此, 生物碱类活性成分共晶可改变原料药的理化性质, 但目前研究仍不够深入, 仍需继续探索。

1.3 酚类 酚类是芳香环上的氢被羟基取代的一类芳香族化合物, 具有抗菌、抗炎和抗氧化等多种药理作用。酚类化合物由于含有羟基, 易与含有羟基、羧基及含氮杂环的药物产生相互作用力形成共晶, 如哌嗪、烟酰胺、异烟肼、茶碱等共晶配体。酚类化合物共晶的研究概况于表3[41,58,71-88], 包括9种酚类活性成分。其中白藜芦醇、香草酸、姜黄素、没食子酸的共晶研究较多。

多酚化合物白藜芦醇, 具有抗炎、抗病毒、保护心血管和神经等作用。但白藜芦醇溶解性差, 代谢快, 导致生物利用度低。Mehta等[71]采用液体辅助研磨制备了白藜芦醇与多种配体的共晶。溶解度实验表明, 白藜芦醇与配体哌嗪和六亚甲基四胺共晶的溶解度分别为白藜芦醇的2.5和1.5倍。两种共晶均提高了白藜芦醇的溶解度。Zhou等[72]以乙醇为溶剂, 采用液体辅助研磨和快速除溶剂方法合成了白藜芦醇-4-氨基苯甲酰胺共晶和白藜芦醇–异烟肼共晶。这两种共晶提高了白藜芦醇的溶解度和稳定性, 并具有良好的机械性能, 更适合片剂制剂开发。Wang等[73]将其与抗病毒药物盐酸金刚烷胺制成共晶。结果表明, 该共晶提高了白藜芦醇的溶解度152倍, 相对生物利用度9.62倍, 并且降低了盐酸金刚烷胺释放速率, 减轻了因盐酸金刚烷胺溶解度过高而引起的毒性作用风险, 协同增强抗病毒作用。此外, Dal Magro等[74]通过超临界溶剂共结晶技术合成姜黄素–白藜芦醇的共晶, 并提高了白藜芦醇的抗氧化活性和溶解度。

1.4 萜类及其他活性成分 除上述黄酮类、生物碱类、酚类活性成分外, 萜类、香豆素类和蒽醌类活性成分的共晶也有研究。表4[53,67,87,89-103]概括了萜类及其他活性成分共晶的研究概况, 包括10种活性成分。萜类

Table 2　Research overview on the cocrystals of alkaloids

API	CCF	Acting force	Property	Ref.
Berberine hydrochloride	Chrysin		●■	[14]
	Myricetin	O-H···O, C-H···O, O-H···Cl	▲●■	[25]
	Dihydromyricetin	O-H···O, C-H···O, O-H···Cl	▲●■	[25]
	Citric acid		●	[50]
	Lactic acid		●	[50]
	L(+)-Lactic acid hydrate		▲●	[51]
	Fumaric acid	*π*-*π*, O-H···Cl	▲●	[52]
	Emodin		●■	[53]
Berberine	Rosiglitazone		■	[54]
	Ibuprofen		●■	[55]
Theophylline	Apigenin	O-H···N		[28]
	Daidzein		▲●■	[28]
	Baicalein	O-H···N, N-H···N, O-H···O, N-H···O		[36]
	Acetaminophen			[56]
	(Phenylthio) acetic acid	*π*-*π*, N-H···O, O-H···N, C-H···O	■	[57]
	Ferulic acid		▲◆	[58]
Caffeine	Myricetin	O-H···O, O-H···N		[20]
	Dihydromyricetin	O-H···O, C-H···O, C-H···N, O-H···N, O-H···O=C		[26]
	Baicalein	*π*-*π*, O-H···O, O-H···N		[37]
	Oxalic acid		▲	[59]
	Furosemide			[60]
Tetramethylpyrazine	3-Iodoacetylbenzoic acid			[61]
	Kaempferol	C-H···O, O-H···O, O-H···N	▲●	[13]
	Myricetin	*π*-*π*, O-H···O, C-H···O, O-H···N	▲●	[13]
	Genistein	*π*-*π*, C-H···*π*, C-H···O, O-H···N	▲	[42]
	Bexarotene	C-H···N		[62]
Theobromine	*P*-Coumaric	O-H···O, O-H···N, N-H···O	▲	[63]
	2,4,6-Trihydroxybenzoic acid monohydrate	*π*-*π*, O-H···O, N-H···O	▲	[63]
	Gallic acid monohydrate	O-H···O, N-H···O, O-H···N	▲	[63]
	Citric acid monohydrate		▲	[63]
	1-Hydroxy-2-naphthoic acid		◆	[63]
Tetrahydroberberine	Phosphomolybdic acid		■	[64]
	Silicotungstic acid		■	[64]
	Phosphotungstic acid		■	[64]
	L-Aspartic acid		▲●■	[64]
	Gallic acid		▲●■	[64]
	Oxalic acid		▲●■	[64]
	Malonate		▲●■	[64]
	Maleic acid		▲●■	[64]
	Fumaric acid		▲●■	[64]
Tetrahydropalmatine	Camphorsulfonic acid		●■	[65]
	Sulfosalicylic acid		●■	[65]
	P-Aminobenzene sulfonic acid		●■	[65]
	Maleic acid		●	[65]
	Fumaric acid		●	[65]
	Methanesulfonic acid		●	[65]
	Sulfamic acid		●	[65]
Matrine	Fe (III)		▲■	[66]
	Rhein			[67]
Nicotine	Tartaric acid			[68]
	Malate			[69]
	3,5-Dinitrosalicylic acid			[70]
	5-Sulfosalicylic acid salt			[70]

化合物是由甲戊二羟酸衍生、并以异戊二烯单元为基本的化合物及其衍生物, 广泛存在于自然界中, 具有抗肿瘤、抗氧化、抑菌等药理活性。其中, 如五环三萜类化合物白桦脂醇结构中含有一个羟基和一个羧基, 可与己二酸、辛二酸和对苯二甲酸形成共晶提高其溶解度。Jia 等[89]采用旋转蒸发法制备了二萜类化合物冬凌草甲素与烟酰胺的共晶。实验结果表明, 冬凌草甲素–烟酰胺共晶提高了冬凌草甲素的溶解性和生物利

Table 3 Research overview on the cocrystals of phenols. ★: Reduced activity or bioavailability

API	CCF	Acting force	Property	Ref.
Resveratrol	Phenazine	C-H···π, O-H···N, C-H···N		[71]
	4,4′-Bipyridine	O-H···N		[71]
	Piperazine	O-H···O, O-H···N	●	[71]
	1,10-Phenanthroline	C-H···π, O-H···N, C-H···N		
	1,4-Diazabicyclo[2.2.2]octane			[71]
	Methenamine	O-H···N	●	[71]
	Acridine	π-π, C-H···π, O-H···N		[71]
	Succinimide	O-H···O, N-H··O, C-H···O		[71]
	N,*N*-Dimethyl-4-aminopyridine	O-H···O, O-H··N		[71]
	4-Aminobenzamide		▲●	[72]
	Isoniazid		▲●	[72]
	Amantadine hydrochloride	C-H···Cl, N-H···Cl, O-H···Cl, N-H···O	●■	[73]
	Curcumin		●■	[74]
Bergenin	*P*-Aminobenzamide	O-H···O, N-H···O	▲●	[58]
	Isonicotinamide	O-H···O, N-H···O	▲●	[58]
	Proline		●	[75]
Oxyresveratrol	Betaine		●	[41]
	L-Proline		●	[41]
	Isonicotinamide		●	[41]
	Nicotinamide		●	[41]
	Urea		●	[41]
	Ethyl maltol		●	[41]
Curcumin	Resveratrol		●■	[74]
	N-Acetylcysteine		●	[76]
	Nicotinamide		●■	[77]
	Ascorbic acid		●	[78]
	Trimellitic anhydride		●■	[79]
	Hydroxyquinolones		■	[79]
Gallic acid	4-Cyanopyridine	π-π, C-H···π, C-H···O、O-H···O, N-H···O	●■	[80]
	2,6-Bis[(pyridin-4-yl)methylene]cyclohexanone	O-H···O, O-H···N	■	[81]
	N-Methyl-3,5-bis((pyridin-3-yl)methylene)-4-piperidone	O-H···O, O-H···N	■	[81]
	N-Methyl-3,5-bis[(pyridin-4-yl)methylene]-4-piperidone	O-H···N, O-H···O	■	[81]
	P-Aminobenzoic acid		●■	[82]
	Succinimide		●■	[82]
	Aminoacetic acid		●★	[82]
	L-Proline		●■	[82]
	Glutaric acid		●■	[82]
	Piperazine		■	[82]
	Caffeine		■	[82]
Paeonol	Carbamazepine	O-H···N, O-H···O	●	[83]
Pterostilbene	Picolinic acid		●■	[84]
	Ethylenediamine		●	[84]
	Ethylenediamine hydrate	N-H···O, O-H···N		[84]
	Theophylline dichloromethane solvate			[84]
	1,4-Diazabicyclo[2.2.2]octane	N-H···O		[84]
	1,4,8,11-Tetraazacyclotetradecane	O-H···N, N-H···N		[84]
	1,4-Dimethylpiperazine	O-H···N		[84]
	2,3,5-Trimethylpirazine	O-H···N		[84]
Ferulic acid	Nicotinamide	O-H···N	▲●	[85]
	Urea	N-H···N	▲●	[85]
	Isonicotinamide	O-H···N	▲●	[86]
Vanillic acid	Caffeine	π-π, C-H···N, C-H···O		[86]
	Theophylline	π-π, C-H···O		[86]
	Theobromine			[86]
	Nicotinamide			[86]
	Isonicotinamide			[86]
	Acridine			[86]
	Urea			[86]
	Andrographolide	O-H···O, O-H=C···O, C-H···O		[87]
	Tinidazole	π-π, C-H···π, O-H···N, O-H···O, C-H···O	▲◆	[88]

用度, 增强了冬凌草甲素对HepG2细胞的抑制作用, 并通过细胞代谢组学预测冬凌草甲素–烟酰胺共晶调控与细胞凋亡和迁移相关的代谢途径来抑制肿瘤细胞生长。

Nisar等[96]采用液体辅助研磨法制备了11-氮杂青蒿素与反式肉桂酸、马来酸和富马酸的共晶, 这3种共晶的形成主要通过药物与配体之间的N-H···O和O-H···O氢键相互作用力连接。此外, Roy等[97]报告了11-氮杂青蒿素与5-溴-水杨酸、4-溴-水杨酸和3,5-二溴水杨酸的共晶。Nisar等[98]还采用溶液法制备了11-氮杂青蒿素与喹啉抗疟药盐酸甲氟喹和*L*(−)-苹果酸的共晶, 极大改善了11-氮杂青蒿素的热稳定性和溶解度。且晶体结构分析表明, 在这两种共晶中, 11-氮杂青蒿素的酰胺官能团既可作为氢键供体也可作为氢键受体。

其他活性成分如香豆素类化合物的共晶也有研究。Chen等[100]采用溶液结晶法制得了滨蒿内酯与3,5-二氟苯甲酸、尿素、乙胺嘧啶和琥珀酰亚胺的4种共晶。其中, 滨蒿内酯–3,5-二氟苯甲酸共晶的不对称单元含有一分子滨蒿内酯和一分子3,5-二氟苯甲酸。滨蒿内酯通过O-H···O氢键与3,5-二氟苯甲酸分子交替连接, 形成两条方向相反的链。相邻的链进一步反向连接, 形成二维网状结构, 进而通过*π*-*π*相互作用堆积形成稳定的晶体。滨蒿内酯–尿素共晶的不对称单元包含两分子滨蒿内酯和两分子尿素, 通过N-H···和C-H···O氢键相互作用形成晶体结构。滨蒿内酯–乙胺嘧啶共晶的不对称单元中具有一分子滨蒿内酯和两分子乙胺嘧啶, 通过*π*-*π*、N-H···N和N-H···O相互作用形成晶体结构。滨蒿内酯–琥珀酰亚胺不对称单元中有一分子滨蒿内酯和一分子琥珀酰亚胺。该晶体结构以*π*-*π*和C-H···O弱氢键相互作用形成堆积结构。此外, 表观溶解度研究结果表明, 滨蒿内酯–尿素共晶的溶解度较滨蒿内酯的两种晶型更高。但尚未有其药效学和药动学的相关研究, 未来仍需进一步探索。

Table 4　Research overview on the cocrystals of terpenes and other active ingredients

API	CCF	Acting force	Property	Ref.
Oridonin	Nicotinamide		●■	[89]
Oleanolic acid	Fumaric acid	O-H···O=C		[90]
	Succinic			[91]
	L-Proline			[91]
	Saccharin			[91]
Betulin	Adipic acid		●	[92]
	Terephthalic acid		●	[93]
Artemisinin	Acetylenedicarboxylic acid		●	[94]
	Orcinol		●	[95]
	Resorcinol		●	[95]
11-Azaartemisinin	Cinnamic	N-H···O, O-H···O		[96]
	Maleic	N-H···O, O-H···O		[96]
	Fumaric acid	N-H···O, O-H···O		[96]
	5-Bromosalicylic acid	N-H···O, O-H···O		[97]
	4-Bromosalicylic acid	N-H···O, O-H···O		[97]
	3,5-Dibromosalicylic acid	N-H···O, O-H···O		[97]
	Mefloquine hydrochlorid		▲●	[98]
	L(－)-Malic acid		▲●	[98]
Andrographolide	Vanillin	O-H···O, O-H=C···O, C-H···O		[87]
	Vanillic acid	O-H···O, O-H=C···O, C-H···O		[87]
	Salicylic acid	O-H···O, O-H=C···O, C-H···O	●	[87]
	Resorcinol	O-H···O, O-H=C···O, C-H···O		[87]
	Guaiacol	O-H···O, O-H=C···O, C-H···O		[87]
Celastrol	Threonine		●■	[99]
	Phenylalanine		●■	[99]
	L-Tyrosine		●■	[99]
Scoparone	3,5-Difluorobenzoic acid	*π*-*π*, O-H···O	●	[100]
	Urea	N-H···O, C-H···O	●	[100]
	Pyrimethamine	*π*-*π*, N-H···N, N-H···O	●	[100]
	Succinimide	*π*-*π*, C-H···O	●	[100]
Emodin	Nicotinamide	O-H···O, O-H···N, N-H···N		[101]
	Berberine hydrochloride	O-H···Cl, O-H···O, C-H···O		[53]
	Berberine hydrochloride ethanol	O-H···Cl, O-H···O		[53]
	Carbamazepine			[102]
Rhein	Matrine	*π*-*π*, O-H···O, N-H···O		[67]
	Gefitinib			[103]

2 展望与挑战

综上所述, 文中报道了45种中药活性成分药物共晶研究。其中, 黄酮类活性成分共晶的研究最为广泛。药物和共晶配体主要通过羰基、酰胺和羟基等官能团产生相互作用力形成共晶。此外, 配体、温度、溶剂、pH值和离子浓度等因素均可能影响共晶的形成。本文所述的16种黄酮类化合物结构中含有多个羟基, 易与含氮环状化合物配体产生氢键和π-π堆积等相互作用力形成共晶; 生物碱类活性成分由于含有氮原子, 常用作配体改善黄酮类活性成分的理化性质, 也易与磺酸类和具有羧基的药物形成共晶; 酚类活性成分易与含氮杂环的药物形成共晶; 萜类活性成分主要与有机酸类配体形成共晶。

药物共晶不仅可改善中药活性成分的物理化学性质, 还可以作为一种新的联合用药方式, 将会进一步提高中药活性成分的应用价值。但目前中药活性成分共晶的研究多选用含氮环状结构如烟酰胺、异烟肼和4,4′-联吡啶等分子作为共晶配体, 在配体的选择上尚存在一定的局限性。尽管近几年中药活性成分共晶的相关研究逐渐增加, 但大多都停留在晶体结构分析和溶解度研究上, 在体内的作用过程及其毒理药理作用机制的研究较少, 并且中药活性成分共晶与剂型相结合的报道也不多。因此, 中药活性成分共晶离临床应用还有很长的距离, 比如共晶是否符合药典和法律的相关规定, 是否可大规模制备生产等还需对中药活性成分共晶深入研究, 以获得更多的支撑数据。随着国家把发展中医药创新推向前所未有的高度, 中药活性成分共晶将会获得科研人员越来越多的研究。

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